European
Thyroid Journal

35th Annual Meeting of the European Thyroid Association

Programme

Krakow, Poland, 10th–14th September 2011

Guest Editors
Peter Laurberg, Aalborg, Denmark
Barbara Jarząb, Gliwice, Poland

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European
Thyroid Journal

Launching Issue

Contents

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A Warm Welcome to the ETA Annual Meeting, the Historical City of Krakow, and to the Launching of the New *European Thyroid Journal*

We are happy to welcome you to the 35th annual meeting of the European Thyroid Association and to Krakow, the historical center of southern Poland. We are proud to use this opportunity to present this launching issue of the new official journal of the ETA: *European Thyroid Journal*.

Publication with peer review is crucial for the development of science as well as quality in patient care. Publishing in the field of medical science and thus furthering discussion of clinical care is a major obligation, and the ETA is now taking up its part in this important task. Publishing scientific material as an international society involves special responsibilities but also opportunities to influence the development of thyroidology and to improve the services to our members.

This launching issue of the journal with program and abstracts will help keep you updated and get the best out of the scientific program of our meeting. Moreover, you can easily flip through the pages and read some abstracts even while having a break and enjoying the sun in one of the open air cafés of Krakow. Hopefully, you will like the feel and layout of *European Thyroid Journal* and be tempted to be one of the first to submit a paper for publication in the new journal. The Editor-in-Chief eagerly awaits your submission of exciting data and great ideas on thyroidology. Electronic submission of papers will be possible as of October 1st 2011.

We have done our utmost to make this into a high quality journal. The first Editor-in-Chief, Wilmar Wiersinga from Amsterdam, is known to most of you for his many achievements including previous presidency of the ETA. Wilmar Wiersinga is widely recognized for his skills and devotion in science, but also for being a great organizer and developer. He will be assisted by several associate editors and a broad range of expert board members.

Our publishing partner, Karger, is our guarantee for high quality. Editor-in-Chief Wilmar Wiersinga and the ETA treasurer George Kahaly have had meetings and discussions with Karger on all the details of the journal. Karger will provide their whole spectrum of publishing facilities, and an electronic publication of the journal will be available free to all ETA members via the ETA website. The printed journal will be available to members at a reduced price. As you can see, technical quality is a hallmark of the Karger publishing house.

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The ETA is a charity organization devoted to the thyroid. The new journal is part of this charity with no publication fees for authors and free access for ETA members. The journal is another good reason to be a member of the ETA. Please take advantage of this great new development in international thyroidology, and give your support in making it a success.

The ETA meeting in Krakow will be remembered as the place where the new journal was launched, and for sure this meeting will be remembered for its good scientific presentations and lively discussions. The great city of Krakow will also stay in our memories. As usual, the Local Organizing Committee has worked hard to find good central facilities for our meeting and show us some of the highlights of the area. Walk around and enjoy the historical atmosphere of the old city of Krakow "on the UNESCO list of World Cultural Heritage", try eating a traditional Polish meal, and if possible visit the interesting surroundings. Some inspiration can be found at www.cracow.org. Last but not least, make new friends and collaborators in the field of thyroidology, and enjoy the friendliness and liveliness of the ETA.

Welcome to Polska!

Peter Laurberg
President of the ETA

Barbara Jarząb
Chairman of the Local Organizing Committee

European
Thyroid Journal

Registration Information

Main Conference Fees

Membership status	before 30th June	30th June – 31st August	1st September – on site
Ordinary Member	125 €	150 €	200 €
Senior Member	125 €	150 €	200 €
Corresponding Member	225 €	250 €	350 €
Junior Member <35 yrs	60 €	80 €	100 €
Research Fellow <30 yrs	125 €	150 €	200 €
Non-Member	450 €	500 €	550 €
Accompanying Person	30 €	40 €	50 €

Pre-Conference Satellite Symposia Fees

ETA-CRN and ESES Meeting	50 €
ICCIDD	40 €
Ultrasonography Course	200 €
3rd PTT 2011 Meeting	detailed information on website: http://pttkrakow2011.cm-uj.krakow.pl

Social Programme

10th Sept. Welcome Reception	free for registered participants and registered accompanying persons
12th Sept. ETA Excursion to Wieliczka	40 €
13th Sept. Gala Dinner	75 €

Day Tickets (only available on site)
Sunday, Monday, Tuesday: 100 € per day
Wednesday: 70 €

Main Conference Registration Entitlements

Delegate registration includes:
– Access to all congress sessions and commercial exhibition
– All congress materials and a name badge
– Programme and Abstract Book
– Refreshment breaks during the congress
– Welcome Reception

Registration does not include:
– Accommodation, tickets to the social events (unless stated) or optional excursions

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Accompanying person registration includes:
– Name badge
– Welcome Reception
– It does not include access to the lecture halls and commercial exhibition

Pre-Conference Satellite to 35th ETA Meeting Symposia Entitlements

– **ETA-CRN and ESES Meeting**
Admission to the Scientific Sessions of ETA-CRN and ESES Meeting, congress material, lunch and coffee breaks
– **ICCIDD**
Admission to the Scientific Sessions of ICCIDD, congress material, lunch and coffee breaks
– **Advanced Thyroid, Parathyroid and Neck Ultrasonography Course**
Admission to the Scientific Sessions of Course, congress material, lunch and coffee breaks

On-Site Registration / Secretariat Desk

The Congress Registration Desk will be located in the entrance area (ground level) of the Auditorium Maximum.

The Secretariat will operate during the following hours:

Saturday	10th September	07.30–19.00
Sunday	11th September	07.30–19.00
Monday	12th September	06.45–16.30
Tuesday	13th September	07.30–18.30
Wednesday	14th September	07.30–12.00

ETA Commercial Exhibition Opening Hours

Sunday	11th September	08.30–18.30
Monday	12th September	08.30–16.00
Tuesday	13th September	08.30–18.00
Wednesday	14th September	08.30–12.00

Saturday, 10th September 2011

Main Hall (Aula Duza)
08.00–15.00

ETA-CRN and ESES Meeting

A joint session of the European Thyroid Association-Cancer Research Network and the European Society of Endocrine Surgeons

Lecture Hall
08.30–17.00

ICCIDD West-Central Europe Regional Meeting

Senate Hall
08.50–15.30

Advanced Thyroid, Parathyroid and Neck Ultrasonography Course

Minor Hall
08.00–17.15

Meeting of the Polish Thyroid Association PTT 2011

PTT 2011 Meeting Poster Exhibition (MTE Hall 08.00–15.00)

19.30

Welcome Reception

Sukiennice (Cloth Hall) at Main Market Square at the Gallery of the 19th century Polish art

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ETA-CRN and ESES Meeting

A joint session of the European Thyroid Association-Cancer Research Network and the European Society of Endocrine Surgeons kindly sponsored by the Polish Society of Endocrinology, Thermo Fisher Scientific, Merck Serono and Genzyme-Poland

Organizing Committee of Joint ETA-CRN and ESES Symposium
Henning Dralle (Halle, Germany), *Marcin Barczyński* (Krakow, Poland), *Barbara Jarząb* (Gliwice, Poland), *Daria Handkiewicz-Junak* (Gliwice, Poland)

ETA-CRN
President: *Ulla Feldt-Rasmussen*, National University Hospital, Copenhagen, DK
Secretary: *Barbara Jarząb*, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
Treasurer: *Georg Brabant*, The University of Lübeck, Germany

ESES
President: *Jean-Françoise Henry*, University Hospital La Timone, Marseille, France
Past President: *Henning Dralle*, Martin-Luther-University, Halle-Wittenberg, Germany
President Elect: *Bruno Niederle*, Medical University of Vienna, Austria
Secretary: *Jean-Louis Kraimps*, University Hospital, Poitiers, France
Treasurer: *Frederic Triponez*, University Hospital of Geneva, Switzerland

Main Hall (Aula Duza)
08.00–15.00

Challenging Questions at the Borderline of Thyroid Cancer Surgery and Follow Up

Chairs: *Ulla Feldt-Rasmussen* (Copenhagen, Denmark)
Henning Dralle (Halle, Germany)

08.00 Registration and coffee
08.30 Presidential Welcome Address: Presidents of ETA-CRN and ESES
08.45 Welcome Address of the Rector of the Collegium Medicum of Jagiellonian University
09.00 Total thyroidectomy for benign thyroid disease improves outcomes of treatment for incidentally diagnosed thyroid cancer
M. Barczyński (Krakow, Poland)
09.25 Discussion
09.40 What to do when a total thyroidectomy has not been performed at initial surgery and in which patients?
F. Borson-Chazot (Lyon, France)
10.05 Discussion
10.20 Is it time to base therapeutic decision on the BRAF status of thyroid tumors?
P. Miccoli (Pisa, Italy)
10.45 Discussion

11.00 Coffee break

11.30 PET-CT and thyroid nodule
S. Leboulleux (Paris, France)
11.55 Discussion
12.10 Medullary thyroid cancer: cut-off for surgical intervention in postoperative hypercalcitoninaemia
H. Dralle (Halle, Germany)
12.35 Discussion
12.50 Is it time to use of tyrosine kinase inhibitors in microdisseminated medullary thyroid cancer?
M. Schlumberger (Paris, France)
13.15 Discussion

13.30 Lunch

14.00 **ETA-CRN General Assembly**

ICCIDD West-Central Europe Regional Meeting

Lecture Hall
08.30–17.00

08.30–09.00 Registration
09.00–09.10 Welcome Address
Barbara Jarzab (Chairman Eta Local Organizing Committee)
Peter Laurberg (President ETA)

Scientific Symposium
Section 1
Chairmen: *Gerard Burrow* (ICCIDD Chairman)
Aldo Pinchera (ICCIDD Regional Coordinator)

09.10–09.20 Regional and Global Prevalence of Iodine Deficiency and Burden of Disease Due to Iodine Deficiency
Maria Andersson (Switzerland)
09.20–09.25 Discussion
09.25–09.35 The WHO Recommendation on Reduction of Daily Salt Intake and its Impact on the USI Program for IDD Prevention
Zbigniew Szybinski (Poland)
09.35–09.40 Discussion
09.40–09.50 Methods Used for Measuring Urinary Iodine Excretion
Stig Andersen (Denmark)
09.50–09.55 Discussion
09.55–10.05 Urinary Iodine Excretion in Monitoring Iodine Nutrition
Hans Bürgi (Switzerland)
10.05–10.10 Discussion
10.10–10.20 Benefits and Risks of Iodine Supplements to Pregnant Women
Francesco Vermiglio (Italy)
10.20–10.25 Discussion

10.25–10.45 Coffee break

Section 2
Chairmen: *Peter Laurberg* (Denmark)
John Lazarus (UK)

10.45–10.55 The Chernobyl Accident 25 Years Later: The Impact of Iodine Deficiency
Aldo Pinchera (Italy)
10.55–11.00 Discussion
11.00–11.10 The Chernobyl Accident: The Polish Experience with Potassium Iodide as a Thyroid Blocking Agent
Janusz Nauman (Poland)
11.10–11.15 Discussion
11.15–11.25 The Fukushima Accident: An Updated Report
Shigenobu Nagataki (Japan)
11.25–11.30 Discussion
11.30–12.00 General Discussion

12.00–13.00 Lunch and Poster Vision

Iodine Nutrition Status in West Central Europe: An Update on Iondine Prophylaxis

Section 1

Chairmen: *Peter Smyth* (Ireland)
Paolo Vitti (Italy)

13.00–13.10	Introduction *Aldo Pinchera* (ICCIDD West Central Europe Regional Coordinator), *Gregory Gerasimov* (ICCIDD Eastern Europe Regional Coordinator)
13.10–14.40	Presentation of country data ICCIDD National Representatives Albania – *Argon Ylli* Belgium – *Rodrigo Moreno-Reyes* Bulgaria – *Roussanka Kovatcheva* Croatia – *Zvonko Kusic* Czech Republic – *Václav Zamrazil* Denmark – *Peter Laurberg* Estonia – *Toomas Podar* Finland – *Georg Alfthan* France – *Philippe Caron* Germany – *Henry Völzke* Greece – *Kostas B. Markou* Hungary – *Endre V. Nagy* Ireland – *Peter Smyth* Italy – *Fabrizio Aghini-Lombardi* Latvia – *Valdis Pirags*
14.40–15.00	Discussion
15.00–15.20	Coffee break

Section 2

Chairmen: *Serjei Hojker* (Slovenia)
Massimo Tonacchera (Italy)

15.20–16.40	Presentation of country data: continuation ICCIDD National Representatives Luxemburg – *Yolande Wageneer* Lithuania – *Albertas Barzda* Macedonia – *Karafilski Borislav* Netherlands – *Robin Peeters* N. Cyprus – *Hasan Sav* Poland – *Zbigniew Szybiński* Portugal – *Edward Limbert* Romania – *Mihaela Simescu* Serbia – *Tanja Knezevic* Slovakia – *Jan Podoba* Slovenia – *Sergej Hojker* Spain – *Lluis Vila* Sweden – *Mehari Gebre-Medhin* Switzerland – *Hans Bürgi* Turkey – *Murat Faik Erdoğan* United Kingdom – *John Lazarus*
16.40–17.00	Discussion and Conclusions
17.00	Closure

Advanced Thyroid, Parathyroid and Neck Ultrasonography Course

Senate Hall
08.50–15.30

08.50–09.00 **Welcome**
Murat Faik Erdoğan (Ankara, Turkey), *Paolo Vitti* (Pisa, Italy)

09.00–10.00 **Pitfalls in the Thyroid Nodule Evaluation**
Paolo Vitti (Pisa, Italy)
Using gray scale for the prediction of malignancy
Using Doppler for the prediction of malignancy
Using elastography for the prediction of malignancy
Choosing the correct nodule to biopsy
Q&A (10 min)

10.10–10.40 **Ultrasound Guided Fine Needle Aspiration and PEI**
Teresa Rago (Pisa, Italy)
Pitfalls for the best aspirations and to obtain best smears
Discussion of different aspiration techniques
How many passes per nodule?
Discussion of the techniques to minimize the discomfort
Discussion of the different techniques of PEI
PEI results for cystic and mixed nodules
Q&A (10 min)

10.50–11.20 Coffee break

11.20–11.50 **Thyroid Cytology**
Fulvio Basolo (Pisa, Italy)
Discuss the current classifications and basic aspects of benign and malignant cytology
Using different markers for cytologic diagnosis
Discuss the variability of adequate vs inadequate FNAC results among cytologists
Q&A (10 min)

12.00–12.45 **Cancer Follow up by Using Thyroid Ultrasound**
Laurence Leenhardt (Paris, France)
Preoperative evaluation of lymph nodes (DTC&MTC)
Postoperative evaluation by Ultrasound and timing
Importance and timing of basal and stimulated Tg
The technique of Tg and calcitonin washouts
Discussion of cut-off values for washouts.
Q&A (15 min)

13.00–14.00 Lunch

14.00–14.30 **Ultrasound Evaluation of Hyperparathyroidism**
Murat Faik Erdoğan (Ankara, Turkey)
Pitfalls in parathyroid USG
How to extend the limitations of PT ultrasound
Atypical localizations
Preoperative Quick PTH for the localization
Q&A (10 min)

14.40–15.30 **Video Presentations by the Lecturers and Interactive Discussion with the Audience**
M.F. Erdoğan, T. Rago, L. Leenhardt, P. Vitti

15.30 **Distribution of the Certificates**

Meeting of the Polish Thyroid Association PTT 2011

Opening Ceremony 19.00, 9th September 2011
Hotel 'Pod Rożą', Floriańska Str. 14
A. Lewiński, A. Hubalewska-Dydejczyk, A. Milewicz

Minor Hall
08.00–17.15
10th September 2011

08.30–10.10 **Molecular Background of Thyroid Diseases**
Chairmen: *M. Karbownik-Lewińska, J. Nauman, S. Sporny*

08.30–09.00 Thyronamines - Past, Present, and Future*
J. Köhrle (Germany)
09.00–09.30 Molecular genetics of thyroid and polyglandular autoimmunity*
*G.J. Kahaly (*Germany)
09.30–09.50 Molecular mechanisms of thyroid hormone action in thyroid gland
A. Piekiełko-Witkowska (Poland)
09.50–10.10 2 oral presentations

10.10–10.30 Coffee break. Poster session

10.30–11.30 **Autoimmune Thyroid Diseases**
Chairmen: *E. Bar-Andziak, R. Junik, W. Zgliczyński*

10.30–10.50 Oxidative stress and thyroid
M. Karbownik-Lewińska (Poland)
10.50–11.10 Autoimmune disturbances in pregnancy
A. Syrenicz (Poland)
11.10–11.30 2 oral presentations

11.30–11.50 Coffee break

11.50–13.30 **Thyroid Cancer**
Chairs: *B. Jarząb, A. Lewiński, J. Brzeziński*

11.50–12.10 Monitoring and important anatomical structure prevention in thyroidectomy
J. Brzeziński, M. Dedecjus (Poland)
12.10–12.40 Fine needle biopsy of thyroid – from morphology and morphometry to molecular diagnostics
A. Lewiński (Poland)
12.40–13.10 Polish consensus of thyroid cancer treatment
B. Jarząb, D. Handkiewicz-Junak (Poland)
13.10–13.30 Discussion

13.30–14.30 Lunch

MTE Hall
08.00–15.00

PTT 2011 Meeting Poster Exhibition

Minor Hall

14.30–16.30 **Challenges in Thyroid Research**
Chairmen: *A. Hubalewska-Dydejczyk, J. Sowiński, M. Niedziela*

14.30–15.00 The treatment of refractory thyroid cancer*
M. Schlumberger (France)

15.00–15.30 Selenium and the thyroid*
L. Duntas (Greece)

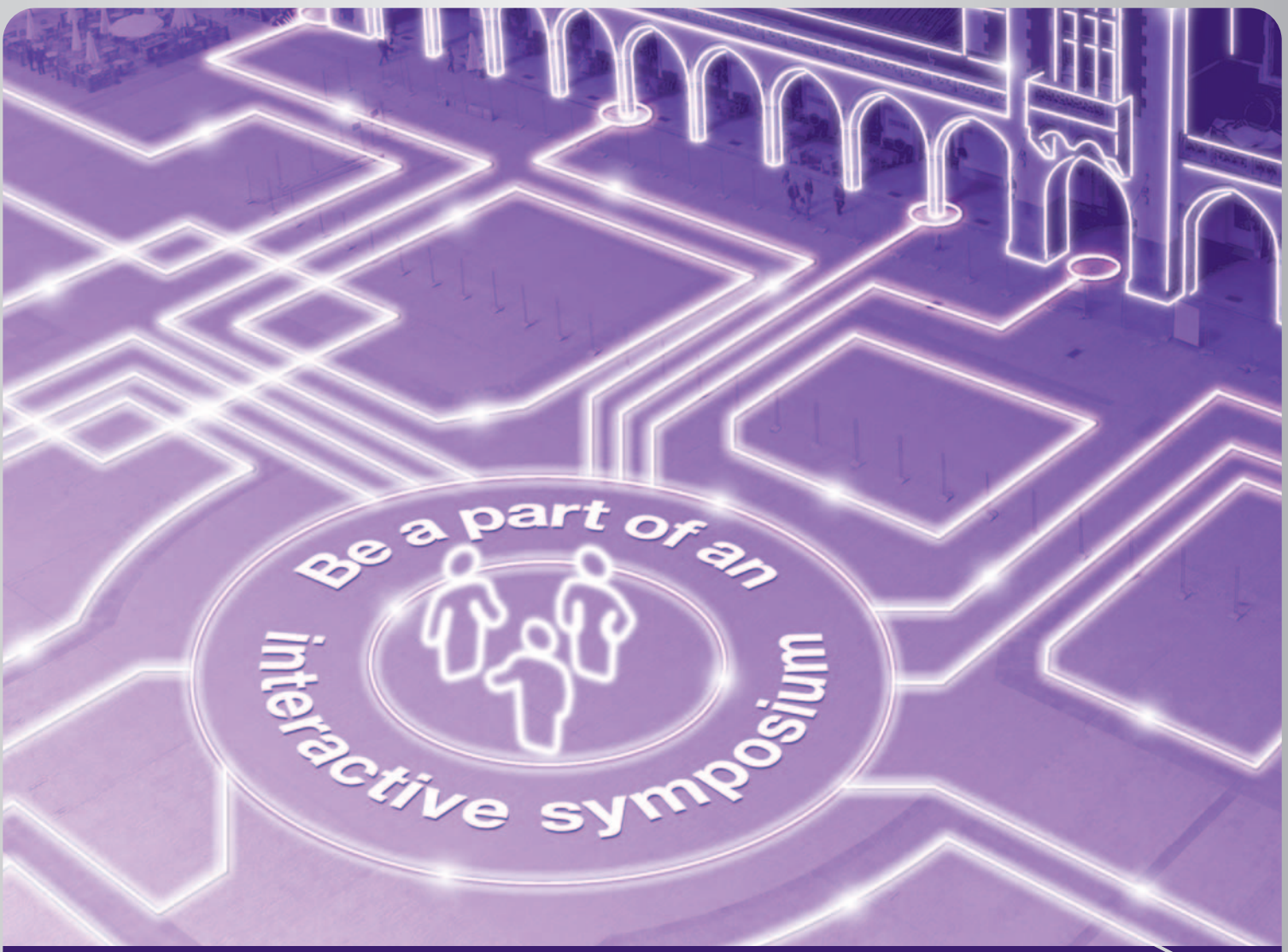
15.30–16.00 New aspects of autoimmune thyroid diseases including Hashimoto's and Graves' disease*
R. Gärtner (Germany)

16.00–16.20 Thyroid dysfunction induced by amiodarone treatment and iodine contrast agents
A. Hubalewska-Dydejczyk (Poland)

16.20–16.30 **Summary and Farewell**

16.30–17.15 **General Assembly of PTT**

*Lectures are simultaneously translated into the Polish language



35th Annual Meeting of the European Thyroid Association: Industry-sponsored symposium

Sharing Real-Life Experiences in Medullary Thyroid Cancer

Sunday 11 September 2011 | 1:00–2:00 pm

Aula Duza/Main Hall of the Jagiellonian University, Kraków, Poland

Programme to include case studies, expert panel discussion and audience interaction

Lunch will be provided

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Sunday, 11th September 2011

Main Hall (Aula Duza)

08.00–10.00

Oral Presentations 1: Topic Highlights (OP01–OP06)

Chairs: *Peter Laurberg* (Aalborg, Denmark); *Barbara Jarząb* (Gliwice, Poland)

08.00–08.20

OP01 **E7080 IN ADVANCED RADIOIODINE (RAI)-REFRACTORY DIFFERENTIATED THYROID CANCER (DTC); RESULTS OF A MULTI-CENTER PHASE II TRIAL**

Sherman SI[1], Jarząb B[2], Cabanillas ME[1], Licitra L[3], Pacini F[4], Martins RG[5], Robinson B[6], Ball DW[7], McCaffrey JC[8], Shah MH[9], Bodenner DL[10], Allison R[11], Newbold K[12], Elisei R[13], Gold A[14], Andresen C[14], O'Brien JP[14], Schlumberger M[15]

[1]The University of Texas MD Anderson Cancer Center, Houston, United States, [2]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland, [3]Istituto Nazionale dei Tumori, Milano, Italy, [4]Azienda Ospedaliera Universitaria Senese, Siena, Italy, [5]Seattle Cancer Care Alliance, Seattle, United States, [6]Royal North Shore Hospital, St. Leonards, Australia, [7]John Hopkins Medical Institutes, Baltimore, United States, [8]H. Lee Moffit Cancer Center, Tampa, United States, [9]Ohio State University School of Medicine, Columbus, United States, [10]University of Arkansas, Little Rock, United States, [11]The Royal Brisbane and Women's Hospital, Herston, Australia, [12]Royal Marsden Hospital, Sutton, United Kingdom, [13]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, [14]Eisai Inc., Woodcliff Lake, United States, [15]Institut Gustave-Roussy, Villejuif, France

08.20–08.40

OP02 **THE CLINICAL PI3K INHIBITOR GDC-0941 RADIOSENSITISES THYROID CARCINOMA CELLS BY INHIBITING BOTH THE PI3K AND HIF-1 SIGNALLING PATHWAYS**

Burrows N[1], Williams J[1], Babur M[1], Resch J[2], Williams K[1], Brabant G[2]

[1]University of Manchester, Hypoxia and Therapeutics Group, School of Pharmacy, Manchester, United Kingdom, [2]University of Lübeck, Clinical and Experimental Endocrinology, Lübeck, Germany

08.40–09.00

OP03 **EFFECTS OF CHRONIC 3-IODOTHYRONAMINE ADMINISTRATION ON LIPID METABOLISM IN RODENTS**

Chiellini G[1], Assadi-Porter FM[2], Haviland J[2], Butz D[2], Frascarelli S[1], Pellegrini S[3], Scanlan TS[4], Zucchi R[1]

[1]University of Pisa, Dip. di Scienze dell'Uomo e dell'Ambiente, Pisa, Italy, [2]University of Wisconsin, Madison, United States, [3]University of Pisa, Dip. di Patologia Sperimentale, Pisa, Italy, [4]Oregon Health & Science University, Portland, United States

09.00–09.20

OP04 **NEUROENDOCRINE C CELLS OF THE MOUSE THYROID ORIGINATE FROM FOREGUT PROGENITORS IN THE ANTERIOR ENDODERM**

Nilsson M[1], Andersson L[2], Westerlund J[2], Carlsson T[1], Parrillo L[3], Zoppoli P[3], Lania G[4], Baldini A[4], Fagman H[1]

[1]Cancer Center Sahlgrenska, Gothenburg University, Institute of Biomedicine, Göteborg, Sweden, [2]Gothenburg University, Institute of Biomedicine, Göteborg, Sweden, [3]IRGS, Biogem s.c.ar.l, Ariano Irpino, Italy, [4]Telethon Institute of Genetics and Medicine, Naples, Italy

09.20–09.40

OP05 **A MULTICENTER RANDOMIZED PROSPECTIVE TRIAL OF PERCUTANEOUS LASER ABLATION VERSUS FOLLOW-UP FOR THE TREATMENT OF COLD THYROID NODULES. SIX-MONTH RESULTS**

Papini E[1], Valcavi R[2], Rago T[3], Vitti P[3], Gambelunghe G[4], De Feo P[4], Bizzarri G[1], Pacella C[2]

[1]Regina Apostolorum Hospital, Department of Endocrinology, Albano Laziale, Italy, [2]Thyroid Disease Center, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, [3]Department of Endocrinology, University of Pisa, Pisa, Italy, [4]Department of Internal Medicine and Endocrine and Metabolic Sciences, Perugia, Italy

09.40–10.00

OP06 **A NOVEL CHIMERIC TSHR BIOASSAY DETECTS BOTH THYROID BLOCKING AND STIMULATING IMMUNOGLOBULINS**

Olivo PD[1], Kim J[1], Larrimer A[1], Klasen R[1], Kanitz M[2], Li Y[1], Kahaly GJ[2]

[1]Diagnostic Hybrids, Inc. (a Quidel Company), Athens, Ohio, United States, [2]Gutenberg University Medical Center, Thyroid Research Laboratory, Mainz, Germany

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Main Hall (Aula Duza)
10.00–10.10

Lissitzky Career Award

The 2011 award is sponsored exclusively by Diagnostic Hybrids, Ohio, USA
Chairs: *Peter Laurberg* (Aalborg, Denmark); *Luigi Bartalena* (Varese, Italy)

10.10–10.30
Coffee break

Minor Hall

10.30–12.00

Symposium 1 (Basic): Local Control of Thyroid Hormone Action

Chair: *Agnieszka Piekielko-Witkowska* (Warsaw, Poland); *Marek Niedziela* (Poznan, Poland)

Control of deiodinase expression in malignancy
Domenico Salvatore (Naples, Italy)
The essential role of D2 in bone
Duncan Bassett (London, UK)
Understanding the HPT axis in MCT8 deficiency
Heike Heuer (Jena, Germany)

Main Hall (Aula Duza)

10.30–12.00

Symposium 2 (Clinical): Pregnancy and Graves' Disease

Chair: *Jacques Orgiazzi* (Lyon, France); *Gerasimos Krassas* (Thessaloniki, Greece)

Preconception counseling in Graves' disease
John Lazarus (Cardiff, UK)
Side effects of antithyroid drugs
Bijay Vaidya (Exeter, UK)
Management of Graves' hyperthyroidism in pregnancy
Luca Chiovato (Pavia, Italy)

Poster Exhibition Area (see pages 31 to 42)

12.00–13.00

Lunch and Poster Discussions

Thyroid Cancer (clinical) 1: Posters PO1-PO10
Chair: *Ulla Feldt-Rasmussen* (Copenhagen, Denmark)

Thyroid Cancer (clinical) 2: Posters PO11-PO19
Chair: *Markus Luster* (Ulm, Germany)

Thyroid Cancer (clinical) 3: Posters PO20-PO29
Chair: *Laura Fugazzola* (Milan, Italy)

Thyroid Cancer (basic/translational) 1: Posters PO30-PO39
Chair: *Clara Alvarez* (Santiago de Compostela, Spain)

Graves' Orbitopathy 1: Posters PO40-PO53
Chair: *Valentin Fadeyev* (Moscow, Russia)

Graves' Hyperthyroidism 1: Posters PO54-PO65
Chair: *Paolo Vitti* (Pisa, Italy)

Thyroid Hormone & Metabolism 1: Posters PO66-PO73
Chair: *Istvàn Szabolcs* (Budapest, Hungary)

Hypothyroidism 1: Posters PO74-PO87
Chair: *Annick van den Bruel* (Bruges, Belgium)

Cytology: Posters PO88-PO101
Chair: *Teresa Rago* (Pisa, Italy)

Pregnancy: Posters PO102-PO115
Chair: *Milos Zarkovic* (Belgrade, Serbia)

Main Hall (Aula Duza)
13.00–14.00

AstraZeneca

AstraZeneca Symposium

Sharing Real-Life Experiences in Medullary Thyroid Cancer

13.00–13.05
Welcome
Barbara Jarząb (Poland)

13.05–13.10
Introduction
Richard Kloos (USA)

13.10–13.50
Case studies
Expert panel discussion with audience interaction
Rossella Elisei (Italy) and *Lori Wirth* (USA)

13.50–14.00
Summary and close
Richard Kloos (USA)

Main Hall (Aula Duza)
14.00–14.45

ETA Harington-de Visscher Prize Lecture

Chairs: *Peter Laurberg* (Aalborg, Denmark), *Luigi Bartalena* (Varese, Italy)

Thyroid cancer: role of RET and beyond
Francesca Carlomagno (Naples, Italy)

14.45–15.00
Coffee break

15.00–15.45
Meet the Expert

MTE 1: MTE Hall
Non-mammalian models to study thyroid development
Luca Persani (Milan, Italy)

MTE 2: Senate Hall
Thyroid hormone resistance and metabolism
Krishna Chatterjee (Cambridge, UK)

MTE 3: Lecture Hall
Cardiovascular involvement in Graves' hyperthyroidism vs. toxic nodular goiter
Bernadette Biondi (Naples, Italy)

MTE 4: Minor Hall
Treatment of difficult cases of thyroid carcinoma
Martin Schlumberger (Paris, France)

Minor Hall
16.00–18.00

Oral Presentations 2: Thyroid Cancer Translational (OP07–OP14)

Chair: *Furio Pacini* (Siena, Italy); *Malgorzata Karbownik-Lewinska* (Lodz, Poland)

16.00–16.15
OP07 **EPIDERMAL GROWTH FACTOR RECEPTOR-TARGETED NON-VIRAL DELIVERY OF THE SODIUM IODIDE SYMPORTER (NIS) GENE IN RADIOIODINE-REFRACTORY DIFFERENTIATED AND ANAPLASTIC THYROID CANCER**
Dolp PA[1], Klutz K[1], Wunderlich N[1], Grünwald GK[1], Willhauck MJ[1], Knoop K[1], Vetter A[2], Rödl W[2], Wagner E[2], Göke B[1], Ogris M[2], Spitzweg C[1]
[1]Ludwig-Maximilians-University, Department of Internal Medicine II, Munich, Germany, [2]Ludwig-Maximilians-University, Department of Pharmacy, Center of Drug Research, Pharmaceutical Biotechnology, Munich, Germany

16.15–16.30
OP08 **OUTCOME OF A CONSERVATIVE MANAGEMENT POLICY FOR FOLLICULAR THYROID CANCER – A PROSPECTIVE LONGITUDINAL COHORT STUDY**
Mackay I[1,2], Craig W[1,2], Smart L[2,3], Krukowski ZH[1,2]
[1]Aberdeen Royal Infirmary, Department of General Surgery, Aberdeen, United Kingdom, [2]University of Aberdeen, Aberdeen, United Kingdom, [3]Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, United Kingdom

16.30–16.45
OP09 **THE IODINE DEFICIENCY-INDUCED ANGIOGENIC PATHWAY IN THYROID CANCER CELLS OCCURS VIA A VEGF-HIF SIGNALLING PATHWAY THAT, IN CONTRAST WITH NON MALIGNANT CELLS, IS INDEPENDENT ON REACTIVE OXYGEN SPECIES**
Gerard A-C[1], Humblet K[1], Derradji H[2], Baatout S[2], de ville de Goyet C[1], Sonveaux P[3], Denef J-F[1], Colin IM[1]
[1]Universite catholique de Louvain, IREC, Pôle de Morphologie, Bruxelles, Belgium, [2]Belgian Nuclear Centre, SCK-CEN, Radiobiology unit, Mol, Belgium, [3]Universite catholique de Louvain, IREC,Pôle de Pharmacologie Thérapeutique, Bruxelles, Belgium

16.45–17.00
OP10 **FAMILIAL PAPILLARY THYROID CANCER PATIENTS DISPLAY AN ELEVATED CHROMOSOME FRAGILITY CHARACTERIZED BY TELOMERIC ASSOCIATION AND TELOMERE LOSS**
Cantara S[1], Pisu M[1], Capuano S[1], Capezzone M[1], Frau D[2], Caria P[2], Marchisotta S[1], Busonero G[1], Formichi C[1], Vanni R[2], Pacini F[1]
[1]University of Siena, Department of Internal Medicine, Endocrinology and Metabolism and Biochemistry, Section of Endocrinology and Metabolism, Siena, Italy, [2]University of Cagliari, Department of Biomedical Technologies and Sciences, Monserrato, Italy

17.00–17.15
OP11 **HUMAN LEUKOCYTE ANTIGEN-G POLYMORPHISM: A POTENTIAL MARKER OF HISTOLOGICAL AGGRESSIVENESS IN PAPILLARY THYROID CANCER**
Dardano A[1], Rizzo R[2], Polini A[1], Stignani M[2], Tognini S[1], Pasqualetti G[1], Colato C[3], Ferdeghini M[3], Baricordi O[2], Monzani F[1]
[1]University of Pisa, Department of Internal Medicine, Pisa, Italy, [2]University of Ferrara, Department of Experimental and Diagnostic Medicine, Ferrara, Italy, [3]University of Verona, Department of Morphological and Biomedical Sciences, Verona, Italy

17.15–17.30
OP12 **HIGH-RESOLUTION-MELTING-CURVE ANALYSIS (HRM) FOR BRAF^{V600E} AND NRAS MUTATION SCREENING IN ROUTINE AIR DRIED THYROID FNA SMEARS IS MORE RELIABLE AND MORE SENSITIVE THAN FLUORESCENCE RESONANCE ENERGY TRANSFER (FRET) PROBES ANALYSIS**
Rehfeld C[1], Krogdahl A[2], Ferraz C[1], Precht Jensen EM[2], Bösenberg E[1], Hegedüs L[3], Paschke R[1], Eszlinger M[1]
[1]University of Leipzig, Division of Endocrinology and Nephrology, Leipzig, Germany, [2]Odense University Hospital, Department of Pathology, Odense, Denmark, [3]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark

17.30–17.45
OP13 **MICRORNA EXPRESSION IN EXPERIMENTAL IN VITRO THYROID TUMORS MODELS**
Floor S[1], Pita JM[1,2], Saiselet M[1], Le Pennec S[1], Libert F[1], van Staveren WCG[1], Maenhaut C[1]
[1]ULB, IRIBHM, Anderlecht, Belgium, [2]de Patobiologia Molecular (CIPM), Português de Oncologia de Lisboa Francisco Gentil, Lisbone, Portugal

17.45–18.00
OP14 **SERUM ANTI-THYROID ANTIBODIES (TAB): A POSSIBLE NEW POSITIVE PREDICTIVE PARAMETER IN HIGH AGGRESSIVE BREAST CANCER (BC)**
Muller I[1], Fiore E[1], Belardi V[1], Sabatini S[1], Giustarini E[1], Vitti P[1], Giani C[1]
[1]University of Pisa, Endocrinology, Pisa, Italy

Main Hall (Aula Duza)

16.00–18.00

Oral Presentations 3: Young Investigators Session (OP15–OP22)

Chair: *Paul Banga* (London, UK);
Marek Ruchala (Poznan, Poland)

16.00–16.15
OP15 **MIR-224 CONTRIBUTES TO TISSUE HYPOTHYROIDISM IN RENAL CANCER, TARGETING THE 3'UTR OF TYPE 1 5´-IODOTHYRONINE DEIODINASE**
Boguslawska J[1], Piekielko-Witkowska A[1], Wojcicka A[1], Master A[1], Nauman A[1]
[1]The Medical Centre of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland

16.15–16.30
OP16 **DEFICIENCY OF THE THYROID HORMONE TRANSPORTER MONOCARBOXYLATE TRANSPORTER 8 ALTERS THYROID MORPHOLOGY IN A PATIENT AND IN MICE**
Wirth EK[1], Sheu S-Y[2], Chiu-Ugalde J[1], Sapin R[3], Klein MO[4], Mossbrugger I[5], Quintanilla-Martinez L[5,6], Krude H[7], Riebel T[8], Rothe K[9], Köhrle J[1], Schmid KW[2], Schweizer U[1], Grüters A[7]
[1]Charité-Universitätsmedizin Berlin, Institut f. Experimentelle Endokrinologie, Berlin, Germany, [2]Universität Duisburg-Essen, Institut für Pathologie und Neuropathologie, Essen, Germany, [3]Université de Strasbourg, Centre National de la Recherche Scientifique, Strasbourg, France, [4]Centre Hospitalier et Universitaire de Nancy, Service D'Endocrinologie, Nancy, France, [5]Helmholtz-Zentrum München, German Mouse Clinic, München, Germany, [6]Eberhard Karls Universität Tübingen, Institut für Pathologie, Tübingen, Germany, [7]Charité-Universitätsmedizin Berlin, Institut für Experimentelle Pädiatrische Endokrinologie, Berlin, Germany, [8]Charité-Universitätsmedizin Berlin, Klinik für Strahlenheilkunde, Pädiatrische Radiologie, Berlin, Germany, [9]Charité-Universitätsmedizin Berlin, Klinik für Kinderchirurgie, Berlin, Germany

16.30–16.45
OP17 **SOMATIC HYPERMUTATION OF THE IMMUNOGLOBULIN HEAVY CHAIN VARIABLE-REGION OF THYROID STIMULATING ANTIBODIES DETERMINES BINDING TO THE TSH-RECEPTOR**
Hargreaves C[1], Dunn-Walters D[2], Banga JP[1]
[1]King's College London School of Medicine, Diabetes and Endocrinology, London, United Kingdom, [2]King's College London School of Medicine, Immunobiology, London, United Kingdom

16.45–17.00
OP18 **DETECTION OF PAX8/PPARG AND RET/PTC REARRANGEMENTS IN ROUTINE AIR DRIED FINE NEEDLE ASPIRATION (FNA) SMEARS**
Ferraz C[1], Krogdahl A[2], Rehfeld C[1], Precht Jensen EM[2], Bösenberg E[1], Hegedüs L[3], Paschke R[1], Eszlinger M[1]
[1]University of Leipzig, Division of Endocrinology and Nephrology, Leipzig, Germany, [2]Odense University Hospital, Department of Pathology, Odense, Denmark, [3]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark

17.00–17.15
OP19 **DUAL-OXIDASE 2 GENETIC MODIFICATIONS IN CHILDREN WITH HYPOTHYROIDISM: IDENTICATION AND FUNCTIONAL ANALYSIS OF VARIANTS AND MUTATIONS**
Molinaro A[1], De Marco G[1], Montanelli L[1], Agretti P[1], Bagattini B[1], Dimida A[1], Ferrarini E[1], Niccolai F[1], Bottai S[1], Ceccarelli C[1], Brozzi F[1], Pinchera A[1], Vitti P[1], Tonacchera M[1]
[1]Università di Pisa, Endocrinology and Metabolism, Pisa, Italy

17.15–17.30
OP20 **RELATIONS BETWEEN MATERNAL FIRST-TRIMESTER AND NEWBORN THYROID HORMONE SERUM LEVELS: RESULTS FROM A LARGE POPULATION-BASED COHORT STUDY**

Medici M[1], de Rijke YB[1,2], Peeters RP[1], Visser W[3], de Muinck Keizer-Schrama SMPF[4], Hooijkaas H[5], Tiemeier H[6,7], Bongers-Schokking JJ[4], Visser TJ[1]

[1]Erasmus Medical Center, Endocrinology, Rotterdam, Netherlands, [2]Erasmus Medical Center - Sophia Children's Hospital, Clinical Chemistry, Rotterdam, Netherlands, [3]Erasmus Medical Center - Sophia Children's Hospital, Obstetrics and Gynecology, Rotterdam, Netherlands, [4]Erasmus Medical Center - Sophia Children's Hospital, Endocrinology, Rotterdam, Netherlands, [5]Erasmus Medical Center, Immunology, Rotterdam, Netherlands, [6]Erasmus Medical Center, Epidemiology, Rotterdam, Netherlands, [7]Erasmus Medical Center - Sophia Children's Hospital, Child and Adolescent Psychiatry, Rotterdam, Netherlands

17.30–17.45
OP21 **IS COMPLETION THYROIDECTOMY FOLLOWING LOBECTOMY FOR LOW RISK THYROID CANCER MANDATORY?**

Craig W[1,2], Krukowski ZH[1,2]

[1]Aberdeen Royal Infirmary, Department of General Surgery, Aberdeen, United Kingdom, [2]University of Aberdeen, Aberdeen, United Kingdom

17.45–18.00
OP22 **SELECTIVE VENOUS CATHETERIZATION IN LOCALIZING OCCULT PERSISTENT MEDULLARY THYROID CARCINOMA**

Hajje G[1], Borget I[2], Baudin E[1], Hartl D[3], Deschamps F[4], Schlumberger M[1], De Baere T[4], Leboulleux S[1]

[1]Institut Gustave Roussy, Endocrinology-Oncology Department, Villejuif, France, [2]Institut Gustave Roussy, Department of Statistics, Villejuif, France, [3]Institut Gustave Roussy, Ear Nose Throat Department, Villejuif, France, [4]Institut Gustave Roussy, Interventional Radiology Department, Villejuif, France

Main Hall (Aula Duza)
18.00–18.30

Special Report: The Fukushima Accident

Chair: *Aldo Pinchera* (Pisa, Italy)
Leszek Krolicki (Warsaw, Poland)

Shigenobu Nagataki (Tokyo, Japan)

Monday, 12th September 2011

Main Hall (Aula Duza)
07.00–08.00

Genzyme Satellite Symposium

Ablation at the Cutting Edge; Defining New Treatment Paradigms for the 21st Century
Chairman: *Martin Schlumberger* (Paris, France)

07.00–07.15
Introduction: what is the rationale for ablation in thyroid cancer management?
Martin Schlumberger (Paris, France)

07.15–07.30
The UK HiLo study: final efficacy results
Ujjal Mallick (Newcastle, UK)

07.30–07.45
The French ESTIMABL ablation study. What are the implications for practice?
Isabelle Borget (Paris, France)

07.45–08.00
Round table discussion and questions

Main Hall (Aula Duza)
08.00–10.00

Oral Presentations 4: Thyroid Autoimmunity (OP23–OP30)

Chair: *Jadwiga Furmaniak* (Cardiff, UK); *Wojciech Zgliczynski* (Poland)

08.00–08.15
OP23 **DIFFERENCES IN THE WAY STIMULATING AND BLOCKING MONOCLONAL AUTOANTIBODIES INTERACT WITH THE TSHR**
Núñez Miguel R[1], *Sanders J*[1], *Young S*[1], *Sanders P*[1], *Kabelis K*[1], *Clark J*[1], *Wilmot J*[1], *Evans M*[1], *Hu X*[1], *Roberts E*[1], *Furmaniak J*[1], *Rees Smith B*[1]
[1]FIRS Laboratories, RSR Ltd, Cardiff, United Kingdom

08.15–08.30
OP24 **CAVEOLINE-1 EXPRESSION DIFFERS ACCORDING TO THE TYPE OF IMMUNE REACTION (TH1/TH2) INVOLVED IN THYROID AUTOIMMUNE DISORDERS**
Marique L[1], *Van Regemorter V*[1], *Craps J*[1], *Senou M*[1], *Gérard A-C*[1], *Many M-C*[1]
[1]UCL, MORF, Brussels, Belgium

08.30–08.45
OP25 **NEWLY IDENTIFIED IMMUNOSUPPRESSIVE NATURAL KILLER (NK) CELLS SUPPRESS ANTIGEN-SPECIFIC CD8+ T CELLS IN THREE MOUSE MODELS FOR AUTOIMMUNITY**
Ehlers M[1], *Papewalis C*[1], *Thiel A*[1], *Jacobs B*[2], *Ullrich E*[2], *Willenberg HS*[1], *Schinner S*[1], *Scherbaum WA*[1], *Schott M*[1]
[1]University Hospital Duesseldorf, Endocrine Unit, Duesseldorf, Germany, [2]University of Erlangen-Nürnberg, Erlangen, Germany

08.45–09.00
OP26 **INVOLVEMENT OF STRESS IN THE PATHOGENESIS OF AUTOIMMUNE THYROID DISEASE: A PROSPECTIVE STUDY**
Effraimidis G[1], *Tijssen JGP*[2], *Wiersinga WM*[1]
[1]Academic Medical Centre, University of Amsterdam, Department of Endocrinology and Metabolism, Amsterdam, Netherlands, [2]Academic Medical Centre, University of Amsterdam, Department of Cardiology, Amsterdam, Netherlands

09.00–09.15
OP27 **ROLE OF THE PRO-PEPTIDE SEQUENCE IN THYROID PEROXIDASE FUNCTION AND MATURATION**
Godlewska M[1], *Banga JP*[2], *Sutton BJ*[3], *Krasuska W*[1], *Weetman AP*[4], *Kemp EH*[4], *Góra M*[5]
[1]Medical Centre of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland, [2]King's College London School of Medicine, Division of Diabetes and Nutrition Sciences, London, United Kingdom, [3]King's College London School of Medicine, Randall Division of Cell & Molecular Biophysics, London, United Kingdom, [4]University of Sheffield, Department of Human Metabolism, Sheffield, United Kingdom, [5]Institute of Biochemistry and Biophysics PAS, Department of Genetics, Warsaw, Poland

09.15–09.30
OP28 **ALCOHOL CONSUMPTION IS PROTECTIVE FOR DEVELOPMENT OF AUTOIMMUNE HYPOTHYROIDISM - A POPULATION-BASED STUDY**
Carlé A[1], Pedersen IB[1], Knudsen N[2], Perrild H[2], Ovesen L[3], Rasmussen LB[4], Jørgensen T[5], Laurberg P[1], The Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr)
[1]Aalborg Hospital, Aarhus University Hospital, Department of Endocrinology & Medicine, Aalborg, Denmark, [2]Bispebjerg Hospital, Endocrine Unit, Medical Clinic I, Copenhagen, Denmark, [3]Slagelse Hospital, Department of Internal Medicine, Slagelse, Denmark, [4]National Food Institute, Technical University of Denmark, Department of Nutrition, Copenhagen, Denmark, [5]Copenhagen County, Research Centre for Disease Prevention and Health, Copenhagen, Denmark

09.30–09.45
OP29 **THYROID AUTOIMMUNITY IN MALIGNANT AND BENIGN BREAST DISEASE BEFORE SURGERY**
Belardi V[1], Giustarini E[1], Fiore E[1], Muller I[1], Sabatini S[1], Pinchera A[1], Giani C[1]
[1]Università di Pisa, Endocrinology, Pisa, Italy

09.45–10.00
OP30 **THYROID AUTOIMMUNITY AND HASHIMOTO'S THYROIDITIS AFTER UNIVERSAL IODINE PROPHYLAXIS: THE 2010 PESCOPAGANO SURVEY**
Provenzale MA[1], Fiore E[1], Frigeri M[1], Puleo L[1], Antonangeli L[1], Rago T[1], Grasso L[1], Pinchera A[1], Aghini-Lombardi F[1], Vitti P[1]
[1]Department of Endocrinology, University of Pisa, Pisa, Italy

Minor Hall
08.00–10.00

Oral Presentations 5: Thyroid Hormone Basic 1 (OP31–OP38)

Chair: *Jacques Dumont* (Brussels, Belgium); *Marek Bolanowski* (Wroclaw, Poland)

08.00–08.15
OP31 **EFFECT OF LACKING GPB5 ON DEIODINASE EXPRESSION IN PERIPHERAL TISSUES THAT EXPRESS THE THYROTROPIN RECEPTOR**
Boelen A[1], van Zeijl CJ[1], Kwakkel J[1], van Beeren HC[1], Surovtseva OV[1], Wiersinga WM[1], Fliers E[1]
[1]Academic Medical Center, Endocrinology and Metabolism, Amsterdam, Netherlands

08.15–08.30
OP32 **ANALYSIS OF MOUSE MUTANTS DEFICIENT IN THE THYROID HORMONE TRANSPORTER OATP1C1**
Mayerl S[1], Visser TJ[2], Darras VM[3], Heuer H[1]
[1]Leibniz Institute for Age Research/Fritz Lipmann Institute, Jena, Germany, [2]Erasmus Medical Center, Rotterdam, Netherlands, [3]Katholieke Universiteit, Leuven, Belgium

08.30–08.45
OP33 **CARDIAC INDUCTION OF THE THYROID-HORMONE DEGRADING ENZYME DEIODINASE TYPE III IN HUMAN ISCHEMIC HEART DISEASE**
Muller A[1], Pol C[1], Janssen R[1], Zuidwijk M[1], Joseph S[2], Cameron D[2], dos Remedios C[2], Visser T[3], Paulus W[1], Simonides W[1]
[1]VU University Medical Center, Amsterdam, Netherlands, [2]The University of Sydney, Sydney, Australia, [3]Erasmus University Medical Center, Rotterdam, Netherlands

08.45–09.00
OP34 **DIFFERENTIAL EXPRESSION PATTERN OF THYROID HORMONE TRANSPORTERS IN THE MOUSE CNS**
Hahn C[1], Müller J[1], Romanova D[1], Mayerl S[1], Friesema EC[2], Visser TJ[2], Heuer H[1]
[1]Leibniz Institute for Age Research/Fritz Lipmann Institute, Jena, Germany, [2]Erasmus Medical Center, Rotterdam, Netherlands

09.00–09.15
OP35 **LIVER THYROID HORMONE CONCENTRATIONS IN RATS ON AMIODARONE OR DRONEDARONE TREATMENT CORRELATE WITH LIVER DEIODINASE ACTIVITIES AND ARE INDEPENDENT OF LIVER THYROID HORMONE TRANSPORTERS**
Beeren HCV[1], Ackermans MT[2], Wiersinga WM[2], Fliers E[2], Boelen A[2]
[1]Academic Medical Centre, University of Amsterdam, Endocrinology, Amsterdam, Netherlands, [2]Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

09.15–09.30
OP36 **SELENIUM AND THYROID HORMONES IN POSTMENOPAUSAL HEALTHY WOMEN**
Hoeg A[1], Gogakos A[2], Murphy E[2], Mueller S[1], Reid D[3], Gluer CC[4], Felsenberg D[5], Roux C[6], Eastell R[7], Köhrle J[1], Schomburg L[1], Williams G[2]
[1]Charité Universitätsmedizin Berlin, Institute for Experimental Endocrinology, Berlin, Germany, [2]Imperial College London, Department of Medicine and MRC Clinical Sciences Centre, London, United Kingdom, [3]University of Aberdeen, School of Medicine and Dentistry, Aberdeen, United Kingdom, [4]Universitätsklinikum Schleswig-Holstein, Kiel, Germany, [5]Free University of Berlin, Berlin, Germany, [6]Paris Descartes University, Paris, France, [7]University of Sheffield, Sheffield, United Kingdom

09.30–09.45
OP37 **REGULATION OF BRAIN TH SIGNALLING DURING THE PERINATAL PERIOD IN EUTHYROID AND HYPOTHYROID PUPS**
Morvan-Dubois G[1], *Ghaddab R*[1], *Seugnet I*[1], *Veillard T*[1], *Perret-Jeanneret M*[1], *Clerget-Froidevaux M-S*[1], *Demeneix B*[1]
[1]UMR7221 CNRS/MNHN, Paris cedex, France

09.45–10.00
OP38 **EFFECTS OF AMIODARONE (AMIO) ON THYROID HORMONE (TH) TRANSPORT AND METABOLISM**
van Heerebeek RE[1], *Mandu N*[1], *Friesema EC*[1], *Chong L-F*[1], *Visser TJ*[1]
[1]Erasmus MC, Internal Medicine, Thyroid Lab, Rotterdam, Netherlands

10.00–10.30
Coffee break

Minor Hall
10.30–12.00

Symposium 3 (Basic): Profiling the Thyroid
Chair: *Mariastella Zannini* (Naples, Italy);
Andrzej Lewinski (Lodz, Poland)

Finding thyroid cancer markers by omics
Dagmar Führer (Essen, Germany)

Profiling thyroid embryology
Roberto Di Lauro (Naples, Italy)

Genome-wide analysis of thyroid signaling
Pilar Santisteban (Madrid, Spain)

Main Hall (Aula Duza)
10.30–12.00

Symposium 4 (Clinical): Where Are the Limits of Overdiagnosis and Overtreatment of Thyroid Disease?
Chair: *Peter Laurberg* (Aalborg, Denmark);
Barbara Jarząb (Gliwice, Poland)

Thyroid nodules: indications to and extent of surgery
Henning Dralle (Halle, Germany)

Thyroid autoimmunity
Stefano Mariotti (Cagliari, Italy)

Subclinical functional abnormalities in the elderly
Simon Pearce (Newcastle, UK)

Poster Exhibition Area (see pages 43 to 51)
12.00–13.00

Lunch and Poster Discussions 2
Thyroid Cancer (clinical) 4: Posters PO116-PO125
Chair: *Chantal Daumerie* (Brussels, Belgium)

Thyroid Cancer (clinical) 5: Posters PO126-PO135
Chair: *Valeriano Leite* (Lisbon, Portugal)

Thyroid Cancer (clinical) 6: Posters PO136-PO145
Chair: *Bengt Hallengren* (Malmö, Sweden)

Thyroid Cancer (basic/translational) 2: Posters PO146-PO154
Chair: *Rosa Marina Melillo* (Naples, Italy)

Graves' Hyperthyroidism 2: Posters PO155-PO165
Chair: *Colin Dayan* (Cardiff, UK)

Thyroid Hormone & Metabolism 2: Posters PO166-PO172
Chair: *Jean-Louis Wemeau* (Lille, France)

Goiter/Nodules 1: Posters PO173-PO185
Chair: *Roland Gärtner* (Munich, Germany)

Imaging in Thyroidology: Posters PO186-PO201
Chair: *Murat Erdogan* (Ankara, Turkey)

Trace elements and environment: Posters PO202-PO211
Chair: *Nils Knudsen* (Smorum, Denmark)

Main Hall (Aula Duza)
13.00–14.00

IBSA

IBSA Satellite Symposium

Levothyroxine Malabsorption: Experience with the Softgel Capsules
Chairmen: *Aldo Pinchera* (Pisa, Italy);
George J. Kahaly (Mainz, Germany)

13.00 Welcome and introduction
George J. Kahaly (Mainz, Germany)

13.05 The pharmacokinetics of levothyroxine softgel capsules
Murray P. Ducharme (Montreal, Canada)

13.15 Novel developments with softgel capsules
Salvatore Benvenga (Messina, Italy)

13.30 Individually tailored dose of thyroxine: a role for gastric acid secretion
Marco Centanni (Latina, Italy)

13.45 Round-table discussion
Moderation: *Aldo Pinchera* (Pisa, Italy)

14.00 End of session

Minor Hall
13.00–14.00

TFI-ETA Patient-Forum

Thyroid Federation International and European Thyroid Association invite all patients to the annual TFI-ETA Patient-Forum.

13.00 Opening
Yvonne Andersson, Sweden (President of TFI)
13.05 "Thyroid cancer, diagnostic, treatment and perspectives"
The latest developments on patient level on thyroid cancer
Martin Schlumberger (Paris, France)
13.25 "Psychological aspects of work with Thyroid Cancer Patients"
The psychological effects of thyroid cancer on patients and how to deal with them
Anna Syska-Bielak (Gliwice, Poland)
13.45 Questions by patients
13.55 Round up
Yvonne Andersson

During the lectures and the questions Polish doctors will be available for translations.

Main Hall (Aula Duza)
14.00–14.45

Merck Serono

ETA Merck Serono Prize Lecture

Chairs: *Peter Laurberg* (Aalborg, Denmark)
Luigi Bartalena (Varese, Italy)

Autoimmunity in Graves' Ophthalmopathy: A Translational Approach
Wilmar Wiersinga (Amsterdam, The Netherlands)

14.45–15.00
Coffee break

15.00–15.45
Meet the Expert

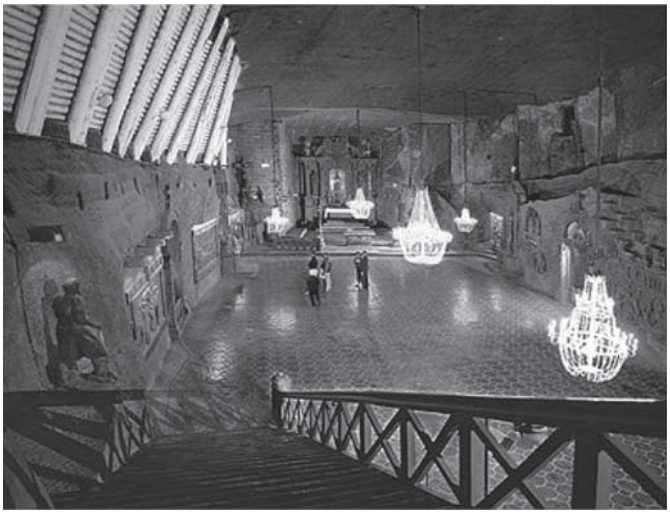
MTE 5: MTE Hall
Non-nuclear thyroid hormone actions
Lutz Schomburg (Berlin, Germany)

MTE 6: Lecture Hall
Rare causes of altered thyroid function tests
Graham Williams (London, UK)

MTE 7: Senate Hall
Thyroid hormones and obesity
Leonidas Duntas (Athens, Greece)

MTE 8: Minor Hall
Guideline-oriented diagnosis and treatment of thyroid nodules
Ralf Paschke (Leipzig, Germany)

16.30
Departure for Excursion to Wieliczka



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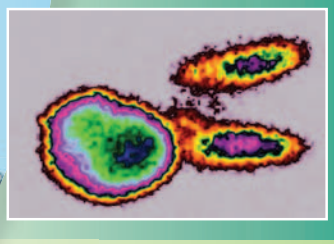
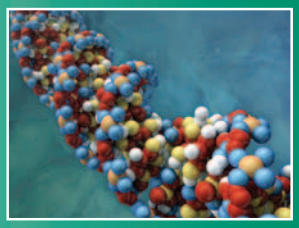
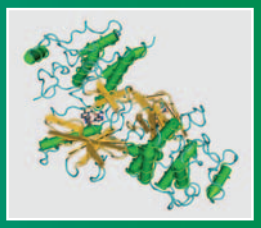
A satellite symposium held during the 35th Annual Meeting of the European Thyroid Association, Kraków, Poland

Challenges and Opportunities in the Treatment of Patients With RAI-Refractory Differentiated Thyroid Cancer (DTC)

Chairpersons:
Marcia Brose, MD, PhD, and Martin Schlumberger, MD







Tuesday, 13 September 2011
13.00 – 14.00

Aula Duza (Main Hall)
Auditorium Maximum of the Jagiellonian University
Kraków, Poland

Lunch will be provided at 12.30

Agenda

13.00 **Welcome and Introduction**
Alicja Hubalewska-Dydejczyk, MD, PhD
Jagiellonian University, Medical College
Kraków, Poland

13.05 **Challenges in Defining RAI-Refractory DTC and Review of the Current Treatment Algorithm**
Martin Schlumberger, MD
Institut Gustave Roussy
Villejuif, France

13.20 **Targeted Therapies in RAI-Refractory DTC: Rationale for Use and Clinical Development**
Marcia Brose, MD, PhD
University of Pennsylvania
Philadelphia, United States

13.40 **Multi-Disciplinary Perspectives in the Treatment of RAI-Refractory DTC: A Case-Study Approach**
Johannes Smit, MD, PhD
Leiden University Medical Center
Leiden, Netherlands
Marcia Brose, MD, PhD
Alicja Hubalewska-Dydejczyk, MD, PhD
Martin Schlumberger, MD

14.00 **Summary and Conclusion**
Marcia Brose, MD, PhD

Bayer HealthCare

Supported by Bayer HealthCare

Main Hall (Aula Duza)

8.00–10.00

Oral Presentations 6: Graves' Disease (OP39–OP46)

Chair: *Matthias Schott* (Düsseldorf, Germany); *Marcin Barczynski* (Krakow, Poland)

08.00–08.15

OP39 **A NOVEL MECHANISM INVOLVED IN THE PATHOGENESIS OF GRAVES OPHTHALMOPATHY (GO) - CLATHRIN IS A POSSIBLE TARGETING MOLECULE FOR INHIBITING LOCAL IMMUNE RESPONSE IN THE ORBIT**

Meyer zu Hörste M[1,2], Ströher E[1], Schmitz-Spanke S[3], Pink M[3], Göthert J[4], Fischer J[5], Gulbins E[2], Eckstein A[1]

[1]University Hospital Essen, Department of Ophthalmology, Essen, Germany, [2]University Hospital Essen, Department of Molecular Biology, Essen, Germany, [3]University Hospital Essen, Department of Hygiene and Occupational Medicine, Essen, Germany, [4]University Hospital Essen, Department of Hematology, Essen, Germany, [5]University Hospital Essen, Department of Pharmacology, Essen, Germany

08.15–08.30

OP40 **THE ECONOMIC BURDEN OF GRAVES´ ORBITOPATHY**

Ponto KA[1], Hommel G[2], Pitz S[1], Pfeiffer N[1], Kahaly GJ[3]

[1]University Medical Center, Ophthalmology, Mainz, Germany, [2]University Medical Center, Medical Statistics, Mainz, Germany, [3]University Medical Center, Dept. of Medicine, Mainz, Germany

08.30–08.45

OP41 **SERUM BAFF CONCENTRATIONS IN PATIENTS WITH GRAVES' DISEASE (GD) AND ORBITOPATHY (GO) BEFORE AND AFTER IMMUNOSUPPRESSIVE TREATMENT**

Vannucchi G[1], Covelli D[1], Currò N[2], Maffini A[1], Dazzi D[3], Bonara P[4], Pignataro L[5], Beck-Peccoz P[1], Salvi M[1]

[1]Endocrine Unit, Fondazione Cà Granda IRCCS, Milan, Italy, [2]Ophthalmology, Fondazione Cà Granda, IRCCS, Milan, Italy, [3]Division of Internal Medicine, Fidenza, Italy, [4]Internal Medicine, Fondazione Cà Granda IRCCS, Milan, Italy, [5]Otolaryngology, Fondazione Cà Granda IRCCS, Milan, Italy

08.45–09.00

OP42 **CIRCULATING CXCL10 AND CCL2 CHEMOKINES IN PATIENTS WITH GRAVES' OPHTHALMOPATHY WITH PREVALENT EXTRAOCULAR MUSCLE INVOLVEMENT: MODULATION BY CYTOKINES AND BY PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ALPHA AGONISTS IN PRIMARY MYOBLASTS**

Ferrari SM[1], Fallahi P[1], Sellari Franceschini S[2], Ferrannini E[1], Minuto M[3], Mancusi C[1], Ruffilli I[1], Antonelli A[1]

[1]University of Pisa, Department of Internal Medicine, Pisa, Italy, [2]University of Pisa, Otorhinolaryngology Unit, Pisa, Italy, [3]University of Pisa, Department of Surgery, Pisa, Italy

09.00–09.15

OP43 **SERUM SELENIUM IS LOW IN NEWLY DIAGNOSED GRAVES`DISEASE AND AUTOIMMUNE HYPOTHYROIDISM. A POPULATION BASED STUDY**

Bülow Pedersen I[1], Knudsen N[2], Carlé A[3], Schomburg L[4], Köhrle J[4], Jørgensen T[5], Perrild H[2], Rasmussen L[6], Ovesen L[7], Laurberg P[3]

[1]Aalborg Hospital. Aarhus University Hospital, Dept. of Endocrinology and Medicine, Aalborg, Denmark, [2]Bispebjerg Hospital, Copenhagen, Denmark, [3]Aalborg Hospital. Aarhus University Hospital, Aalborg, Denmark, [4]Institute for Experimental Endocrinology, Berlin, Germany, [5]Research Centre for Prevention and Health, Glostrup, Denmark, [6]National Food Institute, Copenhagen, Denmark, [7]Slagelse Hospital, Slagelse, Denmark

09.15–09.30

OP44 **HYPERTHYROIDISM, RATHER THAN AUTOIMMUNITY, SEEMS TO DETERMINE QUALITY OF LIFE IN PATIENTS WITH GRAVES´ DISEASE**

Watt T[1,2], Hegedüs L[3], Bonnema SJ[3], Groenvold M[2], Bjorner JB[4], Rasmussen ÅK[1], Feldt-Rasmussen U[1]

[1]Copenhagen University Hospital Rigshospitalet, Dpt. of Medical Endocrinology, Copenhagen, Denmark, [2]University of Copenhagen, Health Service Research, Copenhagen, Denmark, [3]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark, [4]National Research Center for the Working Environment, Copenhagen, Denmark

09.30–09.45
OP45 **COMPARISON OF EARLY TOTAL THYROIDECTOMY WITH ANTITHYROID TREATMENT IN PATIENTS WITH MODERATE TO SEVERELY ACTIVE GRAVES' ORBITOPATHY, A RANDOMIZED PROSPECTIVE TRIAL**

Erdoğan MF[1], Demir Ö[1], Ersoy RÜ[2], Gül K[3], Ünlütürk U[1], Üç ZA[4], Mete T[5], Anıl C[6], Ertek S[7], Çakır B[2], Aral Y[4], Güler S[5], Gürsoy A[8], Erdoğan G[7], Ankara Thyroid Study Group

[1]Ankara University Faculty of Medicine, Endocrinology and Metabolic Diseases, Ankara, Turkey, [2]Ankara Ataturk Education and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [3]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Endocrinology and Metabolic Diseases, Kahramanmaraş, Turkey, [4]Ankara Education and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [5]Ankara Numune Education and Research Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey, [6]Başkent University Faculty of Medicine, Endocrinology and Metabolic Diseases, Ankara, Turkey, [7]Ufuk University Faculty of Medicine, Endocrinology and Metabolic Diseases, Ankara, Turkey, [8]Güven Hospital, Endocrinology and Metabolic Diseases, Ankara, Turkey

09.45–10.00
OP46 **IS THE ASSOCIATION BETWEEN OVERT HYPERTHYROIDISM AND MORTALITY CAUSAL? CRITICAL REVIEW AND META-ANALYSIS**

Brandt F[1], Green A[2], Hegedüs L[1], Brix T[1]

[1]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark, [2]Odense University Hospital, Research Unit of Clinical Epidemiology, University of Southern Denmark and Center for National Clinical Databases, South, Odense, Denmark

Minor Hall
08.00–10.00

Oral Presentations 7: Thyroid Cancer Basic (OP47–OP54)

Chair: *Georg Brabant* (Lübeck, Germany); *Beata Kos-Kudla* (Katowice, Poland)

08.00–08.15
OP47 **THE TARGETED INACTIVATION OF THE TRβ GENE INCREASES RET-PTC$_3$ - INDUCED GROWTH AND NEOPLASTIC TRANSFORMATION OF THE THYROID GLAND**

Selmi-Ruby S[1], D'orazio T[1], Borson-Chazot F[1], Rousset B[1]

[1]Centre de Recherche en Cancérologie de Lyon, UMR Inserm 1052 CNRS 5286, Lyon, France

08.15–08.30
OP48 **TRANSCRIPTOME PROFILING OF LASER-MICRODISSECTED PAPILLARY THYROID CANCER CELLS**

Oczko-Wojciechowska M[1], Swierniak M[1], Rusinek D[1], Rusin A[2], Kowal M[1], Kowalska M[1], Tyszkiewicz T[1], Chekan M[3], Krajewska J[1], Czarniecka A[4], Chmielik E[3], Jarząb B[1]

Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland, [1]Department of Nuclear Medicine and Endocrine Oncology, [2]Center for Translational Research and Molecular Biology of Cancer, [3]Department of Tumor Pathology, [4]Oncology Surgery Clinic

08.30–08.45
OP49 **IGF-I PROLIFERATIVE EFFECTS ARE INHIBITED BY TARGETING PKC IN HUMAN MEDULLARY THYROID CARCINOMA CELLS**

Molè D[1], Gagliano T[1], Gentilin E[1], Bondanelli M[1], Tagliati F[1], degli Uberti DUC[1], Zatelli MC[1]

[1]University of Ferrara, Section of Endocrinology, Dept of Biomedical Sciences and Advanced Therapies, Ferrara, Italy

08.45–09.00
OP50 **CAMP ANALOGS: A NEW PERSPECTIVE IN THE TREATMENT OF POORLY DIFFERENTIATED THYROID CANCER**

Grassi ES[1], de Filippis T[2], Lucchi S[2], Calebiro D[2], Persani L[1,2,3]

[1]University of Milan, Medical Sciences, Milan, Italy, [2]IRCCS Istituto Auxologico Italiano, Laboratory of Endocrine-Metabolic Research, Cusano Milanino, Italy, [3]IRCCS Istituto Auxologico Italiano, Division of Endocrinology and Metabolic Diseases, Milan, Italy

09.00–09.15
OP51 **PODOPLANIN AND PROX 1 IN DIFFERENTIATED THYROID TUMORS**

Janik J[1], Strzyżewska-Jówko I[1], Hanusek K[1], Bardadin K[2], Czerwińska J[2], Górnicka B[3], Kiedrowski M[4], Olszewski W[4], Czarnocka B[1]

[1]Medical Center of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland, [2]Medical Center of Postgraduate Education, Department of Pathology, Warsaw, Poland, [3]Medical University of Warsaw, Department of Pathology, Warsaw, Poland, [4]Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Department of Pathology, Warsaw, Poland

09.15–09.30
OP52 **FUNCTIONAL ANALYSIS OF MOLECULAR PROFILE OF CHILDHOOD/ADOLESCENTS RADIATION INDUCED THYROID CANCER**
Handkiewicz-Junak D[1], Swierniak M[1], Rusinek D[1], Oczko-Wojciechowska M[1], Dom G[2], Maenhaut C[2], Unger K[3], Detours V[2], Bogdanova T[4], Thomas G[3], Kowalska M[1], Chmielik E[5], Jarząb M[6], Swierniak A[7], Jarząb B
[1]Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland, [2]Université Libre de Bruxelles, Institute of Interdisciplinary Research, Bruxelles, Belgium, [3]Imperial College London Hammersmith Hospital, Human Cancer Studies Group, Division of Surgery and Cancer, London, United Kingdom, [4]Institute of Endocrinology and Metabolism, Kiev, Ukraine, [5]Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Tumor Pathology Department, Gliwice, Poland, [6]Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Radiation Therapy Department, Gliwice, Poland, [7]Silesian University of Technology, Gliwice, Poland

09.30–09.45
OP53 **RET SOMATIC MUTATIONS ARE NOT AN EARLY EVENT IN THE TUMORAL TRANSFORMATION OF SPORADIC MEDULLARY THYROID CANCER**
Romei C[1], Cosci B[1], Ugolini C[2], Bottici V[1], Molinaro E[1], Agate L[1], Tacito A[1], Basolo F[2], Miccoli P[2], Vitti P[1], Pinchera A[1], Elisei R[1]
[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University of Pisa, Department of Surgery, Pisa, Italy

09.45–10.00
OP54 **MEK INHIBITION REDUCES THE DEDIFFERENTIATION INDUCED BY EPIDERMAL GROWTH FACTOR, RESTORING THE EXPRESSION OF AND THE IODIDE TRANSPORT MEDIATED BY THE SODIUM IODIDE SYMPORTER (NIS) IN CULTURED THYROCYTES**
Ingeson C[1], Carlsson T[1], Nilsson M[1]
[1]University of Gothenburg, Sahlgrenska Academy, Institute of Biomedicine, Gothenburg, Sweden

10.00–10.30
Coffee break

Minor Hall
10.30–12.00

Symposium 5 (Basic): Thyroid Hormone and Metabolism
Chair: *Ana Aranda* (Madrid, Spain);
Janusz Nauman (Warsaw, Poland)

Local control of thyroid hormone action and energy homeostasis
Antonio Bianco (Miami, USA)

Control of thermogenesis and lipid metabolism by T3 and its analogs. Induction of uncoupling protein 1 in white fat
Maria Jesus Obregon (Madrid, Spain)

The effects of thyroid hormone on muscle metabolism via regulation of uncoupling protein 3
Maria Moreno (Benevento, Italy)

Main Hall (Aula Duza)
10.30–12.00

Symposium 6 (Clinical): Monitoring of Thyroid Cancer
Chair: *Maria Alevizaki* (Athens, Greece);
Alicja Hubalewska-Dydejczyk (Krakow, Poland)

PET scanning (including FDG, I-124, FDOPA) in thyroid carcinoma
Sophie Leboulleux (Villejuif, France)

Use of sensitive Tg assays in the follow-up of DTC
Rossella Elisei (Pisa, Italy)

Follow-up of MTC including imaging and biochemical markers
Barbara Jarząb (Gliwice, Poland)

Poster Exhibition Area (see pages 52 to 60)
12.00–13.00

Lunch and Poster Discussions 3

Thyroid Cancer (clinical) 7: Posters PO212–PO222
Chair: *Clive Harmer* (London, UK)

Thyroid Cancer (clinical) 8: Posters PO223–PO232
Chair: *Nese Colak Ozbey* (Istanbul, Turkey)

Thyroid Cancer (basic/translational) 3: Posters PO233-PO241
Chair: *Christine Spitzweg* (Munich, Germany)

Graves' Hyperthyroidism 3: Posters PO242–PO252
Chair: *Stig Andersen* (Aalborg, Denmark)

Thyroid Hormone & Bone: Posters PO253–PO261
Chair: *Peter Smyth* (Dublin, Ireland)

Hypothyroidism 2: Posters PO262–PO275
Chair: *Agathokles Tsatsoulis* (Joannina, Greece)

Goiter/Nodules 2: Posters PO276–PO289
Chair: *Hans Graf* (Merces, Brazil)

Genetics of Thyroid Disease: Posters PO290–PO297
Chair: *Thomas Brix* (Odense, Denmark)

Thyroid Cell Biology and Thyroid Hormone Action: PO298–PO309
Chair: *Mikael Nilsson* (Göteborg, Sweden)

Main Hall (Aula Duza)
13.00–14.00

Bayer HealthCare

Bayer Healthcare Satellite Symposium

Challenges and Opportunities in the Treatment of Patients with Rai-Refractory Differentiated Thyroid Cancer (DTC)

13.00 Welcome and Introduction
Alicja Hubalewska-Dydejczyk (Krakow, Poland)

13.05 Challenges in Defining RAI-Refractory DTC and Review of the Current Treatment Algorithm
Martin Schlumberger (Villejuif, France)

13.20 Targeted Therapies in RAI-Refractory DTC: Rationale for Use and Clinical Development
Marcia Brose (Philadelphia, United States)

13.40 Multi-Disciplinary Perspectives in the Treatment of RAI-Refractory DTC: A Case-Study Approach
Johannes Smit (Leiden, Netherlands); *Marcia Brose; Alicja Hubalewska-Dydejczyk, Martin Schlumberger*

14.00 Summary and Conclusion
Marcia Brose

14.00–14.45
Meet the Expert

MTE 9: Senate Hall
Signalling pathways in the thyroid
Davide Calebiro (Würzburg, Germany)

MTE 10: Lecture Hall
Novel treatment modalities for thyroid cancer
Jan Smit (Leiden, The Netherlands)

MTE 11: Minor Hall
Thyroid and Pregnancy: results of a survey among ETA members
Kris Poppe (Brussels, Belgium)

14.45–15.00
Coffee break

Main Hall (Aula Duza)
15.00–17.00

Oral Presentations 8: Hypothyroidism, Goiter and Nodules (OP55–OP62)

Chair: *Laszlo Hegedus* (Odense, Denmark); *Jerzy Sowinski* (Poznan, Poland)

15.00–15.15
OP55 **THYROID HORMONES, ANDROGEN RECEPTORS AND TESTICULAR DEVELOPMENT**
Rijntjes E[1], Snaas S[2], Swarts HJM[2], Keijer J[2], Teerds KJ[2]
[1]Charité Universitätsmedizin Berlin, Institute for Experimental Endocrinology, Berlin, Germany, [2]Wageningen University, Department of Animal Sciences, Wageningen, Netherlands

15.15–15.30
OP56 **MICRORNAS EXPRESSION FOR DIFFERENTIATION OF BENIGN AND MALIGNANT THYROID NODULES STARTING FROM CELLS OF FINE NEEDLE ASPIRATION**
Ferrarini E[1], Agretti P[1], Candelieri A[2], Rago T[1], Conforti D[2], Musmanno R[2], Miccoli P[1], Di Coscio G[1], Pinchera A[1], Vitti P[1], Tonacchera M[1]
[1]Università di Pisa, Pisa, Italy, [2]Università della Calabria, Cosenza, Italy

15.30–15.45
OP57 **DIAGNOSTIC VALUE OF ULTRASONOGRAPHY TO DISTINGUISH BETWEEN BENIGN AND MALIGNANT THYROID NODULES. A PROSPECTIVE STUDY WITH 13902 PATIENTS**
Solymosi T[1]
[1]Bugat Hospital, Thyroid Outpatient Department, Gyongyos, Hungary

15.45–16.00
OP58 **CURRENT PRACTICE TO DIAGNOSE AND TREAT THYROID NODULES IN GERMANY**
Bormann R[1], *Adler J-B*[2], *Scholz M*[3], *Paschke R*[1]
[1]Universität Leipzig, Klinik für Endokrinologie und Nephrologie, Leipzig, Germany, [2]Wissenschaftliches Institut der AOK (WIdO), Forschungsbereich Integrierte Analysen, Berlin, Germany, [3]Universität Leipzig, Institut für medizinische Informatik, Statistik und Epidemiologie, Leipzig, Germany

16.00–16.15
OP59 **INTRODUCTION OF THE DANISH IODINE FORTIFICATION PROGRAM: IMPACT ON DRUG AND TREATMENT COSTS**
Cerqueria C[1], *Knudsen N*[2], *Ovesen L*[3], *Laurberg P*[4], *Perrild H*[2], *Rasmussen LB*[5], *Jørgensen T*[1,6]
[1]Research Centre for Prevention and Health, Glostrup, Denmark, [2]Bispebjerg Hospital, Department of Endocrinology and Gastroenterology, Copenhagen, Denmark, [3]Slagelse Hospital, Department of Gastroenterology, Slagelse, Denmark, [4]Aalborg Hospital, Aarhus University Hospital, Department of Endocrinology, Aalborg, Denmark, [5]National Food Institute, Technical University of Denmark, Department of Nutrition, Søborg, Denmark, [6]University of Copenhagen, Faculty oof Health Sciences, Copenhagen, Denmark

16.15–16.30
OP60 **IODINE DEFICIENCY DISORDERS IN THE SO-CALLED HIMALAYAN GOITRE BELT: A TWO DECADE PROFILE**
Chandola-Saklani A[1], *Farswan A*[1], *Bamola VD*[1], *Lakhera PC*[2], *Kathait A*[2], *Kumar D*[2]
[1]Apeejay Stya University, Centre for Biosciences and Clinical Research, Gurgaon, India, [2]HNB Garhwal Central University, Department of Biotechnology, Srinagar Garhwal, India

16.30–16.45
OP61 **LEVOTHYROXINE MONOTHERAPY CANNOT GUARANTEE EUTHYROIDISM IN ALL ATHYREOTIC PATIENTS**
Latina A[1], *Frasca F*[1], *Vigneri R*[1], *Gullo D*[1]
[1]Garibaldi Hospital, University of Catania, Endocrinology Division, Dept. of Clinical and Molecular Biomedicine, Catania, Italy

16.45–17.00
OP62 **NEWBORN SEX RATIO IS ASSOCIATED WITH MATERNAL TSH**
Miñambres I[1], *Ovejero D*[2], *García-Patterson A*[2], *Adelantado JM*[2], *Corcoy R*[2]
[1]Hospital de la Santa Creu i Sant Pau, Endocrinology, Barcelona, Spain, [2]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Minor Hall
15.00–17.00

Oral Presentations 9: Thyroid Cell Biology and Genetics (OP63–OP70)

Chair: *Paolo Beck-Peccoz* (Milano, Italy); *Anhelli Syrenicz* (Szczecin, Poland)

15.00–15.15
OP63 **TSH COMPENSATES THYROID SPECIFIC IGFI RECEPTOR KNOCKOUT AND CAUSES PAPILLARY THYROID TUMOURS**
Müller K[1], *Führer D*[1], *Mittag J*[2], *Klöting N*[1], *Blüher M*[1], *Weiss RE*[3], *Many M-C*[4], *Schmid KW*[5], *Krohn K*[6]
[1]University of Leipzig, Department of Internal Medicine, Division of Endocrinology, Diabetologia and Nephrology, Leipzig, Germany, [2]Karolinska Institute, Department of Cell and Molecular Biology, Stockholm, Sweden, [3]The University of Chicago, Department of Medicine, Section of Adult and Pediatric Endocrinology, Diabetes and Metabolism, Chicago, United States, [4]Universite catholique de Louvain, Medical School, Brussels, Belgium, [5]University of Duisburg-Essen, Institute of Pathology and Neuropathology, Essen, Germany, [6]University of Leipzig, IZKF - Core Unit DNA Technologies, Leipzig, Germany

15.15–15.30
OP64 **MICRORNAS REGULATE THYROID CELL PROLIFERATION INDUCED BY TSH AND THYROGLOBULIN**
Akama T[1], *Kawashima A*[1], *Wu H*[1], *Tanigawa K*[1], *Sue M*[1], *Yoshihara A*[1], *Ishido Y*[1], *Suzuki K*[1]
[1]National Institute of Infectious Diseases, Higashimurayama-shi, Japan

15.30–15.45

OP65 **EXPRESSION, MATURATION AND TURNOVER STUDIES OF PENDRIN VARIANTS WITH NORMAL OR SLIGHTLY REDUCED FUNCTION**

Vezzoli V[1], Cirello V[2], Bazzini C[3], Muzza M[2], Castorina P[4], Maffini A[4], Beck-Peccoz P[2,4], Persani L[1,2], Meyer G[3], Fugazzola L[4]

[1]IRCCS Istituto Auxologico Italiano, Research Laboratory of Endocrinology and Metabolic Disorders, Milan, Italy, [2]University of Milan, Dept of Medical Sciences, Milan, Italy, [3]University of Milan, Laboratory of Molecular and Transport Physiology, Department of Biomolecular Sciences and Biotechnology, Milan, Italy, [4]Fondazione IRCCS Ca' Granda, Endocrine and Genetic Units, Milan, Italy

15.45–16.00

OP66 **A "CUSTOMIZED" CGH-ARRAY THYROARRAY® IDENTIFIES GENETIC DEFECTS IN CONGENITAL HYPOTHYROIDISM NOT DETECTABLE BY PCR AND SEQUENCING**

Moya CM[1], Vallespín E[2], Szkudlarek A[1], Persani L[3], Martín-Pena M[4], Fugazzola L[5], Polak M[4], Visser T[6], Lapunzina P[2], Nevado J[2], Moreno JC[1]

[1]INGEMM- Institute for Medical and Molecular Genetics. La Paz University Hospital, Thyroid Molecular Laboratory, Madrid, Spain, [2]INGEMM- Institute for Medical and Molecular Genetics. La Paz University Hospital, Structural and Functional Genomics Laboratory, Madrid, Spain, [3]IRCCS Istituto Auxologico Italiano, Endocrinology and Metabolic Diseases, Milan, Italy, [4]Necker-Enfants Malades Hospital, Pediatric Endocrinology, Paris, France, [5]Fondazione IRCCS Policlinico, Endocrinology and Diabetology Unit, Milan, Italy, [6]Erasmus Medical Center, Internal Medicine, Rotterdam, Netherlands

16.00–16.15

OP67 **FUNCTIONAL CHARACTERIZATION OF TSHR HINGE REGION RESIDUES IDENTIFIED FURTHER TEN TSH INTERACTION SITES OUTSIDE OF THE LRR**

Mueller S[1], Szkudlinski MW[2], Schaarschmidt J[1], Günther R[3], Paschke R[1], Jaeschke H[1]

[1]University of Leipzig, Department of Internal Medicine, Neurology and Dermatology, Leipzig, Germany, [2]Trophogen Inc., Rockville, United States, [3]University of Leipzig, Institute of Biochemistry, Leipzig, Germany

16.15–16.30

OP68 **BIALLELIC DUOX2 VARIANTS APPEAR INVARIABLY ASSOCIATED WITH PERMANENT CONGENITAL HYPOTHYROIDISM**

Muzza M[1], Zamproni I[2], Persani L[3], Cortinovis F[2], Vigone MC[2], Rabbiosi S[2], Beccaria L[4], Visser TJ[5], Moreno J[6], Weber G[2]

[1]Fondazione IRCCS Cà Granda, Endocrinology Unit, Milan, Italy, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Pediatrics, Milan, Italy, [3]University of Milan, and Istituto Auxologico Italiano, Department of Medical Sciences, Milan, Italy, [4]A. Manzoni Hospital, Pediatric Unit, Lecco, Italy, [5]Erasmus Medical Center, Internal Medicine, Rotterdam, Netherlands, [6]"La Paz" University Hospital, Thyroid Molecular Laboratory-INGEMM- Institute for Medical and Molecular Genetics, Madrid, Spain

16.30–16.45

OP69 **SUBCELLULAR LOCALIZATION OF S6K1 AND S6K2 IS RELATED TO FUNCTIONAL ACTIVITY OF RAT THYROCYTES *IN VITRO***

Khoruzhenko A[1], Cherednyk O[1], Tykhonkova I[1], Filonenko V[1]

[1]Institute of Molecular Biology and Genetics, Department of Cell Signaling, Kyiv, Ukraine

16.45–17.00

OP70 **REGULATION OF H_2O_2 GENERATION BY THYROGLOBULIN IN FRTL-5**

Yoshihara A[1], Kawashima A[1], Tanigawa K[1], Akama T[1], Wu H[1], Sue M[1], Ishido Y[1], Hiroi N[2], Yoshino G[2], Suzuki K[1]

[1]Laboratory of Molecular Diagnostics, Leprosy Research Center, National Institute of Infectious Diseases, Tokyo, Japan, [2]Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Toho University School of Medicine, Tokyo, Japan

Main Hall (Aula Duza)

17.15–18.45

ETA General Assembly

20.00

Gala Dinner

Pałac pod Baranami (The Palace under the Rams), Main Market Square 27

Main Hall (Aula Duza)
08.00–10.00

Oral Presentations 10: Thyroid Cancer Clinical (OP71–OP78)

Chair: *Laurence Leenhardt* (Paris, France); *Marek Dedecjus* (Lodz, Poland)

08.00–08.15
OP71 **TI-RADS SCORE: CLINICAL EFFICIENCY EVALUATED WITH THE BETHESDA SYSTEM IN A ONE-YEAR PROSPECTIVE STUDY ON 2480 NODULES**
Russ G[1], Bienvenu-Perrard M[1], Rouxel A[1], Royer B[1], Bigorgne C[1]
[1]Centre de Pathologie et d'Imagerie, Paris, France

08.15–08.30
OP72 **FOSBRETABULIN TROMETHAMINE (CA4P), A TUBULIN-BINDING VASCULAR DISRUPTING AGENT (VDA), IS ASSOCIATED WITH IMPROVED 1-YEAR SURVIVAL IN ANAPLASTIC THYROID CANCER (ATC) PATIENTS TREATED IN 5 INDEPENDENT PROSPECTIVE STUDIES COMPARED TO A LARGE SINGLE INSTITUTION HISTORICAL SERIES**
Balkissoon J[1], Langecker P[1], Lu S-P[1], Remick S[2], Sosa JA[3], Elisei R[4], Mciver B[5], Bal CS[6], Gramza A[7], Jarząb B[8], Haugen B[9], Gitlitz B[10], Lu C[11], Marur S[12], Licitra L[13], Ondrey F[14], Karandikar SM[15], Ben-Yosef R[16], Khuri F[17], Koussis H[18]
[1]Oxigene, Oncology, South San Francisco, United States, [2]West Virginia University, Medicine, Morgantown, United States, [3]Yale University School of Medicine, Surgery, Division of Endocrine Surgery and Surgical Oncology, New Haven, United States, [4]University of Pisa, Endocrinology, Pisa, Italy, [5]Mayo Clinic, Endocrinology, Rochester, United States, [6]AIIMS, Nuclear Medicine Therapy, New Dehli, India, [7]National Cancer Institute, Head and Neck Oncology, Bethesda, United States, [8]Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice, Poland, [9]University of Colorado, Endocrinology, Aurora, United States, [10]USC Norris Cancer Center, Los Angeles, United States, [11]MD Anderson Cancer Center, Houston, United States, [12]Johns Hopkins University, Baltimore, United States, [13]Istituto dei Tumori, Otolaryngology, Milano, Italy, [14]University of Minnesota, Otolaryngology, Minneapolis, United States, [15]Ruby Hall Clinic, Pune, Maharashtra, India, [16]Tel Aviv Sourasky Medical Center, Head and Neck Oncology, Tel Aviv, Israel, [17]Emory University, Atlanta, United States, [18]Istituto Oncologico Veneto IRCCS, Padova, Italy

08.30–08.45
OP73 **MIRNA EXPRESSION PATTERNS DIFFERENTIATE BETWEEN FOLLICULAR THYROID CARCINOMA (FTC) AND FOLLICULAR THYROID ADENOMA (FA)**
Stokowy T[1,2], Wojtaś B[1], Fujarewicz K[2], Jarząb M[1], Pfeifer A[1], Jarząb B[1], Krogdahl A[3], Hauptmann S[4], Paschke R[5], Eszlinger M[5]
[1]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland, [2]Silesian University of Technology, Systems Engineering Group, Institute of Automatic Control, Gliwice, Poland, [3]Odense University Hospital, Department of Pathology, Odense, Denmark, [4]University of Halle, Institute for Pathology, Halle, Germany, [5]University of Leipzig, Division of Endocrinology and Nephrology, Leipzig, Germany

08.45–09.00
OP74 **COMPARISON OF FOUR STRATEGIES OF RADIOIODINE ABLATION: FINAL RESULTS OF THE RANDOMIZED, PROSPECTIVE ESTIMABL STUDY ON 752 LOW-RISK THYROID CANCER PATIENTS**
Catargi B[1], Borget I[2], Deandris D[2], Zerdoud S[3], Bridji B[4], Bardet S[5], Schvartz C[6], Toubert M[7], Bonichon F[8], Benhamou E[2], Schlumberger M[2], ESTIMABL Study Group
[1]Centre Hospitalier Universitaire, Bordeaux, France, [2]Institut Gustave-Roussy, Villejuif, France, [3]CLCC, Toulouse, France, [4]CLCC, Nantes, France, [5]CLCC, Caen, France, [6]CLCC, Reims, France, [7]APHP, Paris, France, [8]Institut Bergonié, Bordeaux, France

09.00–09.15

OP75 **HILO: MULTICENTRE RANDOMISED PHASE III CLINICAL TRIAL OF HIGH VS LOW DOSE RADIOIODINE, WITH OR WITHOUT RECOMBINANT HUMAN THYROID STIMULATING HORMONE (RHTSH), FOR REMNANT ABLATION FOR DIFFERENTIATED THYROID CANCER**

Mallick U[1], Harmer C[2], Clarke S[3], Moss L[4], Nicol A[5], Clarke P[6], Smellie J[7], McCready R[8], Farnell K[9], Franklyn J[6], Nutting C[10], Yap B[11], Lemon C[12], Wadlsey J[13], Gerrard G[14], Roques T[15], Macias E[16], Whitaker S[17], Abdul-Hamid A[18], Alvarez P[19], Kadalayil L[19], Hackshaw A[19]

[1]Newcastle Hospitals NHS Trust, Northern Centre for Cancer Treatment, High Heaton, United Kingdom, [2]formerly Royal Marsden Hospital, London, United Kingdom, [3]Guys & St Thomas's Hospital, London, United Kingdom, [4]Velindre Hospital, Cardiff, United Kingdom, [5]Southern General Hospital,, Glasgow, United Kingdom, [6]University of Birmingham, Birmingham, United Kingdom, [7]Chelsea and Westminster Hospital, London, United Kingdom, [8]Brighton and Sussex Medical School, Brighton, United Kingdom, [9]Butterfly Cancer Trust UK, Newcastle, United Kingdom, [10]Royal Marsden Hospital, London, United Kingdom, [11]Christie Hospital, Manchester, United Kingdom, [12]Mount Vernon Hospital, Northwood, United Kingdom, [13]Weston Park Hospital, Sheffield, United Kingdom, [14]Cookridge Hospital, Leeds, United Kingdom, [15]Norfolk & Norwich Univ Hospital NHS Trust, Norwich, United Kingdom, [16]East Kent NHS Trust and Canterbury Hospital, Kent, United Kingdom, [17]Royal Surrey County Hospital, Guildford, United Kingdom, [18]Hull & East Yorkshire, Princess Royal Hospital, Hull, United Kingdom, [19]University College London, London, United Kingdom

09.15–09.30

OP76 **NOT ALL NEW RET MUTATIONS SHOW TRANSFORMING ACTIVITY WHEN ANALYZED BY IN SILICO AND IN VITRO ASSAYS**

Elisei R[1], Cosci B[1], Vivaldi A[1], Romei C[1], Gemignani F[2], Landi S[2], Tacito A[1], Ciampi R[1], Bottici V[1], Cappagli V[1], Vitti P[1], Pinchera A[1]

[1]University of Pisa, Department of Endocrinology, Pisa, Italy, [2]University of Pisa, Department of Biology, Pisa, Italy

09.30–09.45

OP77 **THYROID AUTOIMMUNITY AND THYROID CANCER: PATHOLOGICAL AND MOLECULAR STUDY IN A LONGITUDINAL SERIES OF UNSELECTED NODULES**

Boi F[1], Caria P[2], Borghero A[1], Frau DV[2], Cappai A[1], Dettori T[2], Riola A[1], Maurelli I[1], Lai ML[3], Calò PG[4], Nicolosi A[4], Vanni R[2], Mariotti S[1]

[1]University of Cagliari, Department of Medical Sciences 'M. Aresu', Monserrato - Cagliari, Italy, [2]University of Cagliari, Department of Biomedical Science and Technology, Monserrato - Cagliari, Italy, [3]University of Cagliari, Department of Cytomorphology, Cagliari, Italy, [4]University of Cagliari, Department of Surgical and Odontostomatological Sciences, Monserrato - Cagliari, Italy

09.45–10.00

OP78 **CLINICAL SIGNIFICANCE OF ANTI-THYROID ANTIBODIES (AT-AB) TITER TREND IN A LONG-TERM FOLLOW-UP OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA (DTC)**

Lorusso L[1], Agate L[1], Latrofa F[1], Bottici V[1], Molinaro E[1], Viola D[1], Grasso L[1], Pinchera A[1], Vitti P[1], Elisei R[1]

[1]Department of Endocrinology, University of Pisa, Pisa, Italy

Minor Hall

08.00–10.00

Oral Presentations 11: Thyroid Hormone Basic 2 (OP79–OP86)

Chair: *Warner Simonides* (Amsterdam, The Netherlands); *Janusz K. Mysliwiec* (Bialystok, Poland)

08.00–08.15

OP79 **NOVEL TRANSGENIC TOOLS ILLUMINATE THE COORDINATED DEVELOPMENT OF THE THYROID GLAND AND THE CARDIOVASCULAR SYSTEM IN ZEBRAFISH EMBRYOS**

Opitz R[1], Maquet E[1], Horicks F[1], Rodriguez W[1], Costagliola S[1]

[1]ULB, IRIBHM, Brussels, Belgium

08.15–08.30

OP80 **THE THYROID HORMONES INHIBIT TRANSCRIPTIONAL RESPONSES TO THE TRANSFORMING GROWTH FACTOR β**

Ruiz-Llorente L[1], Martín-Orozco RM[1], Ardila S[1], Fanjul LF[1], Aranda A[1]

[1]Inst. Investigaciones Biomedicas (IIB), CSIC-UAM, Madrid, Spain

08.30–08.45

OP81 **EFFECTS OF MCT8 AND MCT10 ON THE BIOLOGICAL ACTIVITY OF T3**

van Mullem AAA[1], Peeters RP[1], Visser TJ[1]

[1]Erasmus MC, Internal Medicine, Rotterdam, Netherlands

08.45–09.00

OP82 **TYPE 3 DEIODINASE IS HIGHLY EXPRESSED IN PROLIFERATING MYOBLASTS AND DURING THE EARLY PHASE OF MUSCLE REGENERATION**

Dentice M[1], Luongo C[1], Ambrosio R[1], Sibilio A[1], Damiano V[1], De Stefano MA[1], Marsili A[2], Fenzi G[1], Larsen PR[2], Salvatore D[1]

[1]Università degli studi di Napoli 'Federico II', Molecular and Clinical Endocrinology and Oncology, Naples, Italy, [2]Brigham and Women's Hospital and Harvard Medical School, Thyroid Section, Division of Endocrinology, Diabetes and Hypertension, Boston, United States

09.00–09.15
OP83 **TISSUE 3-IODOTHYRONAMINE UPTAKE IN VIVO: COMPARISON WITH EXPRESSION OF TRACE AMINE ASSOCIATED RECEPTORS**
Frascarelli S[1], Chiellini G[1], Carnicelli V[1], Ghelardoni S[1], Erba P[2], Manfredi C[2], Mariani G[2], Zucchi R[1]
[1]University of Pisa, Dip. di Scienze dell'Uomo e dell'Ambiente, Pisa, Italy, [2]University of Pisa, Dip. di Oncologia, Pisa, Italy

09.15–09.30
OP84 **UPTAKE AND METABOLIC EFFECTS OF 3-IODOTHYRONAMINE IN RAT LIVER**
Ghelardoni S[1], Chiellini G[1], Frascarelli S[1], Marchini M[1], Saba A[1], Zucchi R[1]
[1]University of Pisa, Dip. di Scienze dell'Uomo e dell'Ambiente, Pisa, Italy

09.30–09.45
OP85 **THE ROLE OF MICRORNA AND PROMOTER METHYLATION IN REGULATION OF THYROID HORMONE RECEPTOR BETA EXPRESSION IN RENAL CANCER**
Wojcicka A[1], Piekiełko-Witkowska A[1], Kedzierska H[1], Boguslawska J[1], Nauman A[1]
[1]The Medical Centre of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland

09.45–10.00
OP86 **DISTURBED ALTERNATIVE SPLICING OF TYPE 2 DEIODINASE IN PITUITARY TUMORS**
Piekielko-Witkowska A[1], Kedzierska H[1], Wojcicka A[1], Grajkowska WA[2,3], Mandat T[4], Matyja EM[2,4], Bonicki W[4], Nauman P[5]
[1]The Medical Centre of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland, [2]M. Mossakowski Medical Research Centre, Polish Academy of Sciences, Department of Experimental and Clinical Neuropathology, Warsaw, Poland, [3]The Children's Memorial Health Institute, Department of Pathology, Warsaw, Poland, [4]M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Neurosurgery, Warsaw, Poland, [5]Institut of Psychiatry and Neurology, Department of Neurosurgery, Warsaw, Poland

10.00–10.15
Coffee break

Minor Hall

10.15–11.45

Symposium 7 (Basic): Thyroid Hormone Disrupters

Chair: *Theo Visser (Rotterdam,* The Netherlands); *Barbara Czarnocka* (Warsaw, Poland)

Thyroid hormone signalling in early development: a new window of vulnerability for endocrine disruption
Barbara Demeneix (Paris, France)

Sunburn and thyroid dysfunction: the effect of UV blockers on the thyroid
Josef Köhrle (Berlin, Germany)

Putting out the thyroid with flame retardants: polybrominated compounds
Tinka Murk (Wageningen, The Netherlands)

Main Hall (Aula Duza)

10.15–11.45

Symposium 8 (Clinical): Perspectives in the Therapy of Graves' Disease

Chair: *George J. Kahaly* (Mainz, Germany); *Tomasz Bednarczuk* (Warsaw, Poland)

Unmet medical needs and therapeutic options in Graves' disease
Luigi Bartalena (Varese, Italy)

Selenium in Graves' hyperthyroidism and orbitopathy
Claudio Marcocci (Pisa, Italy)

The CD-20-positive depleting agent, Rituximab
Laszlo Hegedus (Odense, Denmark)

Main Hall (Aula Duza)

11.45–12.00

Closing Ceremony

Presentation of:
Young Investigators Prize (clinical/basic)
sponsored by Thermo Fisher Scientific
ETA Max Pierre Koenig Poster Prize (clinical)
sponsored by the ETA
ETA Max Pierre Koenig Poster Prize (basic)
sponsored by the ETA

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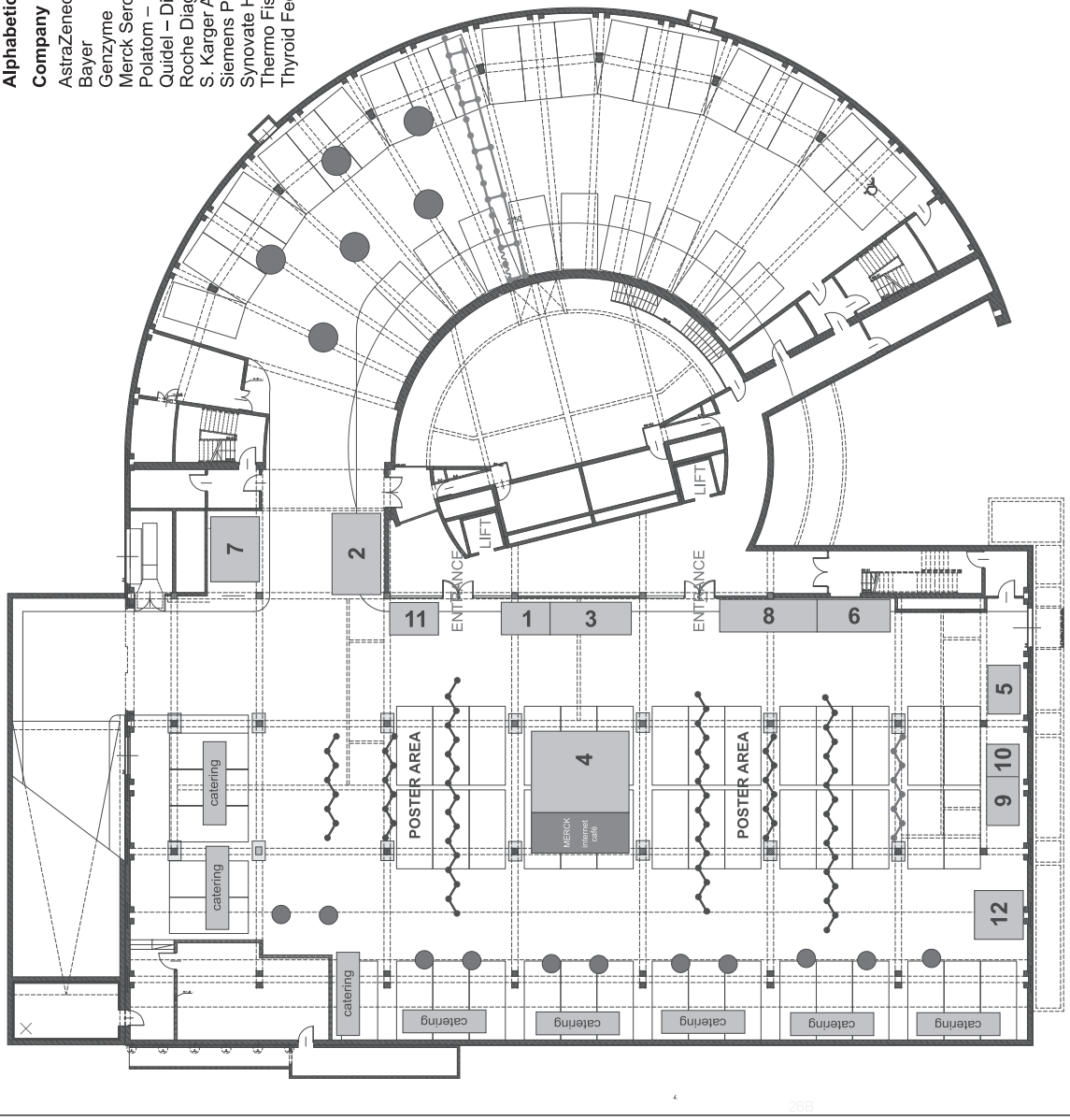
Poster Hall and Exhibition Area

Alphabetical list of Exhibitors

Company Name	Stand no.
AstraZeneca UK Ltd.	1
Bayer	12
Genzyme	3
Merck Serono	4
Polatom – Institute of Atomic Energy	5
Quidel – Diagnostic Hybrids	6
Roche Diagnostics AG	7
S. Karger AG	8
Siemens Poland	9
Synovate Healthcare	10
Thermo Fisher Scientific	2
Thyroid Federation International (TFI)	11



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European
Thyroid Journal

Sunday, 11th September 2011

Poster Exhibition Area

12.00–13.00

Poster Sessions 1

PO1 Thyroid Cancer (clinical) 1

Chair: *Ulla Feldt-Rasmussen* (Copenhagen, Denmark)

P01 **PATIENTS WITH DIFFERENTIATED THYROID CANCER (DTC) WHO UNDERWENT RADIOIODINE REMNANT ABLATION (RRA) WITH LOW ACTIVITY OF ^{131}I EITHER RECOMBINANT HUMAN TSH (RHTSH) OR AFTER THYROID HORMONE THERAPY WITHDRAWAL (THW) SHOW THE SAME OUTCOME AFTER 10 YEARS OF FOLLOW UP**

Molinaro E[1], Giani C[1], Biagini A[1], Pieruzzi L[1], Agate L[1], Bottici V[1], Viola D[1], Pinchera A[1], Vitti P[1], Elisei R[1]

[1]Department of Endocrinology, University of Pisa, Pisa, Italy

P02 **INCREASED INCIDENCE OF DIFFERENTIATED THYROID CANCER IN DENMARK 1943-2008. IS IT INFLUENCED BY IODINE SUPPLEMENTATION?**

Blomberg M[1], Feldt-Rasmussen U[2], Kjaer SK[1,3]

[1]Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, Denmark, [2]Rigshospitalet, Medical Endocrinology PE 2132, Copenhagen, Denmark, [3]Rigshospitalet, Copenhagen University Hospital, Gynaecology, Copenhagen, Denmark

P03 **SORAFENIB IN THE TREATMENT OF RADIOIODINE REFRACTORY THYROID CANCER. A MULTICENTER PHASE II STUDY**

Duntas LH[1], Vlassopoulou V[2], Boutsiadis A[1], Mantzou E[1], Anapliotou M[3], Tsatsoulis A[4]

[1]Evgenidion Hospital/University of Athens, Endocrine Unit, Athens, Greece, [2]Evangelismos Hospital, Department of Endocrinology, Athens, Greece, [3]Private Office, Athens, Greece, [4]University of Ioannina, Department of Endocrinology, Ioannina, Greece

P04 **FOLLOW-UP OF DIFERENTIATED THYROID CANCER (DTC) PATIENTS DEFINED FREE OF DISEASE WITH A SINGLE NEGATIVE RECOMBINANT HUMAN THYROTROPINE (RHTSH) THYROGLOBULIN (TG) STIMULATION TEST**

Biagini A[1], Pieruzzi L[1], Molinaro E[1], Giani C[1], Viola D[1], Valerio L[1], Agate L[1], Bottici V[1], Pinchera A[1], Vitti P[1], Elisei R[1]

[1]Department of Endocrinology, University of Pisa, Pisa, Italy

P05 **EXTRATHYROID EXTENSION AS A PREDICTING FACTOR OF PROGNOSIS IN PAPILLARY THYROID MICROCARCINOMA PATIENTS**

Sung T-Y[1], Lee Y-M[1], Lee A-L[1], Yoon JH[1], Hong SJ[1]

[1]Asan Medical Center, University of Ulsan College of Medicine, Division of Endocrine Surgery, Department of Surgery, Seoul, Korea, Republic of

P06 **ROBOT-ASSISTED GASLESS TRANS-AXILLARY THYROIDECTOMY: SINGLE SURGEON'S EXPERIENCE OF 300 CASES**

Lee Y-M[1], Lee A-L[1], Sung T-Y[1], Hong SJ[1], Yoon JH[1]

[1]Asan Medical Center, University of Ulsan College of Medicine, Division of Endocrine Surgery, Department of Surgery, Seoul, Korea, Republic of

P07 **COMPARISON OF 800MBQ AND 3700 MBQ IODINE-131 FOR THE POST-OPERATIVE ABLATION OF THYROID REMNANT IN PATIENTS WITH LOW RISK DIFFERENTIATED THYROID CANCER**

Caglar M[1], Bozkurt FM[2], Bayraktar M[3]

[1]Hacettepe University, Ankara, Turkey, [2]Hacettepe University, Nuclear Medicine, Ankara, Turkey, [3]Hacettepe University, Endocrinology, Ankara, Turkey

P08 **SIGNIFICANCE OF MICROSCOPIC CENTRAL COMPARTMENT LYMPH NODE METASTASIS IN PAPILLARY THYROID CARCINOMA**

Lee A-L[1], Lee Y-M[1], Sung T-Y[1], Yoon JH[1], Hong SJ[1]

[1]Asan Medical Center, University of Ulsan College of Medicine, Division of Endocrine Surgery, Department of Surgery, Seoul, Korea, Republic of

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P09 **DIAGNOSTIC IMPACT OF ^{18}F-DOPA-PET/CT IN RESIDUAL OR RECURRENT MEDULLARY THYROID CANCER**

Schalin-Jäntti C[1], Kauhanen S[2,3], Seppänen M[2], Kajander S[2], Schildt J[4], Ahonen A[4], Virtanen S[5], Heiskanen I[6], Väisänen M[6], Arola J[7], Lisinen I[2], Korsoff P[8], Ebeling T[9], Sane T[1], Minn H[2,10], Välimäki MJ[1], Nuutila P[2,11]

[1]Division of Endocrinology, Department of Medicine, Helsinki University Hospital, Helsinki, Finland, [2]Turku PET Centre, Turku University Hospital, Turku, Finland, [3]Department of Surgery, Turku University Hospital, Turku, Finland, [4]Helsinki PET Centre, Helsinki University Hospital, Helsinki, Finland, [5]Medical Imaging Centre of Southwest Finland, Turku, Finland, [6]Department of Surgery, Helsinki University Hospital, Helsinki, Finland, [7]Department of Pathology, Helsinki University Hospital, Helsinki, Finland, [8]Department of Medicine, Satakunta Central Hospital, Pori, Finland, [9]Department of Medicine, Oulu University Hospital, Oulu, Finland, [10]Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland, [11]Department of Medicine, University of Turku, Turku, Finland

P10 **PATHOLOGICAL REEVALUATION OF DOUBTFUL CASES OF THYROID CANCER**

Konturek A[1], Barczyński M[1], Stopa M[1], Wierzchowski W[2], Nowak W[1]

[1]Jagiellonian University, Medical College, 3rd Chair and Department of General Surgery, Krakow, Poland, [2]Jagiellonian University, Medical College, Department of Pathology, Krakow, Poland

PO2 Thyroid Cancer (clinical) 2

Chair: *Markus Luster* (Ulm, Germany)

P11 **INCREASED LONG TERM MORTALITY IN PATIENTS WITH DIFFERENTIATED THYROID CANCER AND CONCOMITANT GRAVES' DISEASE**

Pellegriti G[1], Mannarino C[2], Vigneri R[1], Belfiore A[2]

[1]Endocrinology Division, Garibaldi Nesima Hospital, Department of Clinical and Molecular Biomedicine, University of Catania, Catania, Italy, [2]Endocrinology Unit, Department of Clinical and Experimental Medicine, University of Catanzaro, Catanzaro, Italy

P12 **LOBECTOMY FOR PAPILLARY THYROID CANCER: PROGNOSIS AND INDICATIONS**

Matsuzu K[1], Sugino K[1], Ito K[1], Yoshida A[2], Masuda M[3], Ito K[1]

[1]Ito hospital, Tokyo, Japan, [2]1-1-2 Nakao, Asahi-ku, Yokohama, Japan, [3]Yokohama City University School of medicine, Surgery, Yokohama, Japan

P13 **PREVALENCE OF LEVEL VI LYMPH NODES INVOLVEMENT IN PATIENTS WITH PAPILLARY THYROID CANCER STAGED PREOPERATIVELY AS NODE NEGATIVE**

Barczynski M[1], Konturek A[1], Stopa M[1], Richter P[1], Nowak W[1]

[1]Jagiellonian University, Medical College, 3rd Department of General Surgery, Krakow, Poland

P14 **A COMPARISON OF SURGICAL OUTCOMES BETWEEN ENDOSCOPIC AND ROBOTIC THYROIDECTOMY**

Yoo H[1], Chae BJ[1], Seong KY[1], Park WC[1], Song BJ[1], Kim JS[1], Jung SS[1], Bae JS[1]

[1]Catholic University, Department of Surgery, Seoul, Korea, Republic of

P15 **FAMILIAL HISTORY OF THYROID GLAND DISEASES, MALIGNANT TUMOURS AND RISK OF DIFFERENTIATED THYROID CANCER**

Przybylik-Mazurek E[1], Pach D[1], Hubalewska-Dydejczyk A[1]

[1]Jagiellonian University, Medical College, Chair and Department of Endocrinology, Krakow, Poland

P16 **NO INFLUENCE OF MULTIFOCALITY/BILATERALITY ON RECURRENCE-FREE SURVIVAL IN PATIENTS WITH PAPILLARY THYROID CARCINOMA**

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P17 **TIMING OF PROPHYLACTIC THYROIDECTOMY IN PATIENTS WITH FAMILIAL MEDULLARY THYROID CARCINOMA**

Podoba J[1], Podobová M[1], Grigerová M[1], Weismanová E[2], Závodná K[2]

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P18 **THE RISING INCIDENCE OF THYROID CANCER IS MAINLY DUE TO AN INCREASE IN CLINICAL CANCERS: A 40-YEAR STUDY IN 1778 PATIENTS**

Iliadou PK[1], Doumala E[1], Mathiopoulou L[1], Tziomalos K[1], Mitsakis P[1], Fotareli A[1], Chrisoulidou A[1], Boudina M[1], Pazaitou-Panayiotou K[1]

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P19 **DISTRIBUTION OF PERIPHERAL BLOOD MONOCYTE SUBPOPULATIONS IN MALIGNANT AND NON-MALIGNANT THYROID TUMOURS**

Stasiolek M[1], Dedecjus M[2], Bieniek E[1], Pula B[3], Brzezinski J[2], Lewinski A[1]

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PO3 Thyroid Cancer (clinical) 3

Chair: *Laura Fugazzola* (Milan, Italy)

P20 **METASTATIC THYROID CANCER UNRESPONSIVE TO CONVENTIONAL THERAPY TREATED WITH SORAFENIB "OFF-LABEL": AN UPDATE OF OUR EXPERIENCE.**

Cappagli V[1], Bottici V[1], Molinaro E[1], Agate L[1], Viola D[1], Valerio L[1], Mazzeo S[2], Battaglia V[2], Pontillo Contillo B[2], Dal Canto L[3], Vitti P[1], Pinchera A[1], Elisei R[1]

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P21 **DO WE NEED TO PERFORM STIMULATED THYROGLOBULIN (TG) ASSAY AND I-131 SCINTIGRAPHY IN TREATED THYROID CANCER PATIENTS WHO HAVE UNDETECTABLE TG ON THYROXIN?**

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P22 **^{99M}TC-EDDA-HYNIC-TOC SCINTIGRAPHY FOR THE EVALUATION OF MEDULLARY THYROID CANCER IN PERSISTENT HYPERCALCITONINEMIA**

Czepczyński R[1], Gryczyńska M[1], Czarnywojtek A[1], Ruchała M[1], Ziemnicka K[1], Sowiński J[1]

[1]Poznan University of Medical Sciences, Dept. of Endocrinology, Poznan, Poland

P23 **RADIOIODINE ABLATION AFTER RECOMBINANT HUMAN TSH OR THYROID HORMONE WITHDRAWAL IN PATIENTS WITH T3/T4 (TNM STAGE) THYROID TUMORS**

Pitoia F[1], Faure E[2], Abelleira E[1], Schwarzstein D[3], Bueno F[1], Lutfi R[2], Niepomniszcze H[1]

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P24 **THYROID LESIONS PREVALENCE IN INDIVIDUALS SUBMITTED TO CHILDHOOD X-RAY EPILATION FOR TINEA CAPITIS TREATMENT**

Boaventura P[1], Pereira D[1], Oliveira R[2,3], Soares P[1,2], Sobrinho-Simões M[1,2], Teixeira-Gomes J[1]

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P25 **LACK OF THRESHOLD VALUES OF CALCITONIN AND CARCINOEMBRYOGENIC ANTIGEN DOUBLING-TIMES IN RISK PREDICTION IN MEDULLARY THYROID CANCER**

Gawlik T[1], d'Amico A[1], Handkiewicz-Junak D[1], Szpak-Ulczok S[1], Skoczylas A[1], Gubała E[1], Chorąży A[1], Gorczewski K[1], Włoch J[2], Jarząb B[1]

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P26 **LOW RISK THYROID CARCINOMA: DOING MORE GOOD THAN HARM**

Rodrigues FJC[1], Martinho M[1], Azevedo T[1], Martins T[1], Cunha N[2], Rascão MJ[3], Oliveira C[4], Neto J[4], Oliveira S[4], Gilde P[5], Neves A[5], Gomes I[3], Cruz C[5], Valido F[2], Campos B[1]

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P27 **PREPARATION WITH ENDOGENOUS AND EXOGENOUS TSH STIMULATION FOR RAI TREATMENT GIVES COMPARABLE RESULTS IN PATIENTS WITH METASTATIC DIFFERENTIATED THYROID CANCER**

Klubo-Gwiezdzinska J[1,2], Burman KD[1], Van Nostrand D[3], Mete M[4], Wartofsky L[5]

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P28 **MEDULLARY THYROID CARCINOMA (MTC): TRENDS IN CLINICAL CHARACTERISTICS AND OUTCOME IN A REFERRAL CENTRE IN GREECE**

Alevizaki M[1,2], Rentziou G[1], Terzidis K[2], Giakoumi S[1], Anastasiou E[1], Vassileiou V[1], Saltiki K[1,2]

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P29 **THYROID CANCER NECK METASTASES: ULTRASONOGRAPHIC DIFFERENTIATION**

Kusacic Kuna S[1], Bracic I[1], Horvatic Herceg G[1], Bence Zigman Z[1], Tomic Brzac H[1], Dodig D[1]

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PO4 Thyroid Cancer (basic/translational) 1

Chair: *Clara Alvarez* (Santiago de Compostela, Spain)

P30 **IL-32 PROMOTER POLYMORPHISM MODULATES IL-32 EXPRESSION AND INFLUENCES THE RISK AND THE OUTCOME OF EPITHELIAL CELL DERIVED THYROID CARCINOMA**

Plantinga T[1], Costantini I[1], Heinhuis B[2], Huijbers A[3], Kusters B[4], Netea MG[1], Hermus A[3], Dinarello CA[1], Joosten LA[1], Netea RT[3]

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P31 **ENDOGENOUS REGULATORS OF MITOCHONDRIAL BIOGENESIS IN FOLLICULAR THYROID CARCINOMA CELLS**

Le Pennec S[1], Prunier D[1], Bouzamondo N[2], Guillotin D[1], Malthiery Y[1], Savagner F[1,3]

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P32 **NOTCH-1 RECEPTOR AS A PREDICTOR OF POOR PROGNOSIS IN PAPILLARY THYROID CANCER**

Park HS[1], Jung C-K[2], Lee S-H[2], Chae BJ[1], Lim D-J[3], Park WC[1], Song BJ[1], Kim JS[1], Jung SS[1], Bae JS[1]

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P33 **PAPILLARY THYROID CARCINOMA IS PART OF V804M RET GERMLINE MUTATION**

Brauckhoff M[1], Boman H[2], Norman I[3], Blom P[4], Følling I[3], Engebretsen LF[2], Akslen L[5], Kampevold-Larsen K[5], Varhaug JE[1]

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P34 **MTOR INHIBITION HAMPERS CELL VIABILITY IN SELECTED HUMAN MEDULLARY THYROID CARCINOMA PRIMARY CULTURES**

Minoia M[1], Zatelli MC[1], Filieri C[1], Tagliati F[1], Buratto M[1], Ambrosio MR[1], Pelizzo MR[2], degli Uberti EC[1]

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P35 **PAPILLARY THYROID CARCINOMA INDUCED BY BRAF^{V600E} MUTATION IN MICE: GENE EXPRESSION PROFILING**

Rusinek D[1], Chmielik E[2], Świerniak M[1], Kowal M[1], Kowalska M[1], Oczko-Wojciechowska M[1], Przeorek C[1], Kropińska A[1], Widłak W[3], Jarząb B[1]

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P36 **THE α1-ADRENERGIC RECEPTOR ANTAGONIST PRAZOSIN INDUCES APOPTOSIS IN HUMAN MEDULLARY THYROID CARCINOMA CELLS**

Schwach G[1], Fuchs R[1], Ingolic E[2], Stelzer I[3], Hofer D[1], Sadjak A[1], Pfragner R[1]

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P37 **ROLE OF THE WNT/B-CATENIN IN HRAS- AND BRAF-TRANSFORMED THYROID CELLS**

Sastre-Perona AM[1], López-Márquez A[1], Santisteban P[1]

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P38 **INDOLEAMINE 2,3-DIOXYGENASE (IDO) AND THYROID CARCINOMA: RET/PTC APPEARS AS A STRONG GENETIC DETERMINANT FOR IDO EXPRESSION**

Puxeddu E[1], Moretti S[1], Voce P[1], Sponziello M[2], Colella R[3], Melillo RM[4], Fallarino F[3], Bini V[1], Filetti S[2], Avenia N[5], Cavaliere A[3], Puccetti P[3], Santoro M[4]

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P39 **OGG1 AND XRCC1 EXPRESSION IN DIFFERENTIATED THYROID CARCINOMAS**

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PO5 Graves' Orbitopathy

Chair: *Valentin Fadeyev* (Moscow, Russia)

P40 **THE ROLE OF ^{99M}TC-DTPA SPECT IN STAGING AND FOLLOW UP OF DISEASE ACTIVITY BEFORE AND AFTER ORBITAL IRRADIATION IN GRAVES' ORBITOPATHY**

Galuska L[1], Szabados L[1], Leövey A[2], Ujhelyi B[3], Garai I[1], Varga J[1], Nagy EV[4]
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P41 **LOW TITER OF ANTI-TPO IS ASSOCIATED WITH AN INCREASED RISK OF GRAVES´ DISEASE AND OPHTHALMOPATHY**

Lantz M[1], Planck T[1], Åsman P[2], Hallengren B[1]
[1]Skåne University Hospital, Department of Endocrinology, Malmö, Sweden, [2]Skåne University Hospital, Department of Ophthalmology, Malmö, Sweden

P42 **PREDICTIVE FACTORS OF POOR RESPONSE AND OF SEVERITY OF GRAVES OPHTHALMOPATHY IN PATIENTS TREATED WITH ANTI-THYROID DRUGS (ATD) AND RADIOIODINE (131-I)**

Baldys-Waligorska A[1], Sokolowski A[2]
[1]Jagiellonian University, Medical College, Endocrinolgy, Krakow, Poland, [2]Cracow University of Economics, Statistics, Krakow, Poland

P43 **A SMALL DOSE OF RITUXIMAB MAY BE EFFECTIVE IN INDUCING LONG TERM INACTIVATION OF GRAVES' ORBITOPATHY**

Covelli D[1], Vannucchi G[1], Currò N[2], Bonara P[3], Guastella C[4], Pignataro L[4], Beck-Peccoz P[1], Golay J[5], Salvi M[1]
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P44 **THE COURSE OF GRAVES OPHTHALMOPATHY IN PATIENTS TREATED WITH ANTI-THYROID DRUGS (ATD) OR FOLLOWING RADIOIODINE THERAPY (131-I)**

Baldys-Waligorska A[1], Sokołowski A[2], Krzentowska-Korek A[1], Gołkowski F[1]
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P45 **ADMINISTRATION OF ORAL GLUCOCORTICOIDS (DEXAMETHASONE) IN THE TREATMENT OF ENDOCRINE OPHTHALMOPATHY**

Luchina E[1], Lukashova M[1], Meleshkevich T[1]
[1]Non-govermental Institution of Healthcare, Central Clinical Hospital, Endocrinology, Moscow, Russian Federation

P46 **SIDE EFFECTS TO GLUCOCORTICOID THERAPY IN PATIENTS WITH GRAVES´ ORBITOPATHY**

Beleslin BZ[1], Ciric J[1], Zarkovic M[1], Stojkovic M[1], Savic S[1], Knezevic M[2], Trbojevic B[1]
[1]Clinic for Endocrinology, Belgrade, Serbia, [2]Clinic for Ophthalmology, Belgrade, Serbia

P47 **C-REACTIVE PROTEIN AND TSH RECEPTOR ANTIBODIES IN GRAVES' ORBITOPATHY**

Velicanin G[1], Ciric J[1], Beleslin B[1], Stojkovic M[1], Savic S[1], Zarkovic M[1]
[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia

P48 **TWO-YEAR DYNAMIC MONITORING OF PATIENTS WITH ENDOCRINE' OPHTHALMOPATHY TREATED WITH ORAL GLUCOCORTICOIDS**

Lukashova M[1], Luchina E[1], Meleshkevich T[1]
[1]Non-govermental Institution of Healthcare, Central Clinical Hospital, Endocrinology, Moscow, Russian Federation

P49 **EFFECTIVE OF COMPLEX LYMPHATIC THERAPY OF ENDOCRINE OPHTHALMOPATHY, THREE MONTHS AFTER TREATMENT**

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P50 **QUALITY OF LIFE ASSESSMENT IN SERBIAN PATIENTS WITH GRAVES' ORBITOPATHY**

Ciric J[1], Zarkovic M[1], Beleslin B[1], Marina D[1], Bubanja D[1], Trbojevic B[1]
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P51 **ASSESSMENT OF QUALITY OF LIFE IN RUSSIAN PATIENTS WITH GRAVES´ ORBITOPATHY**

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P52 **DIAGNOSTIC GRAVES´ ORBITOPATHY IN PATIENTS WITH MYASTHENIA GRAVIS**

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P53 **FEATURES OF THERAPY OF COMPLICATION FORMS GRAVES´ ORBITOPATHY**

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PO6 Graves' Hyperthyroidism 1

Chair: *Paolo Vitti* (Pisa, Italy)

P54 ***IN VIVO* EFFECTS OF BLOCKING TYPE AND STIMULATING TYPE MONOCLONAL TSHR AUTOANTIBODIES**

Furmaniak J[1], Sanders J[1], Young S[1], Kabelis K[1], Sanders P[1], Evans M[1], Clark J[1], Wilmot J[1], Rees Smith B[1]
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P55 **A CHIMERIC CELL LINE PERFORMS SIGNIFICANTLY BETTER THAN WILD-TYPE IN ANTI-TSHR BIOASSAYS**

Li Y[1], Kim J[1], Larrimer A[1], Klasen R[1], Kanitz M[2], Olivo PD[1], Kahaly GJ[2]
[1]Diagnostic Hybrids, Inc. (a Quidel Company), Athens, Ohio, United States, [2]Gutenberg University Medical Center, Thyroid Research Laboratory, Mainz, Germany

P56 **POST-RADIOIODINE MANAGEMENT OF PATIENTS WITH GRAVES' DISEASE**

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P57 **INCIDENCE OF HYPERTHYROIDISM IN SWEDEN, IN THE YEARS 2003–2005**

Wallin GK[1], Abraham-Nordling M[2], Byström K[3], Lantz M[4], Berg G[5], Calissendorff J[6], Filipsson Nyström H[7], Jansson S[8], Jörneskog G[9], Karlsson A[10], Lundell G[11], Nyström E[7], Ohrling H[12], Örn T[13], Törring O[12], Hallengren B[4]
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P58 **ADRENOCORTICAL RESERVE IN HYPERTHYROIDISM**

Agbaht K[1], Gullu S[1]
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P59 **THE DIFFERENCES IN LYMPHOCYTE AND THYROCYTE INTERACTIONS IN GRAVES' DISEASE AND HASHIMOTO THYROIDITIS**

Ben-Skowronek I[1], Ciechanek R[2], Korobowicz E[3], Szewczyk L[4]
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P60 **DILUTION STUDIES DEMONSTRATE GREATER ANALYTICAL SENSITIVITY OF CHIMERIC TSH-R BIOASSAY VS. TSH-R BINDING AUTOANTIBODIES**

Leschik JJC[1], Kanitz M[1], Diana T[1], Matheis N[1], Li Y[2], Olivo PD[2], Kahaly GJ[1]
[1]Gutenberg University Medical Center, Thyroid Research Laboratory, Mainz, Germany, [2]Diagnostic Hybrids, Inc. (a Quidel Company), Athens, Ohio, United States

P61 **DECREASE IN MAGNESIUM AFTER TOTAL THYROIDECTOMY FOR GRAVES´ DISEASE IS RELATED TO DEVELOPMENT OF PERMANENT HYPOCALCEMIA**

Hammerstad SS[1,2], Norheim I[2], Paulsen T[3], Amlie LM[1], Eriksen EF[2]
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P62 **DOES THE SUPPRESSIVE TREATMENT OF L-THYROXINE IMPAIR HEART FUNCTION IN YOUNG PATIENTS WITH DIFFERENTIATED THYROID CANCER (DTC)?**

Kropinska A[1], Krajewska J[1], Zawisza K[2], Jarząb B[1]
[1]Centre of Oncology, Nuclear Medicine and Endocrine Oncology, Gliwice, Poland, [2]Centre of Oncology, Gliwice, Poland

P63 **EFFECT OF AMIODARONE CONTINUATION OR WITHDRAWAL ON THE RESPONSE TO GLUCOCORTICOIDS IN PATIENTS WITH AMIODARONE DESTRUCTIVE THYROIDITIS**

Tomisti L[1], Bartalena L[2], Brogioni S[1], Dell'Unto E[1], Martino E[1], Bogazzi F[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy, [2]University of Insubria, Department of Clinical Medicine, Varese, Italy

P64 **ANALYSIS OF TSH RECEPTOR AUTOANTIBODY ACTIVITIES IN A SUBJECT WITH LONGSTANDING HASHIMOTO'S THYROIDITIS WHO DEVELOPED GRAVES' DISEASE WITH PRETIBIAL MYXOEDEMA**

Kamath C[1], Young S[2], Kabelis K[2], Sanders J[2], Adlan MA[1], Furmaniak J[2], Rees Smith B[2], Premawardhana LD[1,3]
[1]Caerphilly Miners' Hospital, Medicine, Cardiff, United Kingdom, [2]FIRS Laboratories, RSR Ltd, Cardiff, United Kingdom, [3]University Hospital of Wales, Endocrinology, Cardiff, United Kingdom

P65 **SERUM LEVELS OF CIRCULATING SOLUBLE FAS LIGAND (SFASL) IN CHILDREN WITH AUTOIMMUNE HYPOTHYROIDISM AND AUTOIMMUNE HYPERTHYROIDISM**

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PO7 Thyroid Hormone and Metabolism 1

Chair: *Istvan Szabolcs* (Budapest, Hungary)

P66 **EFFECTS OF TSH ON THERMOGENIC MARKERS IN BROWN ADIPOCYTES**

Martinez-de-Mena R[1], Obregon M-J[1]
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P67 **THYROID HORMONE EFFECT ON MITOCHONDRIAL FUNCTION IS DEPENDENT OF AGE IN LEAN FEMALES**

Toft Kristensen T[1], Feldthusen A-D[1], Anthonsen S[1], Wilms L[2], Pedersen PL[3], Larsen J[4], Kvetny J[5]
[1]Naestved Hospital, Region Zealand, Mitochondrial Research Unit, Naestved, Denmark, [2]Naestved Hospital, Region Zealand, Department of Paediatrics, Naestved, Denmark, [3]Naestved Hospital, Region Zealand, Department of Clinical Biochemistry, Naestved, Denmark, [4]Naestved Hospital, Region Zealand, Department of Clinical Pathology, Naestved, Denmark, [5]Naestved Hospital, Region Zealand, Department of Internal Medicine, Naestved, Denmark

P68 **EFFECTS OF THYROTOXICOSIS ON LEVELS OF GHRELIN, ADIPOCYTOKINES AND ENDOCRINE PANCREAS FUNCTION**

Agbaht K[1], Erdogan MF[1], Emral R[1], Baskal N[1], Gullu S[1]
[1]Ankara University Faculty of Medicine, Endocrinology and Metabolic Disorders, Ankara, Turkey

P69 **GHRELIN AND OBESTATIN CHANGES IN HYPOTHYROIDISM AND HYPERTHYROIDISM AFTER TREATMENT**

Gurgul E[1], Ruchala M[1], Kosowicz J[1], Zamyslowska H[1], Wrotkowska E[1], Sowinski J[1]
[1]Poznan University of Medical Sciences, Department of Endocrinology, Metabolism and Internal Diseases, Poznan, Poland

P70 **IS NON-ENZYMIC PROTEIN GLYCATION OCCURRING IN DIABETES RELATED TO THE PRODUCTION OF ANTI-THYROGLOBULIN ANTIBODIES?***

Hatzioannou A[1], Saradopoulou V[2], Anastasiou E[2], Philippou G[3], Vlassara H[4], Peppa M[4], Lymberi P[1], Alevizaki M[2,3]
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P71 **ANALYSIS OF SERUM LEVELS OF NESFATIN IN PEDIATRIC PATIENTS WITH GRAVES' DISEASE AND HASHIMOTO'S THYROIDITIS**

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P72 **SERUM ADIPONECTIN, RESISTIN, C-REACTIVE PROTEIN, AND LIPOPROTEIN (A) LEVELS IN AUTOIMMUNE THYROIDITIS**

Neves C[1], Sokhatska O[2], Palmares C[2], Esteves C[1], Alves M[1], Ramalho R[2], Carvalho D[1], Medina JL[1], Delgado JL[2]

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P73 **INSULIN RESISTANCE, LIPID PROFILE, C-REACTIVE PROTEIN, AND HOMOCYSTEINE IN PATIENTS WITH GRAVES' DISEASE, AND AUTOIMMUNE THYROIDITIS**

Esteves C[1], Neves C[1], Alves M[1], Pereira M[1], Dias C[2], Ramalho R[3], Palmares C[3], Sokhatska O[3], Guimarães C[3], Carvalho D[1], Delgado JL[3], Medina JL[1]

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PO8 Hypothyroidism 1

Chair: *Annick van den Bruel* (Bruges, Belgium)

P74 **ACUTE ALTERATIONS IN THYROID FUNCTION OF MALE HYPER MARATHON RUNNERS: A NEW CATEGORY OF "EUTHYROID SICK SYNDROME"**

Markou KB[1], Leonidou L[1], Tsekouras A[1], Roupas N[2], Armeni A[2], Markades G[2], Mamalis I[1], Maragos S[3], Vagenakis AG[1], Georgopoulos NA[2]

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P75 **LOWER FREQUENCIES OF CD4+CD25HIGH AND CD4+FOXP3, BUT NOT CD4+CD25+CD127LOW FOXP3+ T CELL LEVELS IN CHILDREN WITH HASHIMOTO'S THYROIDITIS**

Bossowski AT[1], Moniuszko M[2], Dabrowska M[3], Sawicka B[1], Jeznach M[2], Bossowska A[4], Bodzenta-Lukaszyk A[2]

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P76 **CLINICAL SIGNIFICANCE OF TSH CIRCADIAN VARIABILITY IN EUTHYROID INDIVIDUALS AND PATIENTS WITH HYPOTHYROIDISM**

Fadeyev V[1], Sviridonova M[1], Melnichenko G[1]

[1]Federal Endocrinological Research Centre of Russian Federation, Moscow, Russian Federation

P77 **DIFFERENCES IN AUTOIMMUNE THYROID DISEASE PRESENTATION BETWEEN FAMILIAL AND NON-FAMILIAL CASES***

Terzidis K[1], Saltiki K[2], Mantzou E[1], Anastasiou E[2], Alevizaki M[1,2]

[1]Athens University School of Medicine, Evgenidion Hospital, Athens, Greece, [2]Athens University School of Medicine, Dept Medical Therapeutics, Alexandra Hospital, Athens, Greece

P78 **SHORT-TERM COMBINED TREATMENT WITH L-THYROXINE PLUS L-TRIIODOTHYRONINE (LT4 PLUS LT3) DROPS IN PATIENTS WITH PERSISTENT HYPOTHYROIDISM AND MALABSORPTION DURING REPLACEMENT THERAPY WITH L-T4**

Ippolito S[1], Galante F[1], Arpaia D[1], Ferraro A[1], Lombardi G[1], Biondi B[1]

[1]Università degli studi di Napoli 'Federico II', Department of Clinical and Molecular Endocrinology and Oncology, Naples, Italy

P79 **INTERLEUKIN 1 BETA (IL-1 BETA) GENE POLYMORPHISMS (SNP-511 AND SNP+3953) IN HASHIMOTO´S THYROIDITIS AMONG THE POLISH POPULATION**

Lacka K[1], Paradowska-Gorycka A[2], Kramer L[3], Herman W[4], Maciejewski A[5], Lacki JK[6,7]

[1]University of Medical Sciences, Department of Endocrinology, Metabolism and Internal Medicine, Poznan, Poland, [2]Institute of Rheumatology, Department of Biochemistry, Warsaw, Poland, [3]University of Medical Sciences, Department of Computer Science, Poznan, Poland, [4]Outpatient's Unit of Endocrine Diseases, Wschowa, Poznan, Poland, [5]University of Medical Sciences, Student's Scientific Society, Poznan, Poland, [6]Institute of Rheumatology, Warsaw, Poland, [7]University of Zielona Gora, Zielona Gora, Poland

P80 **IMPAIRED L-THYROXINE (L-T4) ABSORPTION AFTER INGESTION OF LARGE AMOUNTS OF PAPAYA FRUIT**

Deiana L[1], Marini S[1], Mariotti S[1,2]

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P81 **PREVALENCE OF THYROID DISEASE IN A POPULATION-BASED SURVEY IN TURKEY: TURDEP-II**

Satman I[1], Colak N[1], Boztepe H[1], Alagol F[1], TURDEP-II Study Group

[1]Istanbul University, Istanbul Medical Faculty, Medicine, Division of Endocrinology, Istanbul, Turkey

P82 **HEMATOLOGIC ABNORMALITIES IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM: CHARACTER AND RELATIONSHIP TO LEVOTHYROXINE TREATMENT**

Strongin LG[1], Nekrasova TA[1], Ledentsova OV[2], Lukushkina AY[1]
[1]Nizhny Novgorod State Medical Academy, Endocrinology, Nizhny Novgorod, Russian Federation, [2]Nizhny Novgorod Regional Diagnostic Center, Endocrinology, Nizhny Novgorod, Russian Federation

P83 **SCREENING FOR UNDIAGNOSED HYPOTHYROIDISM IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN ARMENIA**

Navasardyan L[1], Aghajanova Y[1], Markosyan R[1], Bayburdyan G[1]
[1]Yerevan State Medical University, Endocrinology Department, Yerevan, Armenia

P84 **IS FREQUENCY OF ETIOLOGIES AND INCIDENCE OF CONGENITAL HYPOTHYROIDISM CHANGING?**

Maciel LMZ[1], Magalhaes PKR[1]
[1]University of Sao Paulo, Internal Medicine, Ribeirao Preto, Brazil

P85 **SUBCLINICAL HYPOTHYROIDISM AND THE RISK OF CORONARY HEART DISEASE**

Novakovic T[1], Jovićević L[2], Inić-Kostić B[3], Milinić S[1], Pajović S[1]
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P86 **RISK FACTORS FOR THE DEVELOPMENT OF HYPOTHYROIDISM AFTER RADIOIODINE THERAPY OF FUNCTIONAL THYROID AUTONOMY**

Valuyevich VV[1], Saenko VA[2], Danilova LI[3], Diekmeyer B[4], Ostwald-Lenz E[4], Kaiser KP[4], Rogounovitch TI[2], Mine M[2], Tuzava HA[2], Wieler H[4], Yamashita S[2]
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P87 **CHARACTERISTICS OF CELLULAR PART OF IMMUNE RESPONSE IN POSTMENOPAUSAL WOMEN WITH AUTOIMMUNE THYREOIDITIS**

Karachentcev Y[1], Goncharova O[2], Kravchun N[1], Iliyna I[1]
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PO9 Cytology

Chair: *Teresa Rago* (Pisa, Italy)

P88 **SHOULD WE ASSESS ALL THYROID NODULES BY FINE NEEDLE ASPIRATION BIOPSY FOR THE DIAGNOSIS OF THYROID CANCER? AND IS BRAF MUTATION ANALYSIS HELPFUL?**

Rossi M[1], Trasforini G[1], Buratto M[1], Tagliati F[1], Rossi R[1], degli Uberti EC[1], Zatelli MC[1]
[1]University of Ferrara, Section of Endocrinology, Dept of Biomedical Sciences and Advanced Therapies, Ferrara, Italy

P89 **THE USE OF SET OF GENETIC MARKERS HELP TO DISCRIMINATE BENIGN AND MALIGNANT THYROID NODULES WITH A FINE NEEDLE ASPIRATION PATTERN OF FOLLICULAR PROLIFERATION IN AN AREA OF BORDERLINE IODINE DEFICIENCY**

Niccolai F[1], Agretti P[1], Rago T[1], Scutari M[1], Molinaro A[1], Candelieri A[2], Di Coscio G[3], Basolo F[3], Iacconi P[3], Miccoli P[3], Di Cosmo C[1], Pinchera A[1], Vitti P[1], Tonacchera M[1]
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P90 **CLASS III β-TUBULIN EXPRESSION IN PAPILLARY THYROID CARCINOMA: AN IMMUNOHISTOCHEMICAL ASSESSMENT**

Colato C[1], Gobbato M[1], Dardano A[2], Brazzarola P[3], Monzani F[2], Chilosi M[1], Ferdeghini M[1]
[1]University of Verona, Pathology and Diagnostics, Verona, Italy, [2]University of Pisa, Internal Medicine, Pisa, Italy, [3]University of Verona, Surgery, Verona, Italy

P91 **THE ROLE OF IMMUNOHISTOCHEMISTRY FOR THYROID PEROXIDASE, GALECTIN-3, CYTOKERATIN-19 AND HBME1 IN THE DIFFERENTIAL DIAGNOSIS OF THYROID TUMORS**

Savin S[1], Isic T[1], Marecko I[1], Paunovic I[2], Tatic S[3], Cvejic D[1]
[1]Inst. for the Application of Nuclear Energy - INEP, University of Belgrade, Zemun-Belgrade, Serbia, [2]Clinical Center of Serbia, Belgrade, Serbia, [3]Inst. of Pathology, Medical Faculty, University of Belgrade, Belgrade, Serbia

P92 **DIAGNOSTIC ACCURACY OF FINE NEEDLE ASPIRATION BIOPSY CYTOLOGY AND ULTRASONOGRAPHY IN PATIENTS WITH THYROID NODULES DIAGNOSED AS BENIGN OR INDETERMINATE BEFORE THYROIDECTOMY**

Sugino K[1], Ito K[1], Nagahama M[1], Kitagawa W[1], Shibuya H[1], Okuwa K[1], Yano Y[1], Uruno T[1], Kameyama K[2], Ito K[1]
[1]Ito hospital, Surgery, Tokyo, Japan, [2]Keio University, Pathology, Tokyo, Japan

P93 **NEW CLASSIFICATION OF THE THYROID FNAB RESULTS - THE IMPACT ON FREQUENCY OF PARTICULAR DIAGNOSES FROM FOLLICULAR LESIONS IN POSTENDEMIC AREA**

Woźniak E[1], Sporny S[2], Popowicz B[1], Klencki M[1], Słowińska-Klencka D[1]
[1]Medical University of Lodz, Department of Morphometry of Endocrine Glands, Lodz, Poland, [2]Medical University of Lodz, Department of Dental Pathomorphology, Lodz, Poland

P94 **IN FINE NEEDLE CYTOLOGY SPECIMENS CLASSIFIED THY 4, NUCLEAR INCLUSIONS HAVE A HIGH PREDICTIVE VALUE FOR THYROID CANCER.**

Arena S[1], Latina A[2], Marturano I[2], Muscia V[2], Stornello M[1], Italia S[1], La Rosa GL[2], Vigneri R[2]
[1]ASP 8 Siracusa, Internal Medicine - Section of Endocrinology and Metabolic Diseases, Umberto I Hospital, Siracusa, Italy, [2]University of Catania, Clinical and Molecular Bio-Medicine, Garibaldi-Nesima Hospital, Catania, Italy

P95 **GENOME-WIDE MICRORNA ANALYSIS PERFORMED ON SINGLE IN VIVO FINE-NEEDLE ASPIRATES FROM SOLID COLD THYROID NODULES: A PROSPECTIVE TRANSLATIONAL STUDY**

Rossing M[1], Kaczkowski B[2], Nygaard B[3], Nielsen FC[1], Bennedbæk FN[3]
[1]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [2]The Bioinformatic Center, University of Copenhagen, Copenhagen, Denmark, [3]Herlev Hospital, University of Copenhagen, Herlev, Denmark

P96 **CONTRIBUTION OF ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION CYTOLOGY (UGFNA) TO AMBULATORY SURGICAL MANAGEMENT OF THYROID NODULES - RETROSPECTIVE ANALYSIS OF 132 CONSECUTIVE CASES**

Godinho Matos ML[1], Rangel R[1], Lázaro A[2], Milheiro A[2], Carvalho A[2], Tavares P[3], Coutinho JM[3]
[1]Hospital Curry Cabral, Endocrinology, Lisbon, Portugal, [2]Hospital Curry Cabral, Histopatology, Lisbon, Portugal, [3]Hospital Curry Cabral, Surgery, Lisbon, Portugal

P97 **DIFFICULTIES IN DIAGNOSIS OF FOLLICULAR TUMORS IN FINE NEEDLE ASPIRATION BIOPSY OF THE THYROID GLAND**

Wojtczak B[1], Domosławski P[1], Sutkowski K[1], Głód M[1], Łukieńczuk T[1]
[1]Wroclaw Medical University, 1st Department of General, Gastroenterological and Endocrine Surgery, Wroclaw, Poland

P98 **FREQUENCY AND INTENSITY OF PAIN OCCURRING DURING AND AFTER FINE NEEDLE ASPIRATION BIOPSY OF THYROID NODULES**

Labro S[1], Borget I[2], Laurent S[1], Dauchy S[1], Vielh P[3], Bidault S[4], Girard E[4], Chougnet C[5], Mirghani H[6], Baudin E[5], Hartl D[2], Schlumberger M[5], Leboulleux S[5]
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P99 **THYROID ULTRASOUND AND ULTRASOUND GUIDED FNA WITH THYROGLOBULIN DETERMINATION IN THE FOLLOW-UP OF THROID CANCER PATIENTS**

López-Plasencia Y[1], Marrero-Arencibia D[1], Garcia-Delgado Y[1], Pérez-Martín N[1], Alberiche-Ruano MP[1], Nóvoa-Mogollón FJ[1]
[1]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain

P100 **FINE NEEDLE ASPIRATION BIOPSY IN THYROID NODULAR DISEASE - 10 YEARS OF EXPERIENCE IN A MILITARY UNIVERSITY HOSPITAL**

Marcelino M[1], André S[2], Figueiredo L[3], Lopes C[4], Passos D[1], Vilar H[1], Lopes L[1], Carvalho R[1], Castro J[1]
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P101 **HASHIMOTO'S THYROIDITIS AT US: IMAGING-CYTOLOGIC CORRELATION**

Kim SJ[1], Chong S[1], Chung Y-J[2], Park SJ[3]
[1]Chung-Ang University Medical Center, Chung-Ang University College of Medicine, Department of Radiology, Seoul, Korea, Republic of, [2]Chung-Ang University Medical Center, Chung-Ang University College of Medicine, Department of Internal Medicine Division of Endocrinology, Seoul, Korea, Republic of, [3]Chung-Ang University Medical Center, Chung-Ang University College of Medicine, Department of Surgery, Seoul, Korea, Republic of

PO10 Pregnancy

Chair: *Milos Zarkovic* (Belgrade, Serbia)

P102 **ALTERATIONS IN MILK AND URINARY IODINE VALUES IN EARLY PREGNANCY IN THE ABSENCE OF A SALT IODISATION PROGRAMME**

Smyth PP[1,2], Burns R[3], O'Herlihy C[3,4]

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P103 **PROSPECTIVE STUDY OF CLINICAL EVALUATION AND OUTCOME OF PREGNANT WOMEN FOR THYROID DYSFUNCTION**

Maciel LMZ[1], Saueia-Ferreira SM[1], Magalhaes PKR[1], Navarro AM[1], Duarte G[2], Quintana SM[2]

[1]University of Sao Paulo, Internal Medicine, Ribeirao Preto, Brazil, [2]University of Sao Paulo, Gynecology and Obstetrics, Ribeirao Preto, Brazil

P104 **PREVALANCE OF GESTATIONAL DIABETES MELLITUS IN PATIENTS WITH GESTATIONAL TRANSIENT THYROTOXICOSIS**

Oguz A[1], Tuzun D[1], Ozdemir D[1], Bacı Y[1], Ersoy R[1], Avsar F[2], Cakir B[1]

[1]Ankara Ataturk Education and Research Hospital, Department of Endocrinology and Metabolism, Ankara, Turkey, [2]Ankara Ataturk Education and Research Hospital, Department of Gynecology and Obstetrics, Ankara, Turkey

P105 **PERMANENT BUT NOT TRANSIENT SECONDARY HYPOTHYROIDISM IN A NEWBORN OF MOTHER WITH A PAST HISTORY OF GRAVES' DISEASE: TRANSITION FROM HYPER- TO HYPOTHYROIDISM**

Niedziela M[1]

[1]Poznan University of Medical Sciences, Department of Pediatric Endocrinology and Rheumatology, Poznan, Poland

P106 **THE EFFECT OF SUPEROVULATION STIMULATION ON THYROID FUNCTION IN CARRIERS OF THYROID PEROXIDASE ANTIBODIES**

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P107 **THYROID FUNCTION IN PREGNANT THYROID PEROXIDASE ANTIBODY-POSITIVE WOMEN LIVING IN AN AREA WITH MILD IODINE DEFICIENCY**

Payenok OS[1], Pankiv VI[2]

[1]Medical University, Obstetrics and Gynecology, Lviv, Ukraine, [2]Centre of Endocrinology, Preventive Endocrinology, Kyiv, Ukraine

P108 **THE PECULIARITIES OF THYROID DYSFUNCTION AND ANTI-THYROID PEROXIDASE ANTIBODIES DURING PREGNANCY AND AFTER DELIVERY**

Javashvili L[1], Morchiladze N[2], Tkeshelashvili B[2], Gagua D[2], Dundua T[1], Tananashvili D[1]

[1]Clinic Cortex, Tbilisi, Georgia, [2]D.Gagua Clinic, Tbilisi, Georgia

P109 **ASSESSMENT OF THYROID FUNCTION AND IODINE SUPPLY OF THE GROUP OF HEALTHY PREGNANT WOMEN FROM CENTRAL POLAND**

Krasnodebska M[1], Niedźwiedźka B[2], Kondracka A[1], Bartoszewicz Z[1,3], Bar -Andziak E[1], Bednarczuk T[1,3]

[1]Warsaw Medical University, Chair and Department of Internal Diseases and Endocrinology, Warsaw, Poland, [2]Medical University of Lodz, Department of Obsterics and Gynecology, Lodz, Poland, [3]Medical Research Center Polish Academy of Sciences, Department of Endocrinology, Warsaw, Poland

P110 **A CASE OF PROPYLTHIOURACIL-INDUCED HEPATITIS DURING PREGNANCY, REQUIRING CESSATION OF PROPYLTHIOURACIL AND SUBSEQUENT SUCCESSFUL TREATMENT WITH CARBIMAZOLE**

Taylor PN[1], Bhatt S[2], Dunlop D[3], Quinlan J[2], Robinson A[4]

[1]University of Cardiff, Centre for Diabetes and Endocrine Sciences, Cardiff, United Kingdom, [2]Royal United Hospital, Department of Gastroenterology, Bath, United Kingdom, [3]Royal United Hospital, Department of Obstetrics, Bath, United Kingdom, [4]Royal United Hospital, Department of Endocrinology, Bath, United Kingdom

P111 **DYNAMICS OF CHANGES IN THE ATPO LEVEL IN PREGNANT WOMEN IN EACH TRIMESTER OF PREGNANCY WITH NORMAL AND INCREASED LEVEL OF ATPO**

Kostecka-Matyja M[1], Hubalewska-Dydejczyk A[1], Pach D[1], Basta A[2], Kaim I[2]

[1]Collegium Medicum Jagiellonian University, Department of Endocrinology, Cracow, Poland, [2]Collegium Medicum Jagiellonian University, Department of Obstetrics and Gynecology, Cracow, Poland

P112 **PREVENTATION OF IODINE DEFICIENCY IN PREGNANT AND LACTATING WOMEN: EPIDEMIOLOGICAL STUDIES**

Abdulhabirova F[1], Troshina E[1], Sekinaeva A[1], Platonova N[1]

[1]Federal Endocrinological Scientific Center, Moscow, Russian Federation

P113 **CHANGES IN THE VOLUME OF THYROID GLAND IN PARTICULAR TRIMESTER OF PREGNANCY -OWN OBSERVATION**

Kostecka-Matyja M[1], Pach D[1], Hubalewska-Dydejczyk A[1], Trofimiuk M[1], Buziak-Bereza M[1], Gil J[1], Basta A[2], Kaim I[2]

[1]Collegium Medicum Jagiellonian University, Department of Endocrinology, Cracow, Poland, [2]Collegium Medicum Jagiellonian University, Department of Obstetrics and Gynecology, Cracow, Poland

P114 **SEVERE HYPEREMESIS GRAVIDARUM ASSOCIATED TO PANCREATITIS AND CHOLECYSTITIS**

Gilly O[1], Paul C[1], Ferrari P[2], Anty R[3], Hieronimus S[1], Brucker-Davis F[1]
[1]CHU Nice, Endocrinology, Nice, France, [2]CHU Nice, Biochemistry, Nice, France, [3]CHU Nice, Hepato-Gastroenterology, Nice, France

P115 **HEALTH OF NEWBORNS FROM MOTHERS WITH HASHITOXICOSIS**

Muratova S[1], Nugmanova L[1], Abdazova R[1], Ismailov S[1], Dadamjan R[1]
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Poster Exhibition Area
12.00–13.00
Poster Sessions 2

PO11 Thyroid Cancer (clinical) 4

Chair: *Chantal Daumerie* (Brussels, Belgium)

P116 **THYROID CANCER: A SURVEY OF THE PATIENT JOURNEY IN THE UK**
McGregor KJ[1], Fraser A[1], Farnell K[1], Mallick UK[1], Perros P[2]
[1]Thyroid Cancer Clinic, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom, [2]Royal Victoria Infirmary, Department of Endocrinology, Newcastle upon Tyne, United Kingdom

P117 **VIDEO ASSISTED THYROIDECTOMY IN THE TREATMENT OF THYROID CARCINOMA USING HARMONIC SCALPEL**
Nenkov RN[1], Radev RS[1]
[1]Medical University, Thoracic Surgery, Varna, Bulgaria

P118 **HYPERTHYROIDISM AND CONCURRENT CARCINOMA OF THE THYROID GLAND**
Britvin T[1], Panteleeva E[1], Bogatyrev O[1], Kazantseva I[1], Nechaeva O[1], Shestakova T[1]
[1]MONIKI, Moscow, Russian Federation

P119 **SECOND PRIMARY MALIGNANCIES IN THYROID CANCER PATIENTS**
Giestas AFD[1], Ferreira M[1], Palma I[1], Vilaverde J[1], Borges F[1]
[1]Hospital Santo António, Centro Hospitalar do Porto, Department of Endocrinology, Diabetes and Metabolism, Porto, Portugal

P120 **FACTORS RELATED WITH METASTASIS OF RIGHT RETROESOPHAGEAL LYMPH NODES IN PAPILLARY THYROID CANCER**
Kim SH[1], Chae BJ[1], Seong KY[1], Park WC[1], Song BJ[1], Kim JS[1], Jung SS[1], Bae JS[1]
[1]Catholic University, Seoul, Korea, Republic of

P121 **PAPILLARY THYROID MICROCARCINOMAS ARE DIFFERENT FROM LATENT THYROID CARCINOMAS AT AUTOPSY**
Lee YS[1], Kim BW[1], Chun H-H[1], Chun K-W[1], Chang H-S[1], Park CS[1]
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P122 **SIZE OF CERVICAL LYMPH NODE METASTASES SUCCESSFULLY TREATED BY RADIOIODINE IN PATIENTS WITH DIFFERENTIATED THYROID CANCER**
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P123 **THE PATTERN AND PREDICTIVE FACTORS OF LYMPHATIC METASTASIS IN PAPILLARY THYROID CANCER : PROSPECTIVE STUDY**
Kim MS[1], Nam IC[1], Park JO[1]
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P124 **VIRAL DISEASES AND RISK OF DIFFERENTIATED THYROID CANCER**
Przybylik-Mazurek E[1], Pach D[1], Hubalewska-Dydejczyk A[1]
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P125 **OFF-LABEL TREATMENT OF SUNITINIB IN ADVANCED THYROID CANCER PATIENTS: A CASE SERIES**
Pasqualetti G[1], Dardano A[1], Polini A[1], Tognini S[1], Ricci S[2], Colato C[3], Ferdeghini M[3], Del Tacca M[4], Monzani F[1]
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PO12 Thyroid Cancer (clinical) 5

Chair: *Valeriano Leite* (Lisbon, Portugal)

P126 **EXCELLENT LONG-TERM OUTCOME FOLLOWING 1.1 GBQ RADIOIODINE REMNANT ABLATION FOR DIFFERENTIATED THYROID CANCER**
Powell C[1], Welsh L[1], Haq M[1], Harmer C[1], Pratt B[1], Bhide S[1,2], Harrington K[2,3], Nutting C[3], Newbold K[1]
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P127 **DOES EARLY DECREASE OF CEA OR CALCITONIN MEASUREMENTS AFTER CYTOTOXIC CHEMOTHERAPY CONSTITUTE A SURROGATE MARKER OF SURVIVAL IN MEDULLARY THYROID CARCINOMA PATIENTS?**

Borget I[1], Hajje G[2], Leboulleux S[2], Chougnet C[2], Al Ghuzlan A[3], Hartl D[4], Schlumberger M[2], Baudin E[2]

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P128 **ANALYSIS OF ULTRASOUND ELASTOGRAPHY, POWER DOPPLER, AND B-MODE ULTRASOUND FEATURES IN DIFFERENTIAL DIAGNOSIS OF MALIGNANT LYMPH NODES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA**

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P129 **CLINICAL MANAGEMENT OF THYROID DYSFUNCTION IN AN ADULT ONCOLOGY POPULATION**

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P130 **CLINICOPATHOLOGIC FEATURES OF FAMILIAL NONMEDULLARY THYROID CANCER AT A SINGLE INSTITUTION**

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P131 **THE RISK OF THYROID CANCER RELATED TO THE VESUVIUS IN THE REGION OF CAMPANIA, ITALY**

Arpaia D[1], Montuori P[2], Ciancia G[3], Ippolito S[1], Ferraro A[1], Galante F[1], Lombardi G[1], Pettinato G[3], Triassi M[2], Biondi B[1]

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P132 **TUMOR SIZE DISCREPANCY BETWEEN ULTRASONOGRAPHIC AND PATHOLOGIC SPECIMEN MEASUREMENT IN PAPILLARY THYROID CARCINOMAS**

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P133 **THE SIGNIFICANCE OF DETERMINATION OF THYROGLOBULIN (TG) AND CALCITONIN IN DIAGNOSIS OF THYROID CANCER METASTASES**

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P134 **THE IMPACT OF DIETARY IODINE RESTRICTION ON THE EFFICACY OF LOW DOSE RAI REMNANT ABLATION IN PATIENTS WITH PAPILLARY THYROID CANCER IN IODINE-SUFFICIENT AREA**

Jang HW[1], Sohn SY[1], Kim HJ[1], Bae JC[1], Hur KY[1], Kim JH[1], Min Y-K[1], Lee M-S[1], Lee M-K[1], Kim K-W[1], Lee S-Y[2], Chung JH[1], Kim SW[1]

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P135 **RELATIONSHIP OF CRIBRIFORM-MORULAR VARIANT OF PAPILLARY THYROID CARCINOMA WITH FAMILIAL ADENOMATOUS POLYPOSIS. REPORT OF THREE CASES WITH ANALYSIS OF MUTATIONAL STATUS OF BRAF GENE**

Colato C[1], Marchetti I[2], Di Coscio G[2], Chilosi M[1], Ferdeghini M[1]

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PO13 Thyroid Cancer (clinical) 6

Chair: *Bengt Hallengren* (Malmö, Sweden)

P136 **TSH SUPPRESSION AND THYROXINE DOSE**

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P137 **SUPERIOR PARATHYROID GLANDS ARE LOCATED IN THE FLUID COLLECTION AROUND ZUCKERKANDLE TUBERCLE**

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[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Thyroid Cancer Center, Seoul, Korea, Republic of

P138 **DETECTION OF THYROGLOBULIN ANTIBODIES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA: BE AWARE OF INTERFERENCE OF SERUM THYROGLOBULIN**

Klein Hesselink MS[1], Muller Kobold AC[2], Van der Horst-Shrivers ANA[1], Brouwers AH[3], Plukker JTM[4], Sluiter WJ[1], Links TP[1]

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P139 **CONCURRENT GRAVES´ DISEASE AND AGGRESSIVE BEHAVIOR OF THYROID CANCER: A CASE SERIES AND CONCEPT OF INTERRELATED PATHOGENETIC LINKS**

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P140 **OUR EXPERIENCE WITH RECOMBINANT HUMAN TSH**

Martins R[1], Neves C[2], Alves M[2], Parente B[3], Maia A[3], Meireles E[3], Rodriges E[2], Marinho J[3], Carvalho D[2]
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P141 **THYROGLOBULIN MONITORING AFTER TREATMENT OF WELL-DIFFERENTIATED THYROID CANCER (WDTC)**

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P142 **PROGNOSTIC SIGNIFICANCE OF POST OPERATIVE CERVICAL ULTRASONOGRAPHY AND OUTCOME OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA TREATED BY RADIOIODINE ABLATION AFTER PREPARATION WITH RECOMBINANT HUMAN TSH**

Sami O[1], Golmard JL[2], Du Pasquier Fediaevsky L[1], Rousseau A[1], Hoang C[3], Aurengo A[1], Menegaux F[4], Leenhardt L[1]
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P143 **USEFULNESS OF MEASUREMENT OF SERUM IODINE LEVEL TO ASSESS THE APPROPRIATE LOW IODINE DIET PREPARATION FOR RADIOACTIVE IODINE THERAPY IN THYROID CARCINOMA**

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P144 **CLINICAL FEATURES AND OUTCOME OF DIFFERENTIATED THYROID CARCINOMAS IN YOUNG ROMANIAN PATIENTS DIAGNOSED AFTER CHERNOBYL ATOMIC ACCIDENT**

Coculescu M[1,2], Trifanescu RA[1,2], Goldstein A[2], Belgun M[2], Ioachim D[2], Munteanu A[2], Alexiu F[2]
[1]Carol Davila University of Medicine and Pharmacy, Endocrinology, Bucharest, Romania, [2]C.I. Parhon Institute of Endocrinology, Bucharest, Romania

P145 **SEVERE DIFFUSE GLOMERULAR THROMBOTIC MICROANGIOPATHY OF THE VEGF-INHIBITOR ASSOCIATED TYPE FOLLOWING TREATMENT WITH XL184 OR PLACEBO**

Jabs WJ[1], Horn A[2], Helmchen U[3], Peters U[4], Paschke R[5]
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PO14 Thyroid Cancer (basic/translational) 2

Chair: *Rosa Melillo* (Naples, Italy)

P146 **A GENERAL METHOD TO DERIVE ROBUST ORGAN-SPECIFIC GENE EXPRESSION-BASED DIFFERENTIATION INDICES: APPLICATION TO THYROID CANCER DIAGNOSTIC**

Tomas G[1], Tarabichi M[1], Dumont JE[1], Keutgen X[2], Maenhaut C[1], Fahey III TJ[2], Detours V[1]
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P147 **EPIGENETIC COMPOUNDS HAVE MINOR EFFECTS ON DIFFERENTIATION IN HUMAN THYROID CANCER CELL LINES BUT INDUCE EXPRESSION OF GENES INVOLVED IN IN VITRO ADAPTATION**

Dom GM[1], Chico Galdo V[1], Tomas G[1], Delys L[1], Andry G[2], Weiss Solis D[1], Franc B[3], Libert F[1], Dumont J-E[1], Maenhaut C[1], van Staveren W[1]
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P148 **ESTABLISHMENT AND APPLICATION OF CELL LINES FROM MEDULLARY THYROID CARCINOMA**

Pfragner R[1], Flicker K[2], Hofer D[1], Schwach G[1], Fuchs R[1], Haas HS[1], Svejda B[1,3], Aguiriano-Moser V[1], Sturm S[4], Niederle B[5], Speicher M[2], Studygroup Multiple Endocrine Neoplasia Austria (SMENA)
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P149 **PROGNOSTIC VALUE OF BRAF MUTATIONS IN PAPILLARY THYROID CARCINOMA (PTC)**

Czarniecka A[1], Krajewska J[2], Rusinek D[2], Stobiecka E[3], Jarząb M[4], Oczko-Wojciechowska M[2], Żebracka-Gala J[2], Chmielik E[3], Handkiewicz-Junak D[2], Maciejewski A[1], Półtorak S[1], Włoch J[1], Jarząb B[2]

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P150 **FUNCTIONAL REDUNDANCY: AN ASPECT OF EPH RECEPTORS IN THE THYROID OF EPHA4 KNOCKOUT ADULT MICE**

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P151 **PREDICTIVE VALUE OF MOLECULAR MARKERS THAT INVOLVED IN A GENETIC SIGNATURE IN THYROID TISSUE AND THEIR INVOLVEMENT IN THE TUMOUR DEDIFFERENTIATION PROCESS**

González C[1], Mato E[2], Bell O[2], Lerma E[3], Moral A[4], Pérez JI[4], de Leiva A[1,2]

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P152 **ACTIVITY OF NOVEL WATER SOLUBLE PORPHYRIN POR-EDTA AGAINST MEDULLARY THYROID CARCINOMA CELL LINES**

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P153 **EFFECTS OF CURCUMIN ON THYROID CANCER CELL LINES**

Yu H[1], Bao J[1], Zhang L[1], Song F[2], Tan C[1], Lin X[1], Zhang C[2]

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P154 **EXPRESSION OF SATB1 GENE IN THYROID CARCINOMA CELL LINES**

Ciampi R[1], Carlomagno F[2], Tacito A[1], Cosci B[1], Vivaldi A[1], Romei C[1], Pinchera A[1], Santoro M[2], Elisei R[1]

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PO15 Graves' Hyperthyroidism 2

Chair: *Colin Dayan* (Cardiff, UK)

P155 **PHARMACOLOGICAL CARDIOVERSION THERAPY FOR POST-THYROTOXIC PERSISTENT ATRIAL FIBRILLATION USING ANTIARRHYTHMIC DRUG; BEPRIDIL**

Kunii Y[1], Matsumoto M[1], Noh JY[1], Mukasa K[1], Suzuki M[1], Ohye H[1], Watanabe N[1], Kosuga Y[1], Yoshihara A[1], Sekiya K[1], Sato S[1], Ito K[1], Nakazawa H[1]

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P156 **LONG-TERM CLINICAL OUTCOME IN PATIENTS WITH THYROTOXICOSIS TREATED WITH A 60GY ABSORBED DOSE OF RADIOIODINE**

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P157 **EVALUATING THE RESULTS OF LONG-TERM TREATMENT WITH ANTI-THYROID DRUGS IN GRAVES´ DISEASE**

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P158 **RISK FACTORS OF DEVELOPMENT AND PERSISTENCE OF THYREOTOXIC CARDIOMYOPATHY**

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P159 **GRAVES DISEASE OF MEN AND WOMEN: COMMON AND DIFFERENT SIGNS**

Romanchishen AF[1], Akinchev AL[1], Jakovlev PN[1], Volert VA[1], Atabaev AP[1], Vabalite KV[1]

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P160 **FUNCTIONAL SENSITIVITY OF A NEW ULTRASENSITIVE THYROID-STIMULATING HORMONE ASSAY: FROM INITIAL ASSESSMENT TO ROUTINE FOLLOW-UP**

Reix N[1,2], Heurtault B[1,3], Gasser F[1], Agin A[1,2]

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P161 **THYROTOXICOSIS AND WPW SYNDROME: PROPRANOLOL IS CONTRAINDICATED**

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P162 **TREATMENT OF MILD GRAVES'HYPERTHYROIDISM WITH POTASSIUM IODIDE IN PATIENTS WITH MALIGNANCY REQUIRING ANTI-CANCER DRUG THERAPY**
Okamura K[1], Bandai S[1], Fujikawa M[1], Sato K[1]
[1]Kyushu University, 2nd Dept Int Med, Faculty of Medicine, Fukuoka, Japan

P163 **EVALUATION OF RISK FACTORS IN GRAVES´DISEASE RECURRENCES IN PATIENTS WHO WERE TAKEN CARE IN THE REGIONAL HOSPITAL CENTER OF SAINT-PIERRE IN REUNION ISLAND FROM 1990 TO 2010 : A RETROSPECTIVE STUDY**
Cogne MM[1], Nedelec C[1], Favier F[2]
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P164 **LITHIUM ASSOCIATED THYROTOXICOSIS: A BIPOLAR DIAGNOSIS**
Jorge G[1], Queirós J[1], Nogueira C[1], Vinha E[1], Carvalho D[1]
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P165 **ACQUIRED APLASTIC ANAEMIA WITH SUBSEQUENT AUTOIMMUNE HYPERTHYROIDISM**
Flader M[1], Niedziela M[1,2]
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PO16 Thyroid Hormone and Metabolism 2

Chair: *Jean-Louis Wemeau* (Lille, France)

P166 **INSULIN RESISTANCE, LIPID PROFILE, HIGH SENSITIVITY C REACTIVE PROTEIN AND HOMOCYSTEINE IN PATIENTS WITH AUTOIMMUNE THYROIDITIS**
Alves M[1], Medina JL[1], Neves C[1], Pereira M[1], Dias C[2], Esteves C[1], Palmares C[3], Sokhatska O[3], Ramalho R[3], Guimarães C[3], Carvalho D[1]
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P167 **METABOLIC SYNDROME PARAMETERS AND INSULIN RESISTANCE IN DIFFERENTIATED THYROID CANCER**
Balkan F[1], Usluogulları A[1], Tuzun D[1], Ozdemir D[1], Soytac Inancli S[2], Ersoy R[1], Cakir B[1]
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P168 **THYROID STATUS IN OBESITY SUBJECTS**
Mustafina S[1], Rymar O[1], Simonova G[1], Tolstykh E[1], Sherbakova L[1]
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P169 **HYPOTHYROID TRH-R1 KNOCKOUT MICE EXHIBIT CENTRAL CHANGES IN LEPTIN SIGNALING**
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P170 **REGULATION OF ADIPONUTRIN MRNA AND PROTEIN LEVELS BY T3 IN RAT BROWN ADIPOCYTES**
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P171 **3,5-DIIODOTHYRONINE (T2) ADMINISTRATION TO HYPOTHYROID RATS ENHANCES THE OXIDATIVE CAPACITY OF BROWN ADIPOSE TISSUE**
Lombardi A[1], De Matteis R[2], Busiello RA[1], Napolitano L[1], Senese R[3], Cioffi F[4], Goglia F[5]
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P172 **DOES THE AROMATIC L-AMINO ACID DECARBOXYLASE CONTRIBUTE TO THYRONAMINE BIOSYNTHESIS?**
Hoefig CS[1], Renko K[1], Piehl S[1], Scanlan TS[2], Bertoldi M[3], Opladen T[4], Hoffmann GF[4], Klein J[5], Blankenstein O[5], Schweizer U[1], Köhrle J[1]
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PO17 Goiter/Nodules 1

Chair: *Roland Gärtner* (Munich, Germany)

P173 **STRUCTURAL THYROID DISORDERS AND THYROID CANCER AT PATIENTS WITH ACROMEGALY**
Shestakova T[1], Ilovayskaya I[1], Dreval AV[1], Nechaeva O[1], Tishenina RS[1], Gadzira A[1], Zakharevich E[1]
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P174 **FOLLICULAR THYROID CANCER MOLECULAR MARKERS DISCOVERY**

Wojtas B[1], Pfeifer A[1], Stokowy T[1], Oczko-Wojciechowska M[1], Eszlinger M[2], Kukulska A[1], Musholt T[3], Jarząb M[1], Czarniecka A[4], Stobiecka E[5], Hauptmann S[6], Lange D[5], Paschke R[2], Jarząb B[1]

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P175 **THYROID FUNCTIONAL AUTONOMY AND THYROTOXICOSIS AFTER UNIVERSAL IODINE PROPHYLAXIS: THE 2010 PESCOPAGANO SURVEY**

Puleo L[1], Frigeri M[1], Provenzale MA[1], Grasso L[1], Antonangeli L[1], Fiore E[1], Tonacchera M[1], Scutari M[2], Niccolai F[1], Molinaro A[1], Bagattini B[1], Dimida A[1], Pinchera A[1], Vitti P[1], Aghini-Lombardi F[1]

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P176 **NODULAR DISEASE ASSOCIATED WITH CLINICAL AUTOIMMUNE THYROIDITIS HAS HIGHER RISK OF THYROID CANCER**

Theodoropoulou A[1], Castagna MG[1], Memmo S[1], Serafini A[1], Cipri C[1], Belardini V[1], Maino F[1], Carli AF[2], Caruso G[3], Pacini F[1]

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P177 **CAUSES OF INDIVIDUAL DIFFERENCES IN THYROID SIZE IN ADOLESCENTS: IMPACT OF BODY MASS INDEX**

Emral R[1], Agbaht K[1], Bastemir M[2], Gullu S[1]

[1]Ankara University Faculty of Medicine, Endocrinology and Metabolic Disorders, Ankara, Turkey, [2]Gaziantep Ozel Sani Konukoglu Hastanesi, Endocrinology and Metabolic Disorders, Gaziantep, Turkey

P178 **THE ROLE OF GALECTIN-3, HBME-1, AND CYTOKERATIN-19 IN THE DIFFERENTIAL DIAGNOSIS BETWEEN FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA AND BENIGN THYROIDAL LESIONS: FOLLICULAR ADENOMA, HYPERPLASTIC NODULE, AND NODULAR HYPERPLASIA**

Sengul D[1], Sengul I[2], Oz Atalay F[3], Astarci MH[3], Ustun H[3]

[1]Prof. Dr. A. Ilhan Ozdemir State Hospital, Pathology, Giresun, Turkey, [2]Giresun University Faculty of Medicine, General Surgery, Giresun, Turkey, [3]Ankara Education and Research Hospital, Pathology, Ankara, Turkey

P179 **INTRANODULAR GLUCOSE LEVELS IN THE DIFFERENTIAL DIAGNOSIS OF THYROID NODULES: A PRELIMINARY STUDY**

Aydin C[1], Soytac Inancli S[1], Balkan F[1], Dirikoc A[1], Guler G[2], Ersoy R[1], Cakir B[1]

[1]Ankara Ataturk Education and Research Hospital, Endocrinology and Metabolism, Ankara, Turkey, [2]Ankara Ataturk Education and Research Hospital, Pathology, Ankara, Turkey

P180 **REASON, PREVENTION AND SURGICAL TREATMENT OF BENIGN THYROID DISEASE RELAPSE PATIENTS**

Akinchev AL[1], Romanchishen AF[1], Jakovlev PN[1]

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P181 **COEXISTING KIKUCHI-FUJIMOTO DISEASE AND HASHIMOTO THYROIDITIS IN A YOUNG WOMAN - A CASE REPORT**

Konturek A[1], Barczyński M[1], Stopa M[1], Wierzchowski W[2], Nowak W[1]

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P182 **OUTCOME OF RADIOIODINE THERAPY IN AUTONOMOUS FUNCTIONING THYROID NODULES - A STUDY GROUP**

Ursu HI[1], Podia Igna C[2], Galoiu S[1], Purice M[3], Goldstein A[3]

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P183 **INCREASING RADIOIODINE UPTAKE FOR THE TREATMENT OF NON AUTOIMMUNE MULTINODULAR GOITER**

Pitoia F[1], Abelleira E[1], Salvai ME[1], Niepomniszcze H[1]

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P184 **HIGH RATE OF THYROID CANCER IN PATIENTS WITH THYROGLOSSAL DUCT CYST CARCINOMAS: A CASE SERIES**

Mathiopoulou L[1], Iliadou PK[1], Doumala E[1], Chrisoulidou A[1], Boudina M[1], Pazaitou-Panayiotou K[1]

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P185 **STUDY OF MOLECULAR ALTERATIONS IN SDHB, SDHD AND VHL GENES IN FETAL ADENOMAS**

Vinagre J[1,2,3], Alvelos MI[1,4], Castro P[1,3], Lima J[1,3], Máximo V[1,3], Soares P[1,3], Sobrinho-Simões M[1,3,5]

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PO18 Imaging in Thyroidology

Chair: *Murat Erdogan* (Ankara, Turkey)

P186 **REAL-TIME, HIGH-RESOLUTION ULTRASONOGRAPHY OF THE VOCAL FOLDS IN PATIENTS BEFORE AND AFTER THYROID SURGERY - ADVANTAGES AND DISADVANTAGES**

Dedecjus M[1], Adamczewski Z[2], Brzezinski J[1], Lewinski A[2]

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P187 **USEFULNESS OF REAL-TIME DYNAMIC SONOELASTOGRAPHY IN NON-INVASIVE DIFFERENTIATION OF BENIGN AND MALIGNANT THYROID AND PARATHYROID LESIONS**

Ruchala M[1], Szczepanek E[1], Stangierski A[1], Gurgul E[1], Kilinska L[1], Biczysko M[2], Stawny B[2], Moczko J[3], Drews M[2], Sowinski J[1]

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P188 **DO ULTRASOUND AND ELASTOGRAPHIC PATTERNS OF THYROID CARCINOMAS VARY WITH THEIR SIZE?**

Russ G[1], Rouxel A[1], Bienvenu-Perrard M[1], Bigorgne C[1], Royer B[1]

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P189 **EMPIRIC HIGH DOSE IODINE THERAPY IN THE ERA OF FDG PET/CT: IS IT STILL USEFULL?**

Leboulleux S[1], El Bez I[1], Borget I[1], Déandreis D[1], Elleuch M[1], Chougnet C[1], Mirghani H[1], Hartl D[1], Lumbroso J[1], Baudin E[1], Schlumberger M[1]

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P190 **EVALUATION OF THYROID UPTAKE IDENTIFIED BY 18-F-FDG PET/CT FOR NON-THYROIDAL ILLNESS**

Köse N[1], Ünlütürk U[1], Kanık Özkan E[2], Demir Ö[1], Aras G[2], Erdoğan MF[1]

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P191 **PROSPECTIVE ASSESSMENT OF HARMONIC TISSUE DOPPLER IMAGING ELASTOGRAPHY IN THYROID FOCAL LESIONS**

Adamczewski Z[1], Krawczyk-Rusiecka K[1], Dedecjus M[2], Brzeziński J[2], Lewiński A[1]

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P192 **NOVEL APPLICATION OF SONOELASTOGRAPHY IN DIAGNOSTICS AND TREATMENT MONITORING OF DE QUERVAIN THYROIDITIS**

Szczepanek E[1], Ruchala M[1], Zybek A[1], Czarnywojtek A[1], Moczko J[2], Sowinski J[1]

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P193 **THE VALUE OF SPECT/ CT EXAMINATIONS FOR THE DETECTION OF THYROID FOCAL LESIONS AND RETROSTERNAL GOITER**

Listewnik MH[1], Birkenfeld B[1], Piwowarska-Bilska H[1], Niedzialkowska K[2], Wieliczko W[3], Zorga P[2]

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P194 **CAN WE USE TC-99M MIBI SCINTIGRAPHY FOR THE DIFFERENTIATION OF MALIGNANT AND BENIGN THYROID NODULES?**

Caglar M[1], Akca CK[2], Tezel G[3]

[1]Hacettepe University, Ankara, Turkey, [2]Hacettepe University, Nuclear Medicine, Ankara, Turkey, [3]Hacettepe University, Pathology, Ankara, Turkey

P195 **THE COMPARISON OF TC-99M AND I-123 UPTAKE IN PATIENTS WITH THYROID AUTONOMOUS TISSUE**

Zaletel K[1], Zaveljcina J[1], Gaberšček S[1], Pirnat E[1], Hojker S[1]
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P196 **SOLITARY THYROID NODULES INCIDENTALLY DETECTED BY PET/CT**

Chaushev B[1], Hristozov K[2], Klisarova A[3], Bochev P[3], Krasnaliev I[4], Radev R[5], Nenkov R[5], Dancheva J[3], Siderova M[2]
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P197 **THE ROLE OF THE CONTRAST ENHANCED ECHOGRAPHY IN THE DIAGNOSIS OF THYROID NODULES**

Melle G[1], Orlandi D[2], Monti E[1], Accornero M[1], Turtulici G[2], Giusti M[1]
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P198 **THE ANALYSIS OF THYROID ULTRASOUND ECHOGENICITY IN THE PATIENTS WITH HASHIMOTO´S DISEASE**

Zieleżnik W[1], Małyszek-Tumidajewicz J[1], Stęchły T[2], Stępień B[1], Wójcik W[3], Owczarek A[4]
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P199 **IS SUBTRACTION PROTOCOL FOR PARATHYROID HYPERTHYROIDISM NOT MORE USEFUL IN SPECT/CT ERA?**

Listewnik MH[1], Birkenfeld B[1], Ostrowski M[2], Sulikowski T[2], Borowiecki A[3], Piwowarska-Bilska H[1], Zorga P[4]
[1]Pomeranian Medical University, Nuclear Medicine Department, Szczecin, Poland, [2]Pomeranian Medical University, Clinic of General and Transplantation Surgery, Szczecin, Poland, [3]Pomeranian Medical University, Division of Plastic Surgery, Endocrine and General, Szczecin, Poland, [4]Autonomous Public Clinical Hospital No. 1, Nuclear Medicine Department, Szczecin, Poland

P200 **UTILITY OF SERUM THYROGLOBULIN, TC-99M THYROID SCINTIGRAPHY, NECK I-131 UPTAKE AND ULTRASONOGRAPHY FOR THE EVALUATION OF PATIENTS WITH THYROID CANCER AFTER SURGERY**

Caglar M[1], Temelli B[2], Tuncel M[2]
[1]Hacettepe University, Ankara, Turkey, [2]Hacettepe University, Nuclear Medicine, Ankara, Turkey

P201 **FDG PET/CT IN DIAGNOSTICS OF DIFFERENTIATED THYROID CANCER (DTC)**

Kukulska A[1], Krajewska J[1], Paliczka-Cieslik E[1], d'Amico A[1], Kalemba M[1], Puch Z[1], Roskosz J[1]
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PO19 Trace Elements and Environment

Chair: *Nils Knudsen* (Smorum, Denmark)

P202 **EFFECT OF HAND SCRUBBING ON URINARY IODINE CONCENTRATIONS OF OPERATING ROOM STAFF**

Erdoğan MF[1], Tatar FA[2], Ünlütürk U[1], Cin N[2], Başkal N[1]
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P203 **MULTIPLE PESTICIDES - ENDOCRINE DISRUPTORS-EXPOSURE OF GREENHOUSES WORKERS AND THYROID PARAMETERS AS WELL AS MARKERS OF THYROID AUTOIMMUNITY**

Simescu M[1], Podia Igna C[2], Cargheorgheopol A[3], Ion I[4], Ion A[4], Neagu C[5], Negru M[5], Pribu M[5], Kochanska Dziurowicz A[6]
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P204 **RECOMMENDED NUMBER OF SAMPLES FOR MONITORING OF IODINE NUTRITION AFTER IODINE SUPPLEMENTATION**

Karmisholt J[1,2], Laurberg P[1], Andersen S[1]
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P205 **VARIATION IN THYROID FUNCTION TESTS AMONG INUIT AND CAUCASIANS IN LIVING IN AN ARCTIC ENVIRONMENT**

Andersen S[1], Laurberg P[2]
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P206 **LOW URINE IODINE CONCENTRATION IN MIDDLE AGE WOMEN IN THE NORTHERN SWEDEN**

Nyström HF[1], Bergdahl I[2], Hulthén L[3], Eliasson M[4]
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P207 **EFFECTS OF SELENIUM SUPPLEMENTATION ON TPOAB IN ACTIVE AUTOIMMUNE THYROIDITIS**

Ciric S[1]
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P208 **TIROKID STUDY: STATUS OF IODINE NUTRITION OF SPANISH INFANTS (PRELIMINARY RESULTS)**

Vila L[1], Orellana M[2], Guerrero E[3], Bandrés O[4], Muñoz Z[5], Menéndez E[6], Villar A[7], Moll G[8], Vich F[8], Santiago P[9], López-Guzmán A[10], Sergio D[11], Torres Y[1], Tortosa F[12], Serra-Prat M[13], Iodine Deficiency and Thyroid Disfunction Working Group of SEEN
[1]Hospital Moisès Broggi, Endocrinology and Nutrition, Sant Joan Despí, Spain, [2]Merck-Serono, ME & CMC, Madrid, Spain, [3]Hospital Río Carrión, Palencia, Spain, [4]Hospital Royo Villanova, Endocrinology and Diabetes, Zaragoza, Spain, [5]Departamento de Salud y Consumo (Aragón), Zona Básica de Salud, Ariza, Spain, [6]Hospital Central de Asturias, Endocrinology and Nutrition, Oviedo, Spain, [7]Hospital Clínico Universitario de Valladolid, Endocrinology and Nutrition, Valladolid, Spain, [8]Hospital d'Inca, Endocrinology and Nutrition, Inca, Spain, [9]Complejo Hospitalario Ciudad de Jaén, Endocrinology and Nutrition, Jaén, Spain, [10]Hospital de Ávila, Endocrinology and Nutrition, Ávila, Spain, [11]Fundación Hospital Alcorcón, Endocrinology and Nutrition, Alcorcón, Spain, [12]Hospital de la Vall d'Hebró, Endocrinology and Nutrition, Barcelona, Spain, [13]Hospital de Mataró, Research Unit, Mataró, Spain

P209 **ASSESMENT OF IODINE AND SELENIUM SUPPLEMENTATION IN DIFFERENT REGIONS OF BELARUS**

Mityukova T[1], Drozd V[1], Leonova T[1], Lushchyk M[1], Platonova T[1], Tuzova A[1], Akulevich N[1]
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P210 **THE ACTIVITY OF NA, K-ATPASE OF PLASMA MEMBRANES OF LIVER, KIDNEY, AND HEAD OF RAT BRAIN WITH DIFFERENT IODINE IN THE DIET**

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P211 **THYROID FUNCTION- AND SELENOPROTEIN P STATUS IN PATIENTS WITH CHRONIC KIDNEY DISEASE**

Reinhardt W[1,2], Dolff S[3], Broecker-Preuß M[2], Witzke O[3], Mann K[2], Hoeg A[4], Schomburg L[4], Koehrle J[4]
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Poster Exhibition Area
12.00–13.00
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PO20 Thyroid Cancer (clinical) 7

Chair: *Clive Harmer* (London, UK)

P212 **THE USE OF AN ULTRASENSITIVE THYROGLOBULIN ASSAY IN THE FOLLOW-UP OF PATIENTS WITH THYROID CARCINOMA REQUIRES A REVIEW OF ITS CUT-OFF**

Valerio L[1], Taddei D[1], Nencetti C[1], Molinaro E[1], Agate L[1], Lorusso L[1], Bottici V[1], Viola D[1], Vitti P[1], Pinchera A[1], Grasso L[1], Elisei R[1]
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P213 **THORACIC 131-I UPTAKE AFTER PREVIOUS PNEUMONECTOMY IN PATIENTS TREATED FOR DIFFERENTIATED THYROID CANCER**

Nascimento C[1], Bridji B[2], Dejax C[3], Schlumberger M[1], Leboulleux S[1]
[1]Institut Gustave Roussy, Villejuif, France, [2]Centre René Gauducheau, Saint Herblain, France, [3]Centre Jean Perrin, Clermont-Ferrand, France

P214 **THE ADDITIONAL VALUE OF A SECOND HIGH-DOSE 131I THERAPY IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA WITH THYROGLOBULIN ANTIBODIES**

Klein Hesselink MS[1], Muller Kobold AC[2], Van der Horst-Shrivers ANA[1], Brouwers AH[3], Plukker JTM[4], Sluiter WJ[1], Links TP[1]
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P215 **OUTCOMES FOR PATIENTS WITH ANAPLASTIC THYROID CARCINOMA RECEIVING DIFFERENT TREATMENT MODALITIES**

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P216 **COMPARISON OF PROCALCITONIN STIMULATION TESTS WITH PENTAGASTRIN (PG), AND HIGH-DOSE CALCIUM IN PATIENTS WITH MEDULLARY THYROID CARCINOMA (MTC)**

Kowalska A[1], Pałyga I[1], Gąsior-Perczak DM[1], Antczak G[2], Góźdź S[3]
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P217 **CEREBRAL FOLLICULAR THYROID CANCER METASTASIS. WHEN NEUROSURGERY?**

Badiu C[1], Ruff R[1], Ciubotaru V[2], Terzea D[3], Goldstein A[4]
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P218 **ION- IS ABLATIVE RADIO-IODINE NECESSARY FOR LOW RISK DIFFERENTIATED THYROID CANCER PATIENTS?**

Moss L[1], Harmer C[2], Clarke S[3], Evans C[4], Harrison B[5], Gerrard G[6], Hyer S[7], Farnell K[8], Johnson S[9], Lemon C[10], Lunt C[11], Newbold K[12], Nicol A[13], Nutting C[12], Reed N[14], Stephenson T[5], Wadlsey J[15], Watkinson J[16], Yap B[17], Hackshaw A[11], Mallick U[18]
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P219 **BURKITT LYMPHOMA OF THE THYROID IN A PATIENT WITH AUTOIMMUNE THYROIDITIS**

Trifanescu RA[1,2], Ioachim D[3], Dobrea C[4], Vasilica M[4], Gherlan I[2], Dumitrascu A[2], Poiana C[1,2], Coculescu M[1,2]

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P220 **INFLUENCE OF SMOKING AND ALCOHOL ON SERUM CALCITONIN VALUES**

Trifina E[1], Hajos F[1], Ubl P[1], Hoffmann P[1], Dudczak R[1], Li S[1]

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P221 **TUMOR FORMATION OF THE THYROID GLAND ON THE BASE OF AUTOIMMUNE THYREODITIS**

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P222 **DELAYED TRACHEAL NARROWING SPECULATED TO BE DEVELOPED AFTER ENDOTRACHEAL INTUBATION INJURY IN ROBOT-ASSISTED THYROIDECTOMY**

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PO21 Thyroid Cancer (clinical) 8

Chair: *Nese Colak Ozbey* (Istanbul, Turkey)

P223 **SALVAGE TOTAL LARYNGECTOMY FOR INVASIVE THYROID CANCER; TWO CASE REPORT**

Tomemori T[1], Watanabe R[1], Arai T[1], Kusi M[1], Kujirai K[2], Kondo N[1], Hiruma K[1], Mitsuhashi T[1]

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P224 **DIAGNOSIS OF THYROID CARCINOMA IN A TERCIARY CENTER OVER A PERIOD OF FIFTEEN YEARS**

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P225 **FREQUENCIES AND LEVELS OF ANTI-THYROGLOBULIN ANTIBODY OF PATIENTS WITH I-131 RADIOACTIVE IODINE TREATMENT FOR THYROID CANCER METASTASES**

Kawabe J[1], Higashiyama S[1], Kawamura E[1], Yoshida A[1], Kotani K[1], Kawajiri N[2], Onoda N[2], Shiomi S[1]

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P226 **A CASE OF APLASTIC ANEMIA FOLLOWING THE RADIOACTIVE IODINE THERAPY FOR THYROID CARCINOMA**

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P227 **MANAGEMENT OF ANAPLASTIC THYROID CARCINOMA IN OUR HOSPITAL**

Watanabe R[1], Tomemori T[1], Arai T[1], Kusi M[1], Kujirai K[2], Kondo N[1], Hiruma K[1], Mitsuhashi T[1]

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P228 **BONE METASTASES FROM FOLLICULAR THYROID CARCINOMA. CASE REPORT**

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P229 **MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES TREATMENT: ONE CENTER EXPERIENCE**

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P230 **RADIOIODINE REFRACTORY, POORLY DIFFERENTIATED METASTATIC FOLLICULAR CARCINOMA OF THE THYROID**

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P231 **PARATHYROID CARCINOMA WITH LUNG METASTASIS IN A FOURTEEN-YEAR-OLD GIRL**

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P232 **THYROID DYSFUNCTION IN NON-THYROID CANCER PATIENTS TREATED WITH SUNITINIB**

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PO22 Thyroid Cancer (basic/translational) 3

Chair: *Christine Spitzweg* (Munich, Germany)

P233 **EXPRESSION OF APOPTOSIS-RELATED MOLECULES (GALECTIN-3, BCL-2, BAX AND SURVIVIN) AND APOPTOTIC CELL DEATH IN PAPILLARY VERSUS ANAPLASTIC THYROID CARCINOMA**

Cvejic D[1], Selemetjev S[1], Paunovic I[2], Tatic S[3], Savin S[1]
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P234 **CROSSTALK BETWEEN THE TRANSCRIPTION FACTORS: ZEB1 AND TWIST AND THE TRANSCRIPTIONAL REGULATION OF E-CADHERIN AND SNAIL1 GENES USING A FOLLICULAR TUMOUR CELL LINE WRO ENRICHED FOR ABCG2/BCRP1 TRANSPORTER**

Mato E[1], González C[2], Lerma E[3], Bell O[1], Moral A[4], Pérez JI[4], de Leiva A[1,2]
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P235 **HYPOXIA EFFECTS INDUCED BY $COCL_2$ ON HUMAN THYROID CARCINOMA FTC-133 CELLS**

Bao J[1], Yu H[1], Zhang L[1], Song F[2], Tan C[1], Lin X[1], Zhang C[2]
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P236 **RET/PTC REARRANGEMENTS IN FOLLICULAR HüRTHLE CELL CARCINOMAS**

de Vries MM[1,2], Celestino R[2,3,4], Castro P[2], Eloy C[2,4,5], Máximo V[2,4], van der Wal JE[6], Plukker JT[7], Links TP[8], Hofstra RM[9], Soares P[2,4], Sobrinho-Simões M[2,4,5]
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P237 **SCREENING OF THE RET PROTO-ONCOGENE IN CZECH PATIENTS WITH MEDULLARY THYROID CARCINOMA**

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P238 **VARIABLE MODULATION BY CYTOKINES AND THIAZOLIDINEDIONES OF THE PROTOTYPE TH1 CHEMOKINE CXCL10 IN ANAPLASTIC THYROID CANCER**

Fallahi P[1], Ferrari SM[1], Galleri D[2], Piaggi S[3], Corrado A[1], Di Domenicantonio A[1], Miccoli P[2], Antonelli A[1]
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P239 **ANTITUMOR EFFECTS OF NOVEL AGENTS IN HUMAN NEUROENDOCRINE TUMOR CELLS: AN IN VITRO STUDY**

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P240 **ESTROGEN-RELATED RECEPTOR ALPHA MODULATES A KEY ENZYME OF GLYCOLYSIS : THE LACTATE DEHYDROGENASE**

Mirebeau-Prunier D[1,2], Le Pennec S[1], Jacques C[1], Fontaine J[3], Gueguen N[2], Donnart A[4], Bouzamondo N[2], Malthiery Y[1,2], Savagner F[1,2]

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P241 **ROLE OF GH AND IGF-I ON ONCOGENESIS OF PAPILLARY THYROID CARCINOMA**

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PO23 Graves' Hyperthyroidism 3

Chair: *Stig Andersen* (Aalborg, Denmark)

P242 **LONG TERM OUTCOMES OF TREATMENT WITH ANTI THYROID DRUGS, RADIOACTIVE IODINE AND SURGERY IN HYPERTHYROID PATIENTS**

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P243 **THE CLINICAL IMPORTANCE OF SUPERIOR THYROIDAL ARTERY MEAN PEAK SYSTOLIC VELOCITY IN DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS IN KOREA**

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P244 **CHARACTERISTICS OF THE CARDIOVASCULAR SYSTEM AND MICROCIRCULATION IN PATIENTS WITH UNCOMPENSATED THYROTOXICOSIS**

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P245 **URGENT THYROIDECTOMY IN A PATIENT WITH SEVERE AMIODARONE-INDUCED HYPERTHYROIDISM**

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P246 **TOWARDS EVIDENCE-BASED DOSAGE OF ANTITHYROID DRUGS AND OF THYROXINE IN GRAVES' PATIENTS WHO DISPLAY A SUPPRESSED TSH-LEVEL - THE CASE FOR A TREATMENT GUIDELINE**

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P247 **HOW WOULD YOU TREAT A PATIENT WITH SEVERE GRAVES DISEASE WHO IS RESISTANT TO ANTITHYROID DRUGS?**

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P248 **AN UNUSUAL PRESENTATION OF TSH-SECRETING ADENOMA**

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P249 **A SEVERE GRAVES' DISEASE COEXISTING WITH AN UNUSUAL COURSE OF DIABETES: 30-MONTH FOLLOW-UP**

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P250 **THYROID BLOOD FLOW STUDY MAY AVOID EARLY GRAVES´ DISEASE RELAPSE AFTER ANTITHYROID DRUG WITHDRAWAL.**

Monpeyssen H[1], Tramalloni J[1], Correas JM[1], Poiree S[1], Hélénon O[1]

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P251 **THYROID DYSFUNCTION AND TREATMENT STRATEGY IN PATIENTS ON AMIODARONE THERAPY**

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P252 **FEATURES OF THYROTROPINOMA IN CHILD**

Jercalau S[1], Stoica S[2], Mogos V[3], Spatarelu M[4], Badiu C[5]

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PO24 Thyroid Hormone and Bone

Chair: *Peter Smyth* (Dublin, Ireland)

P253 **OSTEOPROTEGERIN AND RANKL SERUM LEVELS IN YOUNG PATIENTS WITH GRAVE'S DISEASE**

Shepelkevich AP[1], Kholodova HA[1], Korytko SS[2], Leonava TA[3], Tolkachev JV[4]

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P254 **BONE MINERAL DENSITY, BONE MARKERS IN PATIENTS WITH HYPERTHYROIDISM**

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P255 **THYROID DYSFUNCTION AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN**

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P256 **COULD TSH RECEPTOR ANTIBODIES BE PROTECTIVE FOR THE BONE IN PRE- AND POSTMENOPAUSAL WOMEN WITH GRAVES' DISEASE AND GRAVES' ORBITOPATHY?**

Siderova MV[1], Hristozov KH[1], Bocheva YD[2], Petrova MP[1], Boyadzhieva MB[1]

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P257 **BONE METABOLISM IN FEMALE PATIENTS WITH WELL-DIFFERENTIATED THYROID CARCINOMA AFTER CHERNOBYL**

Leonava T[1], Mityukova T[1], Shepelkevich A[2], Akulevich N[1], Lushchyk M[1], Platonova T[1], Tuzava H[1], Drozd V[1]

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P258 **THE BONE PARAMETERS ANALYZE IN PATIENTS WITH LONG TERM LEVOTHYROXINE THERAPY**

Carsote M[1], Ene C[2], Geleriu A[2], Chirita C[2], Trifanescu R[1,2], Radoi V[1], Gruia A[3], Voicu G[2], Poiana C[1,2], Coculescu M[1,2]

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P259 **BONE MINERAL DENSITY (BMD) IN ELDERLY EUTHYROID**

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P260 **ADVANCED PRIMARY BONE HYPERPARATHYROIDISM AS A RESULTS OF DIAGNOSTIC MISTAKES**

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P261 **SERUM OSTEOPROTEGERIN LEVELS IN HYPERTHYROIDISM**

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PO25 Hypothyroidism 2

Chair: *Agathokles Tsatsoulis* (Joannina, Greece)

P262 **SERUM FREE THYROXINE TO FREE TRIIODOTHYRONINE RATIO AS A USEFUL TOOL IN THE DIAGNOSTICS OF THYROID DYSFUNCTION**

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P263 **NEPHROTIC SYNDROME ASSOCIATED WITH HASHIMOTO'S THYROIDITIS**

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P264 **DECREASED HUMAN ERYTHROCYTE DIPHOSPHOGLYCERATE MUTASE (DPGM) CONCENTRATIONS IN HYPOTHYROIDISM**

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P265 **RISK FACTORS AND CLINICAL FEATURES OF FAMILIAL AUTOIMMUNE THYROID DISEASE**

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P266 **BILATERAL SPONTANEOUS ANTEROLATERAL COMPARTMENT SYNDROME IN A NEWLY DIAGNOSED HYPOTHYROID PATIENT**

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P267 **QUALITY OF LIFE OF PATIENTS WITH POSTRADIATION HYPOTHYROIDISM**

Dreval A[1], Nechaeva O[1], Shestakova T[1], Mamedova T[1], Komerdus I[1], Chikh I[1]
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P268 **A CASE OF CONGENITAL HYPOTHYROIDISM WITH HIRSCHSPRUNG´S DISEASE: AN UNUSUAL ASSOCIATION**

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P269 **STUDIES ON THE EFFECT OF ALPHA - LIPOIC ACID IN THE TREATMENT OF HYPOTHYROIDISM**

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P270 **THE TSH - THYROID ANTIBODIES ANALYSE IN 1000 PATIENTS WITH CHRONIC THYROIDITIS: A RETROSPECTIVE STUDY**

Peretianu D[1], Carsote M[2], Goldstein A[3], Trifanescu R[2,3], Staicu D[1], Clodeanu A[1], Poiana C[2,3]
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P271 **SUNITINIB-INDUCED HYPOTHYROIDISM**

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P272 **EVALUATION OF THE PSYCHOEMOTIONAL STATUS OF PATIENTS AFTER RADIOIODINETHERAPY FOR GD BY CATAMNESIS DATA**

Nechaeva O[1], Dreval A[1], Shestakova T[1], Chikh I[1], Komerdus I[1], Mamedova T[1]
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P273 **ELEVATED TSH IN A NEONATE; DRUG INDUCED OR DISEASE MEDIATED?**

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P274 **USE OF HPLC - MASS SPECTROMETRY FOR T4, T3 AND RT3 ANALYSIS AS COMPARED WITH IMMUNOASSAYS**

Badiu C[1], Jercalau S[2], Alexiu F[3], Purice M[3], Silvestro L[4]
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P275 **THYROID DISORDERS IN ADULT POPULATION OF KRAKOW - THE PILOT STUDY**

Buziak-Bereza M[1], Trofimiuk M[1], Hubalewska-Dydejczyk A[1]
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PO26 Goiter/Nodules 2

Chair: *Hans Graf* (Merces, Brazil)

P276 **THYROID NODULES IN PATIENTS WITH MALIGNANCIES**

Poiana C[1,2], Carsote M[1], Trifanescu RA[1,2], Ion OG[3], Ioachim D[2], Goldstein A[2]
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P277 **LATE FOLLOW UP RESULTS AFTER RADIOIODINE AND SURGERY TREATMENT OF TOXIC THYROID ADENOMA**

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P278 **EVALUATION OF THYROID SURGERY: 10 YEARS OF EXPERIENCE IN A MILITARY HOSPITAL**

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P279 **PRE SURGICAL THYROGLOBULIN DETERMINATION AS A MALIGNANT MARKER IN THYROID NODULES**

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P280 **RIEDEL´S THYROIDITIS - A CASE REPORT**

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P281 **A CASE OF THYROID LIPOMATOSIS**

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P282 **TEENAGE GIRLS ENDEMIC GOITER AND FUNCTION OF THE THYROID GLAND AGAINST THE LATENT IRON DEFICIENCY**

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P283 **RETROSPECTIVE ANALYSIS OF 728 CASES OF THYROID PATHOLOGY DATA IN BAOTOU**

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P284 **HISTOLOGICAL AND HISTOMETRICAL CHANGES OF OSTRICH THYROID GLAND DURING SUMMER AND WINTER SEASONS IN TEHRAN-IRAN**

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P285 **THE FREQUENCY OF MIXED PATHOLOGY IN NODULAR GOITER**

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P286 **TGF-β_1 IN THE EXPRESSION OF THYROID DISEASES AND ITS CLINICAL SIGNIFICANCE**

Zhang Y[1], Wei F[1], Ii J[1], Yu Y[2], Chai H[2], Yan B[2], Ji J[2], Fu F[2]

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P287 **ROSUVASTATIN TREATMENT REDUCES THE MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS IN THYROIDS OF AGED MICE**

Werion A[1], Senou M[1], de Bournonville M[1], Many M-C[2]

[1]UCL, Brussels, Belgium, [2]UCL, MORF, Brussels, Belgium

P288 **THYROID TUBERCULOSIS: A CASE SERIES AND REVIEW OF LITERATURE**

Majid U[1], Islam NU[2]

[1]Memon Medical Institute, Medicine, Karachi, Pakistan, [2]Aga Khan University Hospital, Medicine, Karachi, Pakistan

P289 **THYROID FOLLICLE SIZE IS DECREASED NOT ONLY IN AMES DWARF BUT ALSO IN GROWTH HORMONE RECEPTOR KNOCKOUT (GHRKO) MICE**

Gesing A[1,2], Masternak MM[2,3], Lewinski A[4,5], Karbownik-Lewinska M[1,5], Bartke A[2]

[1]Medical University of Lodz, Department of Oncological Endocrinology, Lodz, Poland, [2]Southern Illinois University School of Medicine, Department of Internal Medicine, Geriatrics Research, Springfield, IL, United States, [3]Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland, [4]Medical University of Lodz, Department of Endocrinology and Metabolic Diseases, Lodz, Poland, [5]Polish Mother's Memorial Hospital - Research Institute, Department of Endocrinology and Metabolic Diseases, Lodz, Poland

PO27 Genetics of Thyroid Disease

Chair: *Thomas Brix* (Odense, Denmark)

P290 **THE GENETIC DETERMINANTS OF THYROID FUNCTION MAY BE DIFFERENT BETWEEN CHILDREN AND ADULTS**

Taylor PN[1], Sayers A[2], Evans D[3], Dayan CM[1]

[1]University of Cardiff, Centre for Diabetes and Endocrine Sciences, Cardiff, United Kingdom, [2]University of Bristol, Avon Orthopaedic Centre, Bristol, United Kingdom, [3]University of Bristol, MRC CAiTE, Bristol, United Kingdom

P291 **ASSOCIATION OF THE TYPE 2 DEIODINASE GENE POLYMORPHISM AND THE RISK OF RECURRENT DEPRESSIVE DISORDER**

Gałecka E[1], Gałecki P[2], Szemraj J[3], Lewiński A[1,4]

[1]Medical University of Łódź, Department of Endocrinology and Metabolic Diseases, Łódź, Poland, [2]Medical University of Łódź, Department of Adult Psychiatry, Łódź, Poland, [3]Medical University of Łódź, Department of Medical Biochemistry, Łódź, Poland, [4]Polish Mother's Memorial Hospital – Research Institute, Department of Endocrinology and Metabolic Diseases, Łódź, Poland

P292 **EXPRESSION OF PHOSPHOINOSITIDE 3-KINASE SUBUNITS IN CHRONIC THYROIDITIS**

Wojciechowska-Durczyńska K[1,2], Krawczyk-Rusiecka K[1,2], Cyniak-Magierska A[1,2], Zygmunt A[1,2], Gałecka E[1], Lewiński A[1,2]

[1]Medical University of Lodz, Department of Endocrinology and Metabolic Diseases, Lodz, Poland, [2]Polish Mother's Memorial Hospital - Research Institute, Department of Endocrinology and Metabolic Diseases, Lodz, Poland

P293 **CONGENITAL HYPOTHYROIDISM (CH) DUE TO A NOVEL HOMOZIGOUS MUTATION IN THYROGLOBULIN (TG) GENE**

Bagattini B[1], Montanelli L[1], Ferrarini E[1], De Marco G[1], Agretti P[1], Di Cosmo C[1], Dimida A[1], Vitti P[1], Pinchera A[1], Tonacchera M[1]
[1]University of Pisa, Department of Endocrinology and Metabolism, Pisa, Italy

P294 **ASSOCIATION OF PAPILLARY THYROID CANCER WITH FOXE1 GENE IN POLISH POPULATION**

Jarząb B[1], Kula D[1], Puch Z[1], Kalemba M[1], Handkiewicz-Junak D[1], Kowalska M[1], Tyszkiewicz T[1], Kowal M[1], Polańska J[2]
[1]Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Nuclear Medicine and Endocrine Oncology Department, Gliwice, Poland, [2]Silesian University of Technology, Institute of Automatic Control, Gliwice, Poland

P295 **CORRELATION BETWEEN POLYMORPHISM OF TRAIL AND TGF-β1 GENES AND NODULAR THYROID DISEASE**

Wei F[1], Zhang Y[1], Li J[1], Su R[1], Ren L[1], Wei C[1], Qin W[2]
[1]The First Affiliated Hospital, Bao Tou Medical College, Inner Mongolia Science & Technology University, Department of Endocrinology, Bao Tou, China, [2]The First Affiliated Hospital, Bao Tou Medical College, Inner Mongolia Science & Technology University, Bao Tou, China

P296 **DETECTION OF NOVEL GENETIC CHANGES IN THE RAS GENES IN PAPILLARY THYROID CARCINOMA**

Sykorova V[1], Vaclavikova E[1], Dvorakova S[1], Ryska A[2], Laco J[2], Kodetova D[3], Kodet R[3], Duskova J[4], Astl J[5], Betka J[5], Hoch J[6], Smutny S[6], Cap J[7], Vlcek P[8], Lukas J[9], Bendlova B[1]
[1]Institute of Endocrinology, Department of Molecular Endocrinology, Prague, Czech Republic, [2]Charles University Faculty of Medicine and University Hospital, Fingerland Department of Pathology, Hradec Kralove, Czech Republic, [3]2nd Faculty of Medicine and Faculty Hospital Motol, Department of Pathology and Molecular Medicine, Prague, Czech Republic, [4]1st Faculty of Medicine, Charles University, Institute of Pathology, Prague, Czech Republic, [5]1st Faculty of Medicine and Faculty Hospital Motol, Charles University, Department of Otorhinolaryngology and Head and Neck Surgery, Prague, Czech Republic, [6]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Surgery, Prague, Czech Republic, [7]Charles University Faculty of Medicine and University Hospital, 2nd Department of Internal Medicine, Hradec Kralove, Czech Republic, [8]2nd Faculty of Medicine, Charles University and Hospital Motol, Department of Nuclear Medicine and Endocrinology, Prague, Czech Republic, [9]Na Homolce Hospital, Department of Otorhinolaryngology and Head and Neck Surgery, Prague, Czech Republic

P297 **ADRA2B GENE INSERTION/DELETION POLYMORPHISM AND GRAVE´S DISEASE IN POPULATION OF NOVOSIBIRSK**

Maksimov V[1], Rymar O[1], Mustafina S[1], Mikitinskaya A[1], Ivasko V[1]
[1]Institute of Internal Medicine SB RAMS, Novosibirsk, Russian Federation

PO28 Thyroid Cell Biology and Thyroid Hormone Action

Chair: *Mikael Nilsson* (Göteborg, Sweden)

P298 **RELATIVE QUANTIFICATION OF CYCLOOXYGENASE-2 GENE EXPRESSION LEVEL IN CHRONIC AUTOIMMUNE THYROIDITIS, PAPILLARY THYROID CARCINOMA AND NON TOXIC NODULAR GOITRE**

Krawczyk-Rusiecka K[1,2], Wojciechowska-Durczynska K[1,2], Adamczewski Z[1,2], Cyniak-Magierska A[1,2], Galecka E[1], Lewinski A[1,2]
[1]Medical University of Lodz, Department of Endocrinology and Metabolic Diseases, Lodz, Poland, [2]Polish Mother's Memorial Hospital - Research Institute, Lodz, Poland

P299 **THE TRANSCRIPTION FACTOR PAX8 REGULATES SELENOPROTEIN DIO1 EXPRESSION THROUGH ITS BINDING IN THE 3'UTR REGION**

Leoni SG[1], Ruiz-Llorente S[2], Santisteban P[1]
[1]Instituto de Investigaciones Biomedicas Madrid, Departamento de Fisiopatología Endocrina y del Sistema Nervioso, Madrid, Spain, [2]Memorial Sloan-Kettering Cancer Center, New York, United States

P300 **TRIIODOTHYRONINE CAUSES MIGRATION OF COACTIVATOR TRIP-230 FROM GOLGI APPARATUS TO NUCLEUS VIA INTRACELLULAR ACTIVATION OF PI3K KINASE**

Popławski P[1], Wójcicka A[1], Nauman A[1]
[1]The Medical Centre of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland

P301 **MEMBRANE PERMEATION OF DUOX-GENERATED HYDROGEN PEROXIDE AND ITS BIOLOGICAL EFFECTS ON THYROID CELLS**

Lorenz S[1,2], Krohn K[1,2]
[1]Medizinische Fakultät, Universität Leipzig, Med. Klinik III Forschungslabor Endokrinologie, Leipzig, Germany, [2]Medizinische Fakultät, Universität Leipzig, IZKF, Leipzig, Germany

P302 **THYROID HORMONE REGULATION OF APP (β-AMYLOID PRECURSOR PROTEIN) EXPRESSION IN BRAINS AND BRAIN CULTURED CELLS**

Pascual A[1], Contreras-Jurado C[1], Villa A[1]
[1]Instituto de Investigaciones Biomedicas "Alberto Sols" CSIC-UAM, Madrid, Spain

P303 **THE HINGE REGION OF THE THYROTROPIN RECEPTOR STABILIZES LIGAND BINDING AND DETERMINES DIFFERENT SIGNALING PROFILES OF HUMAN AND BOVINE THYROTROPIN**

Jäschke H[1], Schaarschmidt J[1], Günther R[2], Paschke R[1], Müller S[1]
[1]University of Leipzig, Division of Endocrinology and Nephrology, Leipzig, Germany, [2]University of Leipzig, Institute of Biochemistry, Leipzig, Germany

P304 **PROLIFERATION OF RAT THYROCYTES IS ACCOMPANIED BY INCREASED EXPRESSION OF RIBOSOMAL PROTEIN S6 KINASES S6K1 AND S6K2**

Cherednyk O[1], Kukharchuk V[1], Khoruzhenko A[1], Filonenko V[1]
[1]Institute of Molecular Biology and Genetics, Department of Cell Signaling, Kyiv, Ukraine

P305 **T3-LIKE AND NON-T3-LIKE EFFECTS OF TRIAC**

Kersseboom S[1], Visser TJ[1]
[1]Erasmus MC, Internal Medicine, Rotterdam, Netherlands

P306 **IMPLICATION OF PAX8 IN THE CONTROL OF EPITHELIAL CELL POLARIZATION AND FOLLICLE FORMATION**

Koumarianou P[1], Santisteban P[1]
[1]Instituto de Investigaciones Biomédicas "Alberto Sols", Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Madrid, Spain

P307 **DIFFERENCES IN TRANSPORT MECHANISMS AND CELL MEMBRANE TRAFFICKING BETWEEN PRIMARY AND SECONDARY THYROID HORMONE TRANSPORTERS**

Kinne A[1], Krause G[1]
[1]Leibniz-Institut für Molekulare Pharmakologie, Berlin, Germany

P308 **ANALYSIS OF NEW GENES DIRECTLY REGULATED BY FOXE1 IN RAT THYROID CELLS**

Fernandez LP[1], Santisteban P[1]
[1]Instituto de Investigaciones Biomedicas "Alberto Sols" CSIC-UAM, Physiopathology of Endocrine and Nervous System, Madrid, Spain

P309 **EXPRESSION OF *THRA* GENE IN BLOOD MONONUCLEAR CELLS OF LONG-LIVED HUMANS WITH ADEQUATE THYROID STATUS IS SIGNIFICANTLY REDUCED COMPARED TO YOUNGER AGE GROUPS**

Pawlik-Pachucka E[1,2], Polosak J[1], Budzińska M[2], Puzianowska-Kuznicka M[1,2]
[1]Medical Research Center, Polish Academy of Sciences, Department of Human Epigenetics, Warsaw, Poland, [2]Medical Centre of Postgraduate Education, Department of Biochemistry and Molecular Biology, Warsaw, Poland

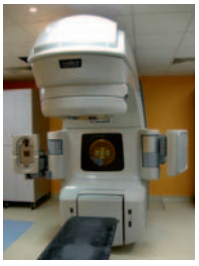
Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch

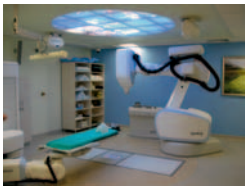
Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology

- **Polish National Cancer Research Institute**
- **founded by Maria Skłodowska-Curie**
- **located in Warszawa, Kraków and Gliwice**

Gliwice Branch is the largest oncology center and cancer research institute in southern Poland, serving the population of 7-10 million people

- **Celebrating this year its 60th anniversary**
- **The largest radiation therapy facilities in Poland, headed by Prof. Bogusław Maciejewski, MD, PhD, and honored with the Gilbert H. Fletcher Medal for contribution to the development of radiotherapy.**
- **Dept. of Nuclear Medicine and Endocrine Oncology is the oldest and the largest multi-disciplinary division of endocrine cancer therapy. Headed by Prof. Barbara Jarząb, is the reference center for thyroid cancer treatment, with approx. 7 000 patients in follow-up.**
- **Large translational and basic molecular biology facilities are applied to accelerate the discoveries in endocrine cancer. Massively parallel sequencing, proteomics, extensive genomic studies from microdissected tumor and transgenic animals are the everyday routine of our research.**





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contact: prof. Barbara Jarząb, bjarzab@io.gliwice.pl , Ms. Emilia Wilk, ewilk@io.gliwice.pl

Jagiellonian University

Jagiellonian University is the oldest institution of higher education in Poland. Established in 1364 by King Casimir III the Great, it is one of the oldest in Europe. Called Studium Generale in its early years, it was modelled after the Universities of Bologna and Padua and was initially composed of three faculties: Liberal Arts, Medicine, and Law. After its restoration in 1400, changes to the Academy's statute made it more resemble the Paris Sorbonne. For over 600 years, many famous Poles and Europeans as Nicolaus Copernicus received their education within the walls of this University.

Today's Jagiellonian University combines tradition with the challenges of the modern world. In compliance with the principles of the Bologna Process, over 50,000 students study in 15 faculties on all three levels of study: Bachelor's, Master's, and Doctoral. The European Credit Transfer and Accumulation System (ECTS) enables students to combine their studies at Jagiellonian University with course-work from other European universities. Teaching staff includes over 3,600 academic instructors, 500 of whom hold the title of Professor. Researchers at Jagiellonian University effectively compete for the grants through European research programs and as many as European Centers of Excellence operate within the University.

Medical College

Faculties of Medicine and Pharmacy were separated from the University in 1949 and formed an autonomous institution, named the Academy of Medicine. In 1993 the Academy of Medicine was reunited with the Jagiellonian University. At present, the Jagiellonian University Medical College consists of three Faculties: Medicine with the Division of Dentistry, Pharmacy with the Division of Medical Analytics and Health Sciences with three Institutes: Nursing and Obstetrics, Public Health, Physio-therapy.

Medical College provides teaching for about 6,000 students and conducts also postgraduate studies and Ph.D. studies in different fields. Over 400 of our students are foreign students of the School of Medicine in English at the Faculty of Medicine which offers the program of medical studies for foreigners from many countries of Europe and other continents.

The School possesses the accreditation of the US Department of Education and the Medical Board of California and offers a curriculum compatible with UE directives. The implementation of ECTS system gives students the opportunity to study in many countries. Alumni of the School find employment in the prestigious hospitals and clinics in their homelands. Medical College has several very active students' organizations (self-governing, sports and scientific) which assemble a vast number of university students.

In the Jagiellonian University Medical College about 1,200 colleagues are employed including 100 titled professors. Medical College cooperates with more than 20 universities from all over the world and the cooperation is focused on joint research, international conferences and the exchange of educational projects, colleagues and students. Students and scientists take part in the international programs Sokrates/Erasmus, Erasmus-Mundus, Leonardo da Vinci, DAAD, Wyszehradzki Fund, UNESCO, 6th and 7th Framework Program UE, EUREKA, COST, Tempus, JRC, E-Ten, e-Content.

Congress General Information

Venue

Auditorium Maximum
of the Jagiellonian University
Krupnicza Str. 33
31-126 Krakow
Poland

Smoking is strictly prohibited in the entire building.

Oral Presentations

All conference rooms are fully equipped with up-to-date presentation systems. Powerpoint is the preferred format for presentations. Presenters must hand over their presentations to the technician in the Speakers Room at least one hour prior to the lecture (not applicable for presenters of the pre-conference). In the media checkpoint, speakers can check their presentation at several working stations.

Poster Displays

Poster boards are 215 cm high and 95 cm wide.
Poster dimensions: 120 cm x 90 cm.
Mounting material will be available on site. Staff will assist you in locating your poster wall and setting up your poster.
Posters should be mounted on the day of the poster discussion session:
PO1–PO115: Sunday 11th September from 8.30 a.m. to 6 p.m.
PO116–PO211: Monday 12th September from 8.30 a.m. to 4 p.m.
PO212–PO309: Tuesday 13th September from 8.30 a.m. to 6 p.m.

Please note that all posters which are not removed will have to be destroyed.

Poster Computer Workstation Display
In order to enable ETA participants access to all posters during the whole meeting, all posters will also be displayed on computer workstations.

Programme Changes

The organisers cannot assume liability for changes in the programme due to external or unforeseen circumstances.

Language

The official Congress language is English. For clinical sessions in Main Hall (Aula Duza) simultaneous translation to Polish is provided.

Name Badges

Entrance to the Congress area will be limited to badge holders only.
If the badge is lost, please contact the Congress registration desk.

Congress Material

The Congress participants who have pre-registered will receive the congress material, together with their name badge from the Pre-Registered desk of the Congress Secretariat.

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Continuing Medical Education

CME points are granted by the European Accreditation Council for Continuing Medical Education (AECCME), an institution of the European Union of Medical Specialists (UEMS), www.uems.net.
Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.
EACCME credits are recognized by the American Medical Association towards the Physician's Recognition Award (PRA). To convert EACCME credit to AMA PRA category 1 credit, contact the AMA.

Visas

A visa may be required by citizens of some Non-European Union countries, please contact your travel agent or the Polish Consulate or Embassy in your country for further advice.
Visas are not required by citizens of the European Union.

Insurance

You are requested to arrange your own health and travel insurance. The Congress organisers take no responsibility for injuries or damages that may occur during the Congress.

Weather

Krakow enjoys a mild continental climate with low humidity. The average temperature in September may vary between 10–20° Celsius, with evening temperatures as low as about 5° Celsius (it may sometimes even drop to 0° Celsius). You may need a raincoat and umbrella.

Air Travel

Krakow's John Paul II International Airport of Balice is situated on the outskirts of the city, 15 km (about 10 miles) from its centre. It has regular direct air connections from and to most major European and American air hubs.

How to get from the Airport to the city centre?

By road:	About 20–30 min. drive to the Krakow city centre. Car rental available 24/7 at the airport.
By bus:	Buses number 192 and 208 connect the airport with the city centre. A detailed bus schedule is available at the Congress Registration Desk and at: www.mpk.krakow.pl
By taxi:	Taxis are available 24/7 from the taxi rank outside the terminal. The journey takes about 20 min. (outside of rush hours) and costs approximately 10–12 €.
By train:	There is a train connection between the Krakow Balice and the Krakow Glowny railway station. The detailed schedule is available at the Registration Desk and at: www.krakowairport.pl. The journey takes about 15 min. and costs 4–6 PLN (1–1,5 €).

Taxi Service

The price of the taxi is approximately 2,8 PLN/km + 7 PLN initial payment. We advise you to use radio-taxi companies, for example MPT +481219191, Barbakan +481219661, or Wawel-Taxi +481219666.

Currency

The local currency, Polish zloty (PLN), is convertible. The exchange rate in Krakow hotels and exchange offices may differ (1 PLN ≈ about 0,25 €; 1 € ≈ about 4 PLN). Please ask about exact rates at the Congress Registration Desk.

Credit Cards

Visa, EC/MC credit cards are accepted in most shops and petrol stations, but American Express and Diners cards only in some of them.

Electricity

The voltage in Poland is 230 V, 50 Hz AC, plugs are European standard. People arriving from the UK will need plug adaptors. US visitors – note change of voltage!

Tipping

Service charges are always included. Extra gratuities are not necessary, but are welcomed. Some 10% is usually expected.

Limited Traffic and Parking Zones

In the centre of Krakow there are 3 limited traffic and parking zones. Parking in these zones requires the payment of a fee. The entrance to the limited traffic and parking zone is announced with a sign (see left). The sign means entrance to a zone where a fee is collected for the vehicle's parking. In this zone it is prohibited to park a vehicle without paying a fee, with the exception of parking vehicles of people or units for whom zero rate has been set and parking of public transport vehicles at specially marked places. Paid parking zone in Krakow is valid on working days from Monday to Friday, from 10 a.m. to 6 p.m., cost 3 PLN per hour.

Car parks in the centre of Krakow:

1. Kopernika street (by Hotel Wyspiański), phone +48 12 422 95 66
2. Westerplatte street 18, phone +48 421 25 60
3. Lubicz street 25, phone +48 501 248 960
4. Biskupi sq, phone +48 607 222 043
5. Underground car park under Na Groblach sq, phone +48 12 292 26 41;
   7 PLN per hour or 66,50 PLN per 24 h
6. Starowiślna street 13/15 (by Pałac Pugetów), phone +48 12 429 43 91;
   4 PLN per hour or 95 PLN per 24 h
7. Galeria Krakowska, phone +48 12 428 99 00
   4 PLN per hour
8. Długa street 72, phone +48 604 077 081
   3,5 PLN per hour or 40 PLN per 24 h

European
Thyroid Journal

Social Programme

Welcome Reception

Sunday, 10th September
19.30 Sukiennice (Cloth Hall) at Main Market Square
Sukiennice (Cloth Hall) built in the 13th century in the centre of Rynek Główny (Main Market Square), enlarged in the Gothic style in the 14th century and remodeled in the mid-16th century in the Renaissance style. It was restored over 1875–1879 and became the city's showpiece facility hosting grand balls and patriotic celebrations. Its location and character made the rooms on the first floor of the Sukiennice a perfect place for the National Museum in Krakow. Initially the Museum shared premises with the Fine Arts Society.
Price per person: included for registered ETA 35th Annual Meeting participants and registered accompanying persons.

ETA Excursion (up to 350 pax)

Monday, 12th September
16:30 bus departure from the main entrance of Auditorium Maximum
Bus arrival to the following hotels: Radisson, Novotel Centrum, Wyspianski, Andels' (the last one is a good place to take a taxi for the participants staying in the hotels out of the city centre)
Reservation online http://www.eta2011.com/p/23/the_wieliczka_salt_mine/ or at the congress Registration Desk (deadline Saturday, 10th September, evening).

Wieliczka Salt Mine - the oldest salt mine in Europe, an impressive underground world of salt lakes, chambers, galleries and a unique Salt Works Museum created by many generations of Polish miners. The underground tourist route goes through galleries and chambers on three levels, with 17th and 19th century chapels and a unique natural crystal cave. In 1978 the Salt Mine was listed by UNESCO as a World Heritage Site.
ETA excursion begins with a nice walk along historic underground salt mine corridors and chambers (wide and high enough for a rather comfortable walk). Our visit will finish with dinner (informal attire) in one of the beautiful salt chambers, some 120 meters underground. The temperature in the Wieliczka Salt Mine is 14° Celsius all year round. Therefore a warm jacket and comfortable walking shoes are recommended.

Price per person: 40 €

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www.karger.com/etj

Gala Dinner

Tuesday, 13th September
20.00 "Pałac Pod Baranami" (Palace under the Rams) on Rynek Główny (Main Market Square 27)
Formal attire
The Gala Dinner of the ETA 35th Annual Meeting will be organized in the Palace "Pod Baranami," (the "Palace under the Rams"), named for the rams decorating its façade. The Palace is on the south corner of the Main Market Square. The Palace's present building was formed out of four adjacent Gothic burghers' houses in the 16th century. At various times it belonged to some of the greatest aristocrats of Poland, including the Ostrowski, Radziwill, Wielkopolski and the Potocki families, the last and present owners. Gothic cross-ribbed vaults are preserved in the cellars. At the turn of the 19th century, the palace was a center of cultural life in the city; today it belongs to the Krakow House of Culture, is home of the legendary cabaret "Piwnica Pod Baranami" and serves as the perfect place to spend the last evening together.

Price per person: 75 €

Auschwitz Memorial Visit*

Sunday, 11th September 14.00–18.30
Tuesday, 13th September 08.30–13.00
Wednesday, 14th September 08.30–13.00
Bus departure from the main entrance of Auditorium Maximum
Online reservation http://eta.mazurkas.pl/pl/auschwitz-memorial or at the Registration Desk

Price per person: 35 €

Tours

*** Reservation and Cancellation Conditions**
Pick-up for all tours is at the congress venue – Auditorium Maximum.
All tours are conducted in English.
Online reservation http://eta.mazurkas.pl/pl/tours or at the Registration Desk
The organizers reserve the right to cancel tours if the minimum number of participants is not reached (please look at the information desk).

Walking Tour of Krakow*

Sunday, 11th September 9.00–11.00
Monday, 12th September 9.00–11.00

The walking tour of Krakow includes all the highlights of the Old Town area that made the city famous. For those who wish to make a short break in the congress hours, the guide will wait at Auditorium Maximum till 09.00. The walk begins at the Barbican and St. Florian's gate, unique masterpieces of 15th century fortifications. Next, down Floriańska Street, we arrive at the spectacular Main Market Square with the Cloth Hall in its centre - a perfect place to buy local souvenirs. In the Main Market square we admire the City Hall Tower, the Romanesque church of St. Adalbert, and St. Mary's Basilica. Inside the Basilica is the famous Gothic altar, a beautiful and unique masterpiece of wooden sculpture made by Veit Stoss. The tour ends at the Collegium Maius, the oldest building of the Jagiellonian University, the Alma Mater of many great scientists including Nicolaus Copernicus.

Price per person: 20 €

Krakow & Wawel Hill Tour*

Monday, 12th September 09.00–13.00
Tuesday, 13th September 14.00–18.00

The guide will take you from Auditorium Maximum. The tour begins at the Jewish District of Kazimierz where one of the largest Jewish communities in Europe lived in the past centuries, to be wiped out by the Nazis. Then a short drive will take you to Wawel Hill to visit the Royal Castle courtyard and the 14th-century Cathedral which witnessed almost all coronations and funerals of the Polish royalty. Leaving Wawel hill you will descend to Kanonicza and Grodzka Streets to reach the Main Market Square - a perfect place for buying local souvenirs, especially in the Cloth Hall which has been the local market place for centuries. The tour will end with a visit to St Mary's Basilica, where the famous Gothic altar sculpted in wood by Veit Stoss is located and where every hour the brave trumpeter of Krakow still calls out his warning.

Price per person: 35 €

Jewish Heritage Walk with Dinner*

Sunday, 11th September 16.00–22.00

In the past, Kazimierz was a distinct town with its own Market Square and Town Hall, and a thriving culture which blossomed in the 16th century. At that time the Old Synagogue, one of the oldest and best known Judaic shrines in Poland, was erected. Inside the Old Synagogue there is now an exhibition showing the history and culture of the Jewish community of Krakow. We next visit the Remu'h Synagogue and its adjoining Jewish cemetery of the Renaissance period. The dramatic history of the Jewish community was presented by Steven Spielberg, who directed the movie "Schindler's List" and filmed it in the actual Kazimierz settings.
The present Kazimierz is famous for its unique ambience and lots of nice restaurants. Our walk will finish with dinner in one of them.

Price per person: 60 €

Wieliczka Salt Mine Tour*

Wednesday, 14th September 09.00–13.30

A visit to the Wieliczka Salt Mine - a world class tourist attraction where an ETA Excursion is also organized on Monday, 12th September (see above). Over seven centuries, many generations of Polish miners created an underground world of salt exceptional in its beauty, with richly decorated underground chapels carved from salt - including the most beautiful Chapel of the Blessed Kinga. Salt crystals cover the original linings of the galleries and wooden mining machinery. We view underground salt lakes and some 20 excavated chambers at 3 levels. The main chamber is located 130 meters below ground level. The chambers are decorated with beautiful statues sculpted in salt. The Wieliczka Salt Mine is listed by UNESCO as the World's Cultural and Natural Heritage.

Price per person: 35 €

Nowa-Huta Tour*

Tuesday, 13th September 09.00–13.00

Immediately after World War II, when Poland, liberated by the Red Army, became a part of the Soviet Union sphere of influence, the Communist authorities in Krakow decided to build a "new socialist city for the working class" to create a counterweight to the old town of the bourgeoisie and intellectuals. The city was designed in the style of social-realism and is the only such example in Poland. The tour shows typical living quarters from the 50's of the twentieth century, and modern church architecture – the first church wasn't built here until 1968. Earlier, the authorities forbade the construction.

Price per person: 30 €

ETA Gallery – Exhibition of Paintings, Prints and Photographs

Auditorium Maximum

Krakow is a major artistic community and one of the oldest in Poland. A commercial exhibition of the artists of Krakow showing paintings, prints and photographs has been arranged especially for ETA-2011 participants in the congress venue. We encourage you to view this exhibition to appreciate some of the achievements of Krakow's artists and to buy unique souvenirs from your stay in Krakow. Oil paintings, traditional and experimental prints and large-format photography which combine the present and the past are shown.
We invite you to visit and enjoy this exhibition at level 2 Auditorium Maximum from Sunday (08.00–18.00) till Wednesday (08.00–14.00).

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Krakow General Information

Wawel Royal Castle

Vistula river and Wawel Castle

Krakow, a city on the Vistula River, is the cradle of Polish culture and history. For five centuries Krakow was the capital of Poland, the seat of kings, and home of great scholars and artists from the whole world. Krakow has a rich history and offers traditional hospitality. Although Krakow is no longer Poland's capital, it retained its leading position in arts and sciences, combining history and tradition with modern science and technology. At the turn of the century, in the year 2000, Krakow became the European Capital of Culture, the first Polish city to be awarded this prestigious title.

Krakow's Old Town with the Wawel Castle and the Kazimierz district were placed on the first World Heritage List, created by UNESCO in 1978 – among the 12 most valuable objects in the world, along with the pyramids of Egypt and the Great Wall of China.

The Main Market Square is the largest medieval square in Europe – it was laid out in 1257 when Krakow received its city privileges.

Krakow is the most famous and most visited city in Poland. With a population of over 800 000 it is a centre of science, industry and culture, with the Jagiellonian University one of the oldest universities in Europe. Over 180 000 students attend the Jagiellonian and many other universities, academies and colleges in Krakow.

The numerous tourist attractions in Krakow make the time in the city exciting and very enjoyable. In the evenings, visitors may be attracted by the special ambience of its cafes, pubs and restaurants where they can not only have a delicious meal, but also relax in the beautiful interiors.

Jewish Cemetery, Kazimierz

Main Market Square and the Cloth Hall,
where the Welcome Reception is being held

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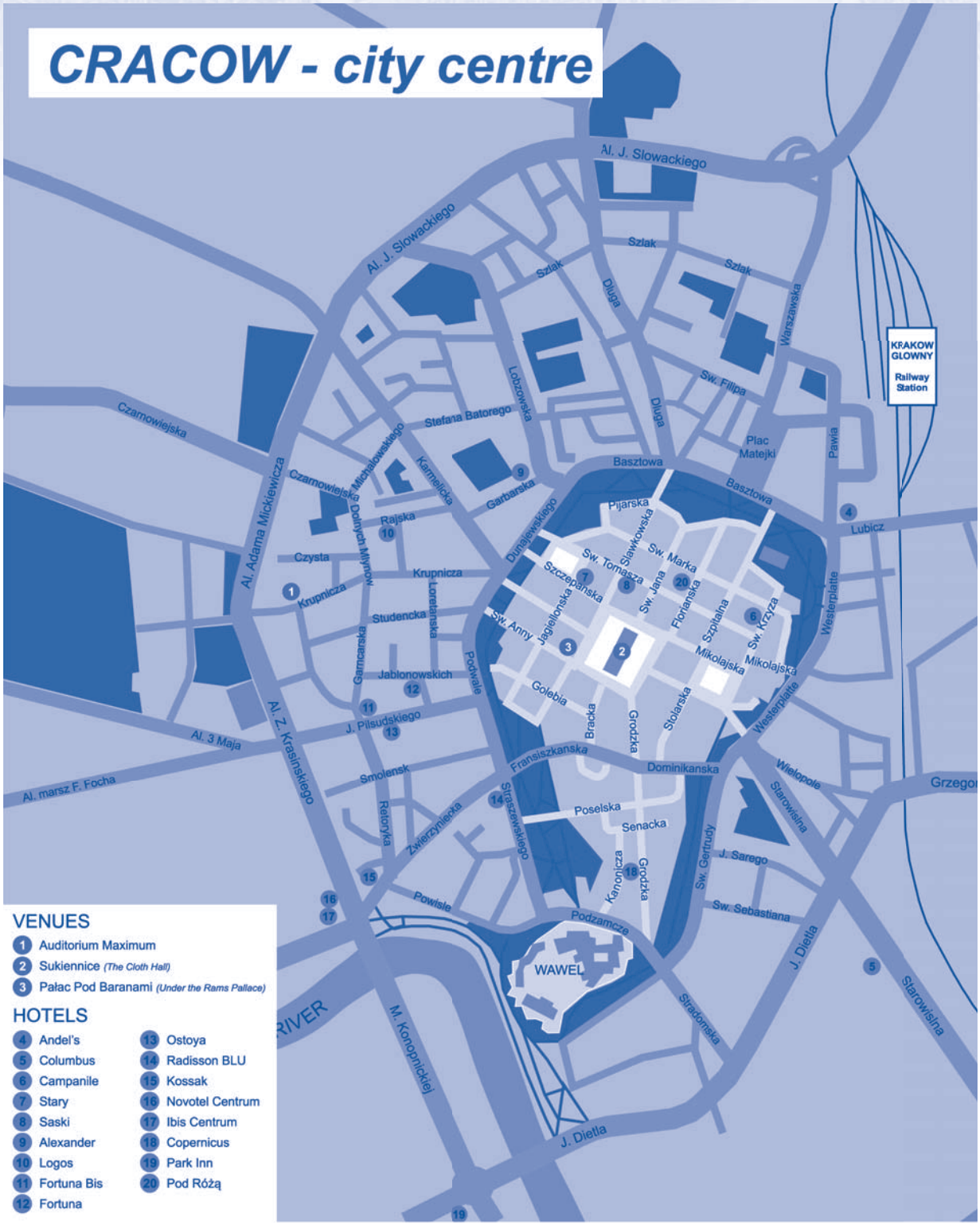
Map of Krakow



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The 36th European Thyroid Association meeting will be held at the Palazzo dei Congressi in Pisa, Italy from September 8-12, 2012.
We are looking forward to hosting our prestigious Annual Meeting that, as usually, will allow experts to exchange data and ideas in order to increase knowledge and improve strategies concerning thyroid research. The discussions will include all aspects of thyroid research and treatment.

For many years Pisa has been one of the most important centres in the world for the study of the thyroid. We believe that hosting the ETA Congress will be a prestigious event not only for the city, but also for the group of thyroidologists who work in Pisa, and the other Italian groups.

Pisa welcomes its visitors with its art, folkloristic events and, of course, the Leaning Tower.
The Leaning Tower is not the unique point of interest of this old city that has beautiful small sites that deserve a visit, just walking in the old streets.
Furthermore, enchanting surrounding territories set in the Tuscan landscape are famous for their history, beauty, and gastronomy. Florence is also easy to reach from Pisa and offers an exceptional artistic patrimony, glorious testimony of its secular civilization.

We hope that ETA 2012 will be a scientifically successful meeting in the friendly and welcoming city of Pisa. We look forward to seeing you here in September 2012.

36TH ANNUAL MEETING OF THE EUROPEAN THYROID ASSOCIATION

PISA / CONGRESS PALACE
8/12 SEPTEMBER 2012

European
Thyroid Journal

35th Annual Meeting of the European Thyroid Association

Abstracts

Krakow, Poland, 10th–14th September 2011

Guest Editors
Peter Laurberg, Aalborg, Denmark
Barbara Jarząb, Gliwice, Poland

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OP1 Topic Highlights

OP01

E7080 IN ADVANCED RADIOIODINE (RAI)-REFRACTORY DIFFERENTIATED THYROID CANCER (DTC); RESULTS OF A MULTI-CENTER PHASE II TRIAL

Sherman SI[1], *Jarzab B*[2], *Cabanillas ME*[1], *Licitra L*[3], *Pacini F*[4], *Martins RG*[5], *Robinson B*[6], *Ball DW*[7], *McCaffrey JC*[8], *Shah MH*[9], *Bodenner DL*[10], *Allison R*[11], *Newbold K*[12], *Elisei R*[13], *Gold A*[14], *Andresen C*[14], *O'Brien JP*[14], *Schlumberger M*[15]

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Background: E7080 is an oral multi-targeted kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT and PDGFRβ. Partial responses (PR) were observed in thyroid, endometrial, renal and other cancers in phase I studies of E7080.

Methods: 58 patients (pts) with advanced, RAI-refractory DTC (papillary, follicular or Hurthle Cell) and disease progression by RECIST criteria during the prior 12 months were enrolled between Oct 2, 2008 and Feb 5, 2010. Pts may have received prior VEGFR-targeted treatment. Pts were treated with a starting dose of E7080 24 mg once daily until disease progression. Response Rate (RR) by RECIST was the primary end point of this study.

Results: All 58 pts are included in the safety and efficacy analyses. Median age 62; M:59%, F:41%. 35% of pts required dose reduction for management of toxicity, and treatment was discontinued in 23% due to toxicity. The most common adverse events were hypertension 64% (Gr 3: 4%), fatigue 55% (Gr3: 7%), diarrhea 45% (Gr3: 5%), decreased appetite 44% (Gr3: 2%), weight loss 43% (Gr3: 4%), and proteinuria 39% (Gr3: 7%). 5 pts (8.6%) experienced Gr 4 events. Confirmed PRs were observed in 29 pts (PR: 50%, 95% CI: 37-63) based on investigator assessment. 65% of PRs were identified at first on-therapy imaging at ~8 wks. For pts who received prior VEGFR-targeted treatment (n=17) PR=41%; with no prior VEGFR-targeted treatment (n=41) PR=54%. Median Progression Free Survival (PFS) is 12.6 mo (95% CI: 10.4-14.1) (minimum follow-up: 8 mo., with 34% events observed). Updated PFS will be reported.

Conclusions: E7080 administered orally at a dose of 24 mg once daily to patients with RAI-refractory DTC is associated with manageable toxicity and a RR of 50%. These results identify E7080 as a promising potential new therapy for treatment of patients affected with RAI-refractory DTC.

OP02

THE CLINICAL PI3K INHIBITOR GDC-0941 RADIO-SENSITISES THYROID CARCINOMA CELLS BY INHIBITING BOTH THE PI3K AND HIF-1 SIGNALLING PATHWAYS

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Phosphoinositide-3 kinase (PI3K) and Hypoxia-Inducible Factor-1 (HIF-1) signalling are associated with aggressive disease in many cancers. The transcription factor HIF-1 plays a key role in hypoxia-mediated tumour progression. In addition to hypoxia, PI3K-signaling induces HIF-1. Both pathways promote desensitisation to chemo/radiotherapy. PI3K and HIF-1 activity correlate with aggressiveness in thyroid-cancer. The effect of these pathways on radiation response however, is unclear.

We aimed to determine the effect of the PI3K-inhibitor GDC-0941 on sensitivity to radiation under varying O_2 tensions in thyroid-carcinoma cells.

In follicular thyroid carcinoma (FTC) cells, HIF-1α expression and activity increased with increasing doses of radiation. This increase was not seen in anaplastic cells (ATC) suggesting a tumour-type specific effect. Radiation also induced HIF-1α in immortalised 'normal' thyroid cells exposed to anoxia but not normoxia. GDC-0941 inhibited radiation induced increases in HIF-1α activity and expression in FTC and normal cells. Cell lines treated with GDC-0941 had a greater number of DNA double-stranded breaks 1hr and 24hr post irradiation confirmed by analysis of gH2AX-positive foci under varying O_2 tensions. This suggests that GDC-0941 has a radio-sensitising effect on thyroid carcinoma cells. Analysis of PI3K activity in irradiated primary FTC xenografts by assessment of pAKT expression revealed that radiation increased PI3K activity. This radiation-induced increase was inhibited in mice treated with 12.5mg/kg GDC-0941 twice daily by oral gavage.

This is the first data showing an important therapeutic role of a PI3K-inhibitor in combination with radiotherapy in the treatment of thyroid-carcinoma. Additionally to PI3K, other pathways contribute to radio-desensitisation, such as HIF-1 which is also inhibited. With the known desensitising effects of PI3K and HIF-1 on radiation treatment, a combined approach using radiation with a PI3K-inhibitor may improve the therapeutic response. This is currently being explored in vivo.

OP03

EFFECTS OF CHRONIC 3-IODOTHYRONAMINE ADMINISTRATION ON LIPID METABOLISM IN RODENTS

Chiellini G[1], *Assadi-Porter FM*[2], *Haviland J*[2], *Butz D*[2], *Frascarelli S*[1], *Pellegrini S*[3], *Scanlan TS*[4], *Zucchi R*[1]

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Objectives: 3-iodothyronamine (T1AM) is an endogenous derivative of thyroid hormone which does not interact with nuclear thyroid hormone receptors but rather with G protein-coupled receptors. In the present study, we investigated the metabolic effects of chronic T1AM administration in rodents.

Methods: Mice were treated for a week with 10 mg/Kg per day T1AM, monitoring food intake and body weight. Real-time sampling of breath carbon in exhaled CO_2 ($^{13}CO_2/^{12}CO_2$ delta value) was performed by cavity ring down spectroscopy (CRDS). This is a noninvasive method to monitor daily substrate utilization for energy expenditure. Since the natural enrichment

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with ^{13}C is greater in carbohydrate than in lipid, increased lipid utilization is displayed by CRDS as a more negative $^{13}C/^{12}C$ ratio. In a parallel study, adipocytes obtained from rats subjected to chronic T1AM treatment were used to investigate gene expression by two-colour microarray analysis, using the Whole Rat Genome G4131F microarrays.

Results: A significant weight loss was observed in mouse after one week of exogenous T1AM administration (7.5±0.4 g, P< 0.01). Notably, the weight loss was found not to be associated with any change in food intake. After T1AM withdrawal mice regained only part of lost weight over the following weeks, suggesting a long-lasting effect. Shifts in $^{13}CO_2/^{12}CO_2$ delta values shortly after T1AM indicated a switch from carbohydrate to lipid metabolism, which might account for increased fat burning. Microarray experiments showed that 378 genes were differentially expressed (268 up-regulated and 110 down-regulated) in adipocytes and pathway analysis revealed changes consistent with decreased adipogenesis, increased lipolysis and increased cellular cholesterol uptake.

Conclusions: Lipid metabolism appears to be a target of T1AM. T1AM induces a metabolic switch leading to lipid mobilization, which might provide novel opportunities in the treatment of obesity and dyslipidemia.

OP04

NEUROENDOCRINE C CELLS OF THE MOUSE THYROID ORIGINATE FROM FOREGUT PROGENITORS IN THE ANTERIOR ENDODERM

Nilsson M[1], Andersson L[2], Westerlund J[2], Carlsson T[1], Parrillo L[3], Zoppoli P[3], Lania G[4], Baldini A[4], Fagman H[1]

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Objectives: Textbooks infer neural crest as the embryonic origin of neuroendocrine C cells in the thyroid gland. The contribution of neuroectoderm to the C-cell population was originally discovered in classical quail-chick grafting experiments. However, recent genetic tracing in mice has failed to identify calcitonin-producing C cells in Wnt1 descendants, suggesting another source of the C-cell lineage in mouse.

Methods and Results: We demonstrate here by *in situ* hybridization and immunofluorescence microscopy that newly differentiated C cells invading the embryonic mouse thyroid co-express forkhead transcription factors Foxa1 and Foxa2, both of which are ubiquitous markers of definitive endoderm and critically involved in the organogenesis of foregut derivatives. Spatiotemporal analysis in early thyroid development indicates that Foxa1+/Foxa2+ progenitors committed to a C-cell fate are integral part of the endoderm epithelium forming the ultimobranchial bodies, and that Foxa1 and Foxa2 are independently and gradually induced before calcitonin is expressed. Lineage tracing using Rosa26 reporter identifies calcitonin production among Tbx1 descendants, further supporting a non-crest origin of mouse C cells. Thyroid progenitors of the follicular cell lineage are exclusively devoid of Foxa2 expression at all developmental stages. Solely C cells express Foxa2 in the adult thyroid. Moreover, transcriptional analysis reveals Foxa2 expression in human medullary thyroid carcinoma.

Conclusions: The anterior endoderm is a novel source of embryonic C-cell precursors and Foxa2, a bona fide regulator of endoderm development and differentiation, is a potential biomarker of C-cell-derived tumors. These findings challenge the current concept of a neural crest origin of thyroid C cells in higher vertebrates.

OP05

A MULTICENTER RANDOMIZED PROSPECTIVE TRIAL OF PERCUTANEOUS LASER ABLATION VERSUS FOLLOW-UP FOR THE TREATMENT OF COLD THYROID NODULES. SIX-MONTH RESULTS

Papini E[1], Valcavi R[2], Rago T[3], Vitti P[3], Gambelunghe G[4], De Feo P[4], Bizzarri G[1], Pacella C[2]

[1]Regina Apostolorum Hospital, Department of Endocrinology, Albano Laziale, Italy, [2]Thyroid Disease Center, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, [3]Department of Endocrinology, University of Pisa, Pisa, Italy, [4]Department of Internal Medicine and Endocrine and Metabolic Sciences, Perugia, Italy

Aim of the study: To compare clinical and ultrasound (US) changes induced in cold thyroid nodules by US-guided laser ablation (LA) versus follow-up and to assess side effects and efficacy of the technique in different centers.

Patients: Two hundred consecutive patients were referred to four different thyroid centers and randomly assigned to a single LA treatment (Group 1) or follow-up (Group 2). Entry criteria: solid thyroid nodule with a volume > 5 and < 18 ml, repeated benign cytological findings, normal thyroid function, no previous thyroid gland treatment.

Methods: LA treatment was performed according to the previously described technique. Group 1: LA was performed with a 1.064 nm neodymium yttrium-aluminum garnet laser with 2 fibers and an output power of 3 watts. Energy delivery was 3600 Joules for nodules up to 13 ml and 7200 in two illuminations for nodules larger than 13 ml. Volume and local symptoms changes were evaluated one and six months after LA. Side effects and complications were registered.

Results: A significant nodule volume reduction was found at six months (delta volume vs baseline - 47,06% ± 8,66; p = 0.0001). A reduction > 50% was observed in 49,44% of cases. The mean volume reduction in the different centers was 40%, 52%, 40% and 56%. Local symptoms complain decreased from 81% to 44% of cases (p = 0,001). The procedure was well tolerated. One case of vocal cord paresis and one case of low grade fever were reported. All complications resolved spontaneously. In Group 2 nodule volume and local symptoms did not change significantly at six months.

Conclusions: A single LA induced a significant nodule reduction and improvement of local symptoms without relevant complications. Efficacy and side effects were similar in different centers. Follow-up group presented a not significant change of nodule volume and local symptoms.

OP06

A NOVEL CHIMERIC TSHR BIOASSAY DETECTS BOTH THYROID BLOCKING AND STIMULATING IMMUNOGLOBULINS

Olivo PD[1], Kim J[1], Larrimer A[1], Klasen R[1], Kanitz M[2], Li Y[1], Kahaly GJ[2]

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Aims: A novel bioassay was developed for the detection of thyroid-stimulating immunoglobulins (TSI) based on a CHO cell line (CHO-MC4) expressing a chimeric TSH-receptor (TSHR). Here we describe a complementary assay for detection of thyroid-blocking immunoglobulins (TBI) using the same transgenic cell line.

Methods: To detect blocking activity CHO-MC4 cells were induced with bovine TSH (bTSH) mixed with an anti-TSHR blocking MAb or human serum samples. Blocking activity was defined as percent inhibition of luciferase expression relative to induction with bTSH alone. MAbs K1-70 and M-22 were purchased from RSR (Cardiff, U.K.). All samples were also measured for TSHR autoantibody (TRAb) (ELISA, Kronus) and TSI (Thyretain™).

Results: Luciferase expression of bTSH-stimulated CHO-MC4 cells decreased in response to the blocking MAb K1-70 in a dose-dependent manner. Fifty euthyroid control sera demonstrated inhibition between 7 to 52% allowing us to establish a preliminary 95th percentile cut-off of 50% inhibition. TRAb-positive and TSI-negative sera from patients with autoimmune hypothyroidism reduced luciferase expression to background levels (100% inhibition). Serial dilution experiments demonstrated titers of blocking activity in these samples of up to 1:200. The TBI bioassay was over 20-fold more sensitive than the TRAb assay with the K1-70 MAb showing an IC50 of 1.34±0.09 ng/ml vs IC50 of 29.73±3.27 ng/ml.

The TBI bioassay was also capable of detecting TSI. Using a stimulating MAb (M-22) or TSI-positive sera, we observed luciferase expression above that seen with bTSH alone i.e. negative inhibition. The dose-response of M-22 stimulatory activity in both assays was essentially identical with 50% effective concentrations (EC50) of 0.14 ng/ml and 0.16 ng/ml in the TSI and TBI assays, respectively. Serial dilution of TSI-positive sera tested in both assays also showed equivalent dose-response curves.

Conclusions: This novel bioassay with CHO-MC4 cells is a unique tool for detecting both stimulating and blocking TSHR autoantibodies.

OP2 Thyroid Cancer Translational

OP07

EPIDERMAL GROWTH FACTOR RECEPTOR-TARGETED NON-VIRAL DELIVERY OF THE SODIUM IODIDE SYMPORTER (NIS) GENE IN RADIOIODINE-REFRACTORY DIFFERENTIATED AND ANAPLASTIC THYROID CANCER

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In contrast to differentiated thyroid cancer, which can be efficiently treated by the application of radioiodine due to the expression of the sodium iodide symporter (NIS), therapeutic options for radioiodine-refractory differentiated and anaplastic thyroid cancers are limited. Aiming at establishment of radioiodine therapy in these thyroid cancer types we have started to evaluate novel polyplexes for non-viral NIS gene delivery in a variety of thyroid cancer cell lines. We have used nanoparticle vectors based on linear polyethylenimine (LPEI), shielded by polyethylene glycol (PEG), and coupled with the synthetic peptide GE11 as an epidermal growth factor (EGF) receptor-specific ligand, that have been demonstrated to own high potential for systemic gene delivery. First, we have analyzed EGFR expression levels in various radioiodine-refractory differentiated and anaplastic thyroid cancer cell lines (SW1736, ML-1, Hth74, B-CPAP, FTC-133) by FACS-analysis. Thyroid cancer cells were then incubated with LPEI-PEG-GE11/NIS and control polyplexes (LPEI-PEG-Cys/NIS) lacking the EGFR-specific ligand, followed by analysis of transfection efficacy by iodide uptake assay. SW1736 and ML-1 showed the highest levels, B-CPAP and Hth74 intermediate levels, and FTC-133 cells the lowest levels of EGFR expression. Transduction efficacy correlated well with EGFR expression levels reaching highest levels with a 7-10-fold increase in perchlorate-sensitive iodide uptake activity in SW1736 and ML-1 cells as compared to mock transfected cells. Incubation with untargeted polymers (LPEI/PEG-Cys/NIS) resulted in a very low iodide uptake activity in all cell lines, demonstrating the EGFR-specificity of these polymers.

In conclusion, these results clearly demonstrate the feasibility of EGFR-targeted NIS gene transfer in radioiodine-refractory and anaplastic thyroid cancer cells using non-viral, synthetic polymers, that allow to pursue systemic *in vivo* NIS gene delivery in thyroid cancer animal models in future studies.

OP08

OUTCOME OF A CONSERVATIVE MANAGEMENT POLICY FOR FOLLICULAR THYROID CANCER- A PROSPECTIVE LONGITUDINAL COHORT STUDY

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Objectives: To describe long term outcomes of conservatively managed follicular thyroid cancer(FTC) from a UK endocrine surgical unit

Methods: 124 patients presenting with FTC since 1977 were entered into a prospectively collected database and followed up annually. There was a conservative approach to extent of surgery and radio-iodine use(RAI) throughout, based on risk stratification. Demographic, pathological, operative and outcome data were recorded and analysed using PASW v18, including subgroup analysis of minimal FTC(MFC).

Results: 34 males and 94 females (mean follow-up 183 months) had 61 (49%)MFC v 63 (51%) FTC. Hurthle cell variant(HTC) occurred in 9(15%) MFC & 16(25%) FTC. MFC were significantly younger, mean age 45yrs v 56yrs FTC($p < .001$, t test). Tumour size was significantly smaller: mean 35mm MFC v 47mm FTC. There were 71% AMES low risk patients overall: TNM (v5) stage was I 44%, II 44%, III 4% & IV 7%. 10(16%) MFC and 20(32%) FTC had total thyroidectomy: the remainder had lobectomy. 114(92%) had curative resections(100%MFC). 28(23%) patients had RAI. 33(27%) patients died:7 due to FTC and 1 due to MFC. Following curative resection 25 year cancer specific survival was 93%(FTC) and 96%(MFC). Variables associated with increased risk of death from TC were age>45yrs, size >5cm, HTC, metastases and extrathyroidal spread but not extent of surgery. After curative resection recurrence developed in 9(8%): 2(3%) of 61 MFC and 7(13%)of 53 FTC. Variables associated with recurrence were male sex, size >4cm and HTC($p=.009 \chi^2$). 8(7%) required reoperation, 1 in MFC for benign disease. Disease free survival was 64% for high risk and 98% for low risk patients at 25 years

Conclusions: These results are comparable to studies advocating routine total thryoidectomy and adjuvant RAI. They confirm that clinical risk stratification within a specialist unit reliably identifies patients at low risk of death and recurrence who may avoid completion total thyroidectomy.

OP09

THE IODINE DEFICIENCY-INDUCED ANGIOGENIC PATHWAY IN THYROID CANCER CELLS OCCURS VIA A VEGF-HIF SIGNALLING PATHWAY THAT, IN CONTRAST WITH NON MALIGNANT CELLS, IS INDEPENDENT ON REACTIVE OXYGEN SPECIES

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Iodide deficiency (ID) induces angiogenesis in benign thyroid via a ROS-HIF-VEGF signalling pathway. As the incidence of thyroid cancer increases in ID areas, mechanisms that govern angiogenesis in response to ID differ when non malignant or malignant cells are considered. The aim of this work is to study ID effects on angiogenesis in thyroid cancer cells in vivo and in vitro. In vivo, RET-PTC and wild type (wt) mice were made ID. The thyroid blood flow, and VEGF mRNA and protein expression were measured. In vitro, benign PCCL-3, and malignant TPC-1, R082-w1, and 8305c cells were made ID. The roles of ROS and HIF were analysed after N-acetylcystein (NAC)-induced ROS inhibition and echinomycin-induced inhibition of HIF-1 binding to HRE sites. VEGF mRNA and HIF-1a protein expression was measured. In vivo, ID RET-PTC and wt mice had a similar increase in blood flow. Basal VEGF mRNA was higher in RET-PTC mice, but not influenced by ID. In vitro, ID induced a marked VEGF mRNA and a moderate HIF-1a protein increase in the three cancer cell lines. While in PCCL-3 cells, ID-induced activation of the ROS-HIF-VEGF pathway was transient, the increase in VEGF and HIF-1a lasted longer in cancerous cells. Echinomycin induced a total (8305c), partial (TPC-1), or no (R082-w1) inhibition of ID-induced VEGF mRNA. ROS inhibition by NAC had no effect on ID-induced VEGF mRNA, while reducing HIF-1a expression in R082-w1 and 8305C cells, but not in TPC-1 cells. In conclusion, as in non malignant tissues, ID induces in vivo angiogenesis in malignant thyroid. In vitro, and in contrast with non malignant cells, the increase in VEGF mRNA lasts longer and is not influenced by ROS. These results indicate that ID-induced angiogenic pathway in cancerous cells differs from that of normal cells, which may infer for altered thyrocyte-driven vascular control.

OP10

FAMILIAL PAPILLARY THYROID CANCER PATIENTS DISPLAY AN ELEVATED CHROMOSOME FRAGILITY CHARACTERIZED BY TELOMERIC ASSOCIATION AND TELOMERE LOSS

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Background: Genomic instability has been proposed to play a pivotal role in cancer development by favoring the accumulation of genetic alterations. We demonstrated that familial papillary thyroid cancer (FPTC) patients display an imbalance, at the germinal level, in telomere-telomerase complex characterized by short telomeres that may play a role in the susceptibility to develop FPTC.

Aim: To study the presence of chromosome breakage, telomeric associations and fusions (index of chromosome instability) in FPTC patients, unaffected family members and healthy subjects.

Methods: T-lymphocyte cultures were obtained from peripheral blood of 13 FPTC patients (4 males and 9 females), 6 unaffected family members (2 males and 4 females) and 10 healthy subject (4 males and 6 females). At least 200 methaphases/sample were evaluated for spontaneous chromosomal instability (telomere fusions+breakage), for chromosome breakage (gaps, breaks, centric fissions, acentric fragments, rings, min/dmin), and telomeric associations. Dark telomeres together with doublets signals were also evaluated.

Results: FPTC patients displayed an increased spontaneous chromosome instability both with conventional (Giemsa, p=0.045) and molecular (FISH, p=0.026) cytogenetic analysis compared to other categories. In Giemsa studies, FPTC patients showed an elevated frequency of telomeric association compared to healthy subjects (p=0.00034) but not compared to unaffected family members (p=0.34). By FISH analysis, we found that FPTC patients have shorter telomeres compared to other groups (p< 0.0001). In addition, FPTC patients have a significantly increased number of acrocentric fusions (p=0.04), acrocentric fusions+non acrocentric fusions (p=0.039), acentric fragments with double telomeric signal (p=0.005), dark telomeres (p=0.015), doublets (p=0.033) and sister chromatid fusions (p=0.0001) compared to healthy subjects but not unaffected family members. Only acentric fragments with double telomeric signal and sister chromatid fusions were significantly higher also compared to unaffected family members (p=0.023 and p=0.012, respectively).

Conclusions: Our data confirm and extend previous evidence of elevated chromosome instability in FPTC patients.

OP11

HUMAN LEUKOCYTE ANTIGEN-G POLYMORPHISM: A POTENTIAL MARKER OF HISTOLOGICAL AGGRESSIVENESS IN PAPILLARY THYROID CANCER

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Objectives: The human leukocyte antigen-G (HLA-G) is a non-classical HLA-class Ib molecule with multiple immunoregulatory properties. Growing evidences support the role of HLA-G in the immune escape. An insertion/deletion polymorphism, a 14 bp sequence, is located in exon 8 of the HLA-G gene. This polymorphism might influence the HLA-G mRNA stability. Aim of the study was to evaluate the prevalence of the 14 bp insertion (+14 bp) and deletion (-14 bp) polymorphism in the HLA-G gene in patients affected by papillary thyroid carcinoma (PTC) as well as autoimmune thyroiditis (HT). The possible association between HLA-G 14 bp polymorphism and PTC aggressiveness was also assessed.

Methods: We studied 182 patients (147 F) with PTC and 120 patients (104 F) with HT; 245 healthy subjects (191 F), matched for sex and age, served as control groups. HLA-G polymorphism was studied by PCR techniques.

Results: The frequency of the 14 bp insertion polymorphism was significantly higher in patients with PTC and HT as compared to healthy controls (0.48 and 0.46 vs 0.38, p=0.0003 and p=0.01, respectively). Among PTC patients, a significant correlation was found between +14 bp allele and advanced TNM stage (rho: 0.37, p< 0.0001), as well as higher tumour aggressiveness, expressed as lymph node and/or multifocality and/or thyroid capsule invasion (rho: 0.39, p< 0.0001). Moreover, a positive correlation between the +14 bp allele and cancer dimension was observed (rho: 0.15, p< 0.05).

Conclusions: Our preliminary data show, for the first time, an increased frequency of the 14 bp insertion polymorphism in PTC patients, suggesting a potential role of the polymorphism in PTC immune escape and aggressiveness. Cooccurrences of HT and thyroid cancer have been repeatedly reported; so, the polymorphism may be also involved in the increased prevalence of PTC in patients with autoimmune thyroiditis.

OP12

HIGH-RESOLUTION-MELTING-CURVE ANALYSIS (HRM) FOR BRAF^{V600E} AND NRAS MUTATION SCREENING IN ROUTINE AIR DRIED THYROID FNA SMEARS IS MORE RELIABLE AND MORE SENSITIVE THAN FLUORESCENCE RESONANCE ENERGY TRANSFER (FRET) PROBES ANALYSIS

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Some of the inherent limitations of the sensitive and specific Fine Needle Aspiration Biopsy (FNAB) of thyroid nodules can probably be overcome by molecular analysis. To further increase sensitivity we retrospectively evaluated the possibility to improve the FNAB differential diagnosis by detecting the BRAF^{V600E} and NRAS mutations in routine FNAB smears by HRM, performed in thyroid FNAB for the first time, compared to the previously described FRET.

After DNA isolation and extraction from archived FNAB smears and corresponding FFPE samples, sets of 49 / 99 FNAB and corresponding FFPE samples were screened for the BRAF^{V600E} or NRAS mutations, respectively, using the Roche LightCycler 480 system. QPCR and sub-sequent FRET- and HRM-analysis were conducted for each sample.

HRM-analysis of FNAB and FFPE samples revealed more mutation positive samples (FNAB: BRAF: +60%, NRAS: +333%; FFPE: BRAF: +38%, NRAS: +10%) and less unreliable results (FNAB: BRAF: -100%, NRAS: -33%; FFPE: BRAF: -40%, NRAS: -20%) compared to FRET. This means HRM screening for the BRAF^{V600E} and NRAS mutations in conventional, air-dried FNAB and FFPE samples is more reliable and more sensitive than FRET-analysis - and is therefore superior to the latter.

Further 80 FNAB and the corresponding FFPE samples underwent HRM-screening for the BRAF^{V600E} mutation. Positive BRAF^{V600E} and NRAS results were identified in 1 of 79 and 5 of 54 indeterminate, 7 of 28 and 4 of 28 malignant FNAB, respectively. Additionally, NRAS mutations were identified in 3 of 16 non-neoplastic and in 1 of 1 non-diagnostic FNAB. Concordance between positive screened FNAB and FFPE results was obtained for each mutation in 6 samples.

HRM is more reliable and more sensitive than FRET-analysis. To demonstrate the diagnostic potential of HRM for the analysis of routine air dried FNAB the analysis of more samples and the identification of rearrangements will be required.

OP13

MICRORNA EXPRESSION IN EXPERIMENTAL *IN VITRO* THYROID TUMORS MODELS

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Objectives: To validate the use of the classical *in vitro* models of thyroid tumors for the analysis of microRNAs. We analysed primary cultures of human thyrocytes treated with TSH (as model of autonomous adenomas) or with EGF/Serum (as model of papillary carcinomas) and 6 cell lines (BCPAP, 8505c, FTC-133, TPC-1, WRO and K1) as model for carcinomas.

Methods: miRNA expression profiles were investigated in each model by microarrays (Exiqon V11.0) and the data were compared to the corresponding thyroid tumors.

Results – Conclusion: Treatment of thyroid cells in primary culture with TSH or EGF/Serum had only a small impact on miRNA expression, as observed by hierarchical clustering or MDS (Multidimensional Scaling) analysis. The observed patterns appeared to be more representative of the culture procedure than being the consequence of the specific type of stimulation performed.

For the cell lines, their oncogenic mutational status was first evaluated and discordances with the published data were demonstrated.

Our result show that the 6 cell lines investigated, deriving form differentiated and undifferentiated tumors types, have evolved in vitro into a common dedifferentiated phenotype. All those 6 cell lines are more similar to each other than to the original tumor types from which they are derived. Their microRNA expressions profiles are close to in vivo undifferentiated tumors and these cell lines are thus better models for anaplastic thyroid carcinomas. These results are in accordance with previously published data on mRNA expression profiles.

OP14

SERUM ANTI-THYROID ANTIBODIES (TAB): A POSSIBLE NEW POSITIVE PREDICTIVE PARAMETER IN HIGH AGGRESSIVE BREAST CANCER (BC)

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Objectives: Prognostic value of TAb in high aggressive BC evaluating patients survival.

Methods: The study group included 47 women (mean age: 53.1±10.1 yrs, mean±SD) submitted to radical mastectomy for high malignancy ductal infiltrating BC with axillary node involvement. All patients were evaluated for thyroid disorders after breast surgery and before any adjuvant therapy. After surgery all patients were submitted to the same protocol of adjuvant chemo-hormonal therapy. Estrogen Receptor (ER) was measured in 43/47 (91.5%) BC specimens.

Results: 31/47 (65.9%) patients were alive (survivors group: SG) and 16/47 (34.1%) were dead (deaths group: DG), five years after BC diagnosis. The overall prevalence of TAb was 15/47 (31.9%): 14/31 (45.1%) in SG and 1/16 (6.2%) in DG (p=0.008). Five years mortality was 15/32 (46.9%) in TAb- and 1/15 (6.7%) in TAb+ patients (p=0.01). 8/47 (17.0%) patients had Hashimoto's thyroiditis and 7 of them (87.5%) were in SG. ER was detected in 19/30 (63.0%) patients in SG and 3/13 (23.1%) in DG (p= 0.01). Five year mortality was 10/21 (47.6%) in ER- and 3/22 (13.6%) in ER+ patients (p=0.008). According to Proportional Hazard Regression Model, the presence of more than 3 axillary lymph node metastasis [odds ratio (OR) 8.53; p=0.006], the absence of ER expression (OR 7.72; p=0.004) and the absence of TAb (OR 18.40; p=0.01) were related to a higher mortality rate.

The worst prognosis was observed in AbT-/ER- patients [5 years mortality rate: 9/13 (69.2%)] and all the 7 patients TAb+/ER+ were alive after 5 years.

TAb were detected in 8/21 (38.1%) ER- and in 7/22 (31.8%) ER+ patients; no relation was found between ER expression and TAb positivity (p=NS).

Conclusions: Patients with RE+/TAb+ have a better prognosis. The absence of a significant relationship between these two parameters suggests an independent prognostic role of TAb in high malignancy degree BC.

OP3 Young Investigator Session

OP15

MIR-224 CONTRIBUTES TO TISSUE HYPOTHYROIDISM IN RENAL CANCER, TARGETING THE 3'UTR OF TYPE 1 5´-IODOTHYRONINE DEIODINASE

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Objectives: Numerous cancers exhibit aberrances in thyroid hormone pathways. One of the resulting conditions, associated with tumor metastasis and development, is the tissue-specific hypothyroidism. Among other cancers, tumor-specific hypothyroidism is observed in clear cell Renal Cell Carcinoma (ccRCC), possibly resulting from loss of type 1 deiodinase (DIO1). One of the factors contributing to lowered DIO1 in ccRCC could be aberrant expression of microRNAs, frequently observed in cancers. These short RNAs recognize specific sequences in 3'UTR of target gene and prevent from its translation. We aimed to identify microRNAs that bind DIO1 3'UTR and therefore contribute to tissue hypothyroidism in renal cancer.

Methods and Results: Using *in silico* analysis, we identified 7 miRNAs potentially targeting *DIO1* 3'UTR, of which two (miR-224 and miR-383) appeared to be functional. Direct interaction of miR-224 and miR-383 with DIO1 transcript was confirmed in HeLa cells in a reporter gene assay, using reporter construct with DIO1 3'UTR cloned downstream of luciferase. Transfection of Caki-2 (ccRCC) cell line with pre-mir-224 caused 1.4 fold decrease in DIO 1 mRNA, while transfection with anti-mir-224 (miRNA inhibitor) resulted in 1.5 increase of DIO1.

Analysis of *DIO1* and miRNA expression in 32 paired-tissue samples (tumor and contralateral pole of ccRCC kidney, not infiltrated by cancer) revealed that 2.7 fold *DIO1* reduction in tumor was concomitant with increased expression of miR-224 (4-fold) and miR-383 (2.7 fold). Tumor-specific changes in miR-224 negatively correlated with T3 levels in analyzed tissue samples.

Conclusion: We demonstrated that *DIO1* 3´UTR is a functional target of miR-224 and miR-383. miR-224 mediates loss of DIO1 in ccRCC, what results in decreased intratumoral T3 concentration. These results provide evidence for a new mechanism regulating the expression of type 1 iodothyronine deiodinase and suggest that microRNAs may possibly contribute to intracellular hypothyroidism in ccRCC.

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OP16

DEFICIENCY OF THE THYROID HORMONE TRANSPORTER MONOCARBOXYLATE TRANSPORTER 8 ALTERS THYROID MORPHOLOGY IN A PATIENT AND IN MICE

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Context: Thyroid hormones need transmembrane transport proteins to cross the plasma membrane of neurons and other cells. One specific thyroid hormone transporter is the monocarboxylate transporter 8 (MCT8). Mutations in *MCT8* lead to a severe form of X-linked psychomotor retardation, the Allan-Herndon-Dudley syndrome, which is characterized by elevated plasma T_3 and low/normal T_4. The exact molecular mechanisms leading to this phenotype remain unknown. MCT8 is expressed in thyrocytes and was recently shown to contribute to thyroid hormone release from the thyroid gland itself.

Objective: To characterize the potential impact of *MCT8*-deficiency on thyroid morphology in a patient and in *Mct8*-deficient mice.

Design: Increasingly suspicious thyroid morphology in a patient carrying the A224V mutation was monitored by ultrasound imaging for over ten years. After thyroidectomy, a histopathological analysis was carried out. These findings were compared with histological analyses of mouse thyroids from the *Mct8*$^{-/y}$ model.

Results: We show that an inactivating mutation in *MCT8* leads to a unique, progressive thyroid follicular pathology in a patient. After thyroidectomy, histological analysis revealed gross morphological changes including hyperplastic nodules, microfollicular areas with stromal fibrosis, and a small focus of microfollicular structures with nuclear features reminiscent of papillary thyroid carcinoma. These findings are supported in an *Mct8*-deficient mouse model in which we found papillary thyroid carcinoma in aged animals. After complete thyroidectomy of the affected Mct8 patient and his substitution with levothyroxine, the preoperative, inadequately low T_4 remained decreased, while increasing levothyroxine dosages led to T_3 serum concentrations above the normal range.

Conclusions: We describe a novel phenotype of *Mct8*-deficiency that leads to pathological changes of the thyroid itself and implies a new potential mechanism for thyroid pathology. Our results suggest that extrathyroidal deiodination contributes to the peculiar hormonal constellation in *MCT8*-deficient patients. Other *MCT8*-deficient patients should be closely monitored for potential thyroid abnormalities.

OP17

SOMATIC HYPERMUTATION OF THE IMMUNOGLOBULIN HEAVY CHAIN VARIABLE-REGION OF THYROID STIMULATING ANTIBODIES DETERMINES BINDING TO THE TSH-RECEPTOR

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Introduction: Graves' disease is an autoimmune disease where antibodies to TSH-receptor (TSHR) stimulate the gland to produce excessive thyroid hormone causing hyperthyroidism. Knowledge of factors responsible for production of the pathogenic thyroid stimulating antibodies (TSAbs) is fundamental to understanding the molecular basis of the condition.

We described two monoclonal TSAbs derived from one mouse undergoing autoimmune hyperthyroidism. Immunoglobulin (Ig) gene sequence analysis showed that both TSAbs were derived from the same clonotype, but varied in their hypermutation, thus providing an opportunity to study the effect of hypermutation on antigenic specificity.

Methods: To study the binding properties of the germline clonotype, we synthesised the germline *IGH* and *IGK* genes shared by the two mAbs (KSAb1 and KSAb2). The synthetic construct was cloned for expression as recombinant Fab (rFab) and purified to homogeneity. We also assessed the contribution of the somatically hypermutated *IGH* and *IGK* by creating two swap constructs: Swap 1 comprises the mutated KSAb1 *IGK* and germline *IGH*, Swap 2 comprises the mutated KSAb1 *IGH* and the germline *IGK*. Swap constructs were expressed as rFabs; Swap 1 was purified to homogeneity and Swap 2 was partially purified. Binding of rFabs to TSHR was examined by competitive inhibition of ^{125}I-TSH binding to TSHR, stimulation of the TSHR second messenger cAMP and by flow cytometry.

Results: The germline rFab failed to recognise TSHR. Interestingly, Swap 2 rFab inhibited ^{125}I-TSH binding to TSHR, whilst Swap 1 rFab did not, showing the importance of the *IGH* in determining receptor binding.

Conclusion: We show for the first time that TSAbs responsible for Graves' disease develop from non-reactive precursor B cells, which acquire TSHR recognition and pathogenicity as a result of somatic hypermutation. The availability of non-reactive precursor antibody provides an opportunity to examine the role of infectious agents in Graves´ disease.

OP18

DETECTION OF *PAX8/PPARG* AND *RET/PTC* REARRANGEMENTS IN ROUTINE AIR DRIED FINE NEEDLE ASPIRATION (FNA) SMEARS

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Fine needle aspiration biopsy (FNAB) is the most sensitive method to select suspicious nodules for surgery. Limitations of FNAB diagnosis, like the "indeterminate" FNAB category, can probably be overcome by molecular analysis. As *PAX8/PPARG* and *RET/PTC* rearrangements were detected in follicular carcinomas (FTC) and papillary carcinomas (PTC), respectively, its detection in FNAB smears could improve the diagnosis. Up to date, these rearrangements have been analyzed only in frozen or in formalin-fixed paraffin-embedded (FFPE) tissue.

This study aimed to establish for the first time the feasibility to extract RNA from routine air dried FNA smears to detect these rearrangements with RT-PCR.

We analyzed the presence of *PAX8/PPARG* and *RET/PTC* rearrangements in a series of 106 routine FNA smears and the corresponding FFPE tissues using RT-PCR assay. We analyzed the 4 variants of *PAX8/PPARG* and *RET/PTC1* and *3* with specific probes.

PAX8/PPARG was detected in 4 of 106 FFPE samples (4%) and in 6 of 106 FNAB smear samples. In 3 samples it was possible to match FFPE to FNAB. *PAX8/PPARG* was present in 4 of 20 (20%) FTC and in 3 of 54 follicular adenoma (FA) (6%). Similarly, *RET/PTC* was found in 3 of 106 FFPE samples (3%) and in 4 of 106 FNAB smear. 2 of 25 (8%) PTC and 3 of 54 FA (6%) carried this rearrangement. No sample carried both rearrangements simultaneously.

These results demonstrate for the first time the feasibility to extract RNA from routine air dried FNAB smears to detect *PAX8/PPARG* and *RET/PTC* rearrangements with RT-PCR. The introduction of molecular analysis of routine air dried FNAB smears in every day practice comprising also other mutations could provide substantial improvements for the clarification of the indeterminate FNAB category and therefore also reduce the rate of diagnostic surgeries.

OP19

DUAL-OXIDASE 2 GENETIC MODIFICATIONS IN CHILDREN WITH HYPOTHYROIDISM: IDENTICATION AND FUNCTIONAL ANALYSIS OF VARIANTS AND MUTATIONS

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Objective: To identify DUOX2 mutations in children with CH or isolated hyperthyreotropinemia, a eutopic thyroid gland and an iodine organification defect.

Patients: 8 children with CH and 2 children with isolated hyperthyreotopinemia. In all the children LT4 was stopped to verify thyroid function when they were 3 years. In all the children a partial organification defect was shown after 123-I scintigraphy and perchlorate test. In all the children TPO, DUOX2, DUOXA2 genes were analyzed. The functional activity of the DUOX2 variants was studied in vitro. HeLa cells were seeded and co-transfected with the wtDUOX2, DUOX2 mutants or the empty vector in the presence of DUOXA2. After transfection the H2O2 was determined by reaction with Amplex Red reagent in the presence of peroxidase. DUOX2 expression was also determined in transfected HeLa cells by on chip flow cytometry using Agilent 2100 bioanalyzer.

Results: No TPO mutations were identified. Direct sequencing of the DUOX2 gene revealed a monoallelic deletion S965FsX994 in three children. One children showed H678R, R701Q, P982A heterozygous mutations and one child showed only the P982A mutation. The functional studies showed: H678R, R701Q and P982A mutants had the same activity of wtDUOX2 in terms of H2O2 production. Mutant S965fsX994 determined an almost complete inhibition of the H2O2 generation in HeLa cells. Cytofluorimetric analysis showed an expression at the cell surface of H678R, R701Q and P982A mutants similar to that of wtDUOX2, while S965fsX994 mutant was significantly less expressed with respect to wtDUOX2.

Conclusions: In 10 children with CH or isolated hyperthyreotropinemia and a eutopic thyroid we found one mutant of the DUOX2 gene (S965fsX994) determining a reduction in H2O2 production when expressed in vitro; this mutant was found in three children with CH. Other 3 gene variants (H678R, R701Q and P982A) identified didn't show a significant reduction in H2O2 production.

OP20

RELATIONS BETWEEN MATERNAL FIRST-TRIMESTER AND NEWBORN THYROID HORMONE SERUM LEVELS: RESULTS FROM A LARGE POPULATION-BASED COHORT STUDY

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Objectives: Abnormal serum thyroid hormone (TH) levels during pregnancy are associated with a wide range of pregnancy complications and adverse neonatal outcomes. However, limited data from large studies are available on the relationship between maternal TH levels during pregnancy, and their associations with TH levels in the newborn.

Methods: First-trimester serum TSH, FT4, TT4 and TPO-antibody (TPOab) levels were determined in 5214 pregnant women from a Caucasian population-based cohort study. TSH and FT4 levels were also determined in cord serum in a random selection of 2720 of their newborns. The associations between maternal TH parameters were studied, together with their associations with newborn TH parameters.

Results: Between week 9 and 18 of gestation, maternal TSH levels increased (0.22±0.08 mU/L, $p=8.8x10^{-6}$), FT4 levels decreased (-2.63±0.21 pmol/L, $p=5.9x10^{-84}$), TT4 levels increased (19.7±2.5 pmol/L, $p=9.5x10^{-49}$), and TPOab positivity decreased (-4.7±1.7 %, p=0.006). Serum TSH and FT4 levels were inversely associated (β=-0.36±0.04 pmol/L, $p=7.1x10^{-31}$). TPOab positive subjects had higher TSH (3.30±0.07 vs 1.49±0.02, $p=6.3x10^{-39}$) and lower FT4 levels (14.6±0.2 vs 15.2±0.1, p=0.007) compared to TPOab negative subjects. In addition, TPOab positivity was associated with more subclinical hypothyroidism (15.1% vs 1.5%, $p=7.1x10^{-34}$) and hypothyroidism (3.1% vs 0.1%, $p=5.2x10^{-9}$).

Higher first-trimester maternal TSH and FT4 levels were associated with higher newborn TSH (β=0.45±0.14, $p=2.1x10^{-6}$) and FT4 (β=0.09±0.02, $p=3.9x10^{-5}$) levels, respectively, even when studied in mothers and newborns with normal range TSH and FT4 levels.

Conclusions: In this large population-based cohort study, we convincingly confirm previously reported associations between maternal TH parameters. We additionally show a substantial increased risk of (subclinical) hypothyroidism in TPOab positive mothers. We observed a strong association between first trimester maternal and newborn TH parameters, suggesting an effect on the thyroid setpoint of the newborn, the exact biological basis of which needs to be determined in future studies.

OP21

IS COMPLETION THYROIDECTOMY FOLLOWING LOBECTOMY FOR LOW RISK THYROID CANCER MANDATORY?

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Objectives: Current guidelines for management of differentiated thyroid cancer (DTC) recommend total thyroidectomy for the majority of DTC cases, and management within a multidisciplinary team. The aim of this study was to assess the necessity of completion total thyroidectomy after initial lobectomy and subsequent TSH suppression for AMES low risk DTC managed with a consistently conservative policy in one specialist unit.

Methods: This is a prospective computerised population based study of DTC in North East Scotland of patients undergoing initial treatment in our endocrine surgery unit between 1977- 1999, allowing for minimum 10 year follow up. Statistical analyses were carried out using PASW v18.

Results: Between 1977-1999, 268 patients were diagnosed with primary thyroid malignancy, of whom 226 were DTC (41% follicular, 59% papillary), with median age 44 years (IQR 32-56), 26% male. No statistically significant differences in histological subtype were seen by age or sex. Median follow up was 18.6 years with minimal loss to follow-up.

Of these 226 DTC, 179 patients were classified as AMES "low risk" based on information available at the time of surgery. 130 (73%) underwent less than total or near total thyroidectomy (126 lobectomy) as primary operation. 7 (5%) of these 130 patients have required completion thyroidectomy, 4 for benign disease. 18 of 179 "low risk" patients underwent radioiodine (RAI) treatment: none of the group avoiding RAI died of disease. There was one cancer-specific death in 179 'low risk' patients: this patient died of distant metastases 14 years following surgery and adjuvant RAI. Median 18.8 years disease free survival and 19.2 years overall survival were achieved, our cancer-specific survival data comparing favourably with published series.

Conclusion: A conservative policy towards completion total thyroidectomy following lobectomy for DTC is safe within a specialist unit: current guidelines may be too aggressive.

OP22

SELECTIVE VENOUS CATHETERIZATION IN LOCALIZING OCCULT PERSISTENT MEDULLARY THYROID CARCINOMA

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Background: Persistent elevated calcitonin (CT) levels are frequent after initial surgery for medullary thyroid carcinoma (MTC). The localization of residual tumor is often difficult with conventional imaging techniques. Selective venous catheterization (SVC) for CT measurements can be used to localize residual tumor.

Objective: To determine the optimal cut-off defining a positive SVC and to evaluate the utility of SVC in MTC patients with persistent elevated serum CT levels.

Patients and Methods: Monocentric retrospective study including 46 patients who underwent SVC and at least a neck ultrasonography and a neck and chest computed tomography for persistent elevated CT levels. True positive SVC was defined in case of a gradient correlated with abnormal imaging procedures and/or pathology and/or relapse during further follow-up. SVC results were classified as positive or negative using a gradient cut-off level (as compared to the peripheral venous sample) corresponding to the CT level that maximized the sum of sensitivity plus specificity, as deduced from the ROC curve.

Results: The gradient cut-off showing maximized sensitivity (76%) and specificity (56%) was 1.6 times the peripheral venous CT level. According to this cut-off, SVC permitted to detect a positive gradient in 32 patients (70%), including 28 true-positives and 4 false-positives. Among patients with a gradient, 20 had normal imaging procedures, 24 were re-operated and 19 had metastasis. The postoperative CT level decreased by more than 50% in 10 patients and was normalized in 3 patients. Among the 14 patients with no gradient, 5 were classified as true-negatives and 9 as false-negatives because of abnormal imaging (5 cases), metastases on pathology (3 cases that underwent surgery) and one case of morphological recurrence in bone.

Conclusion: ROC curve analysis shows that the best cut-off for the CT gradient is 1.6, allowing SVC to reach a sensitivity of 76% and a specificity of 56%.

OP4 Thyroid Autoimmunity

OP23

DIFFERENCES IN THE WAY STIMULATING AND BLOCKING MONOCLONAL AUTOANTIBODIES INTERACT WITH THE TSHR

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We have determined the crystal structures of 3 human monoclonal autoantibodies which have high affinity for the TSHR, M22 and K1-18 with potent thyroid stimulating activity and K1-70 with strong blocking activity. The crystal structure of K1-18 Fab was solved at 1.65Å and compared to the crystal structures of M22 (1.65Å) and K1-70 (2.22Å) Fabs. The electrostatic surface potentials of the 3 MAbs are different although all are highly charged, consistent with the known importance of charge-charge interactions for binding of TSHR autoantibodies to the TSHR.

Analysis of the electrostatic surface potentials in structures of the TSHR (aa 22-260; TSHR260) in complex with K1-70 (1.9Å) or M22 (2.55Å) showed unique complementarities between the TSHR and antibody interacting surfaces. Charge-charge interaction mapping allowed us to predict the position of K1-18 on the TSHR and this was confirmed in studies of the effects of TSHR mutations on the stimulating activity of K1-18.

K1-18 is predicted to bind to the TSHR in a similar orientation to M22 but rotated about the TSHR260 vertical axis by ~200°. K1-18 is positioned on the TSHR in a similar orientation to TSH with the K1-18 light chain (LC) mimicking the interactions of the TSHα chain and the heavy chain (HC) mimicking the interactions of the TSHβ chain. In contrast the M22 HC mimics the interactions of TSHα chain and the M22 LC mimics the interactions of the TSHβ chain. However, K1-70 blocking MAb HC and LC do not mimic TSHα and TSHβ chains in their interactions with the TSHR.

Consequently electrostatic surface potentials of TSHR MAbs can be used in conjunction with the effects of TSHR mutations on MAb activity to predict binding sites on the TSHR. This approach should be helpful in elucidating how ligand binding triggers TSHR activation.

OP24

CAVEOLINE-1 EXPRESSION DIFFERS ACCORDING TO THE TYPE OF IMMUNE REACTION (TH1/TH2) INVOLVED IN THYROID AUTOIMMUNE DISORDERS

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Caveolin-1 (Cav-1) is a component of the thyroxisome assembling thyroperoxidase (TPO) and dual oxidase (Duox) at the cell/colloid interface where H2O2 is immediatly used for hormonal synthesis.

Aim: To analyse Cav-1 expression in TH2 and TH1 autoimmune disorders.

We analysed « in vivo » 3 types of thyroid samples (n = 5) 1) controls (paranodular tissues), 2) Graves' disease, 3) Hashimoto thyroiditis (HT). We detected by immunohistochemistry Cav-1, TPO, Duox, T4, Peroxiredoxin (PRDX5) and catalase (H2O2 detoxification), 4-hydroxynonenal (HNE, oxidative stress), caspase-3 (apoptosis), and cyclin D1 (cell proliferation).

« In vitro », human thyrocytes were exposed or not to TH1 cytokines (IL1, IFNg) and Cav-1 mRNA expression was measured by RT-PCR.

In stimulated Graves' thyrocytes, Cav-1, TPO and Duox were overexpressed but well apically located and T4 was detected in the colloid. HNE labelling was strong as that of PRDX5 and catalase. Very few nuclei were labelled with caspase-3 and cyclin D1.

In HT, the observations were at the opposite, at least in follicles with large lumina and columnar cells. There, Cav-1 was absent and TPO and Duox were mislocalized in the cytoplasm. T4 was not detected in the colloid but well in the cytoplasm, and the expression of HNE, PRDX5 and catalase was high. Numerous nuclei expressed caspase-3 but also cyclin D1. This could be correlated with the down-regulation of Cav-1 by TH1 cytokines. Indeed, « in vitro », Cav-1 mRNA levels were decreased by TH1 cytokines exposure.

Conclusion: Apical co-localization of cav-1, TPO and Duox is essential to maintain normal iodination, as in Graves' disease. Disruption of the thyroxisome like in Hashimoto thyroiditis leads to intracellular iodination, oxidative stress and apoptosis, temporarly compensated by an increased proliferation. Down-regulation of Cav-1 by TH1 cytokines leads to hypothyroidism and cell destruction.

OP25

NEWLY IDENTIFIED IMMUNOSUPPRESSIVE NATURAL KILLER (NK) CELLS SUPPRESS ANTIGEN-SPECIFIC CD8+ T CELLS IN THREE MOUSE MODELS FOR AUTOIMMUNITY

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The role of natural killer (NK) cells in autoimmunity has not been clarified in detail yet. Using three autoimmunity mouse models including TAZ10 mice for autoimmune thyroiditis and two type 1 diabetes mellitus mouse models (T1DM), we identified a new subset of NK cells with regulatory function. These cells can be generated from conventional NK cells by incubation with

interleukin-18 and are characterized by the expression of the surface markers c-Kit (CD117) and programmed death-1 ligand (PD-1L). *In vitro* analyses demonstrated a direct lysis activity of IL-18-stimulated c-Kit$^+$ NK cells against activated antigen-specific CD8$^+$ T cells in a PD-1 / PD-1L-dependent manner whereas unstimulated c-Kit$^-$ NK cells did not. *In vivo* application of IL-18 enhanced the frequency of c-Kit$^+$ / NK1.1$^+$ / CD45$^+$ NK-cells, too. In TAZ10 mice we have seen an increase of c-Kit$^+$ NK-cells up to 3.41% ± 0.35% following treatment with IL-18. Flow cytometry analyses of untreated non-obese diabetic mice revealed a large increase of splenic and lymphatic c-Kit$^+$ NK cells at 8 weeks of age, a time point of acceleration of adaptive cytotoxic immunity. Adoptive transfer of unstimulated c-Kit$^-$ and IL-18-stimulated c-Kit$^+$ NK cells into streptozotocin-treated mice led to a delayed disease development and a partial diabetes prevention in the c-Kit$^+$ NK cell treated group. Consistent with these data, mild diabetes was associated with increased numbers of c-Kit$^+$ NK cells within the pancreatic islets. The in vivo follow-up analyses in TAZ10 mice, the model of autoimmune thyroiditis, are ongoing. Our results demonstrate for the first time a direct link between innate and adaptive immunity in autoimmunity with IL-18-stimulated c-Kit$^+$ NK cells displaying a possible role as immunosuppressors within this context.

OP26

INVOLVEMENT OF STRESS IN THE PATHOGENESIS OF AUTOIMMUNE THYROID DISEASE: A PROSPECTIVE STUDY

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Background: An association between stress and autoimmune thyroid disease (AITD) has been reported, but all studies so far on this topic have been retrospective.

Objective: To evaluate prospectively the relationship between stress and i)de novo occurrence of thyroid antibodies and ii)development of overt autoimmune hyper-/hypothyroidism.

Study design: Two nested case-control studies in a cohort of 790 euthyroid women who were 1st or 2nd degree relatives of AITD patients. Follow-up was 5-yr, with annual assessments including questionnaires on stressful life events, daily hassles, and mood. In study A, cases were subjects who developed TPOAb but remained euthyroid during follow-up (called event). In study B, cases were subjects who developed overt hypothyroidism (TSH>5.7mU/l and FT4< 9.3pmol/l) or overt hyperthyroidism (TSH< 0.4mU/l and FT4>20.1pmol/l) during follow-up (called event). For each case, two controls were selected, matched for age and duration of follow up; controls in study A remained TPOAb negative, and in study B remained without overt hyper-/hypothyroidism.

Outcomes: Contrast in questionnaire responses between cases and controls at baseline, at 1-yr prior to the event and at time of event.

Results: Exposure to stress was not different between subjects who developed or did not develop TPOAb (study A). No differences were observed in stress questionnaires between hyper-/hypothyroid cases and controls at any time point, but hypothyroid cases had less negative feelings than controls at time of diagnosis (study B).

In subjects with normal TSH and no thyroid antibodies both at baseline and during the follow up, we observed stressful life events decreased but stress from daily hassles increased during the 5-yr follow up, whereas the mood state didn´t change during this period.

Conclusion: The data do not support the notion that stress is involved in the pathogenesis of AITD. Stress from daily hassles increases but stressful life events decrease with advancing age.

OP27

ROLE OF THE PRO-PEPTIDE SEQUENCE IN THYROID PEROXIDASE FUNCTION AND MATURATION

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Thyroid peroxidase (TPO), the key enzyme involved in thyroid hormone synthesis, is a powerful autoantigen in autoimmune thyroid diseases. This membrane-associated protein undergoes posttranslational modifications such as glycosylation, heme incorporation, dimer formation, and proteolytic processing in the N-terminal region. Due to propeptide deletion, in human thyroid cells the mature TPO looses at least 100 amino acids in the N-terminus to yield mature enzyme. It is postulated that the TPO pro-peptide may play a role as an intramolecular chaperone. In this study we investigate whether the prosequence is essential for the TPO structure, function and transport. We generated TPO cDNA truncated at N-terminal residue (TPOΔpro) and subsequently stably transfected to the CHO cells. Wild type TPO (TPOwt) expressed in CHO cells was used as control. Using immunodetection and densytometric analysis we showed that the deletion of the pro-sequence did not influence expression level of TPO in comparison with TPOwt. Upon SDS-PAGE under non-reducing conditions, we observed dimer formation for both TPOwt and TPOΔpro. Furthermore, we tested by flow cytometry the reactivity of TPO constructs with anti-TPO antibodies and confirmed that the pro-sequence deletion did not disturb TPO transport to the membrane of CHO cells. ELISA and flow cytometry analysis revealed that the conformation of epitopes recognized by a panel of human anti-TPO antibodies was not considerably affected in TPOΔpro. Deletion of the pro-peptide resulted in significant reduction in enzymatic activity. Study of the carbohydrate content showed that TPOΔpro at the cell surface, similarly as TPOwt, bore predominantly complex-type N-glycans, whereas intracellular TPOΔpro is more diversified and contains complex oligosaccharide or high-mannose-type structures. In conclusion, the pro-sequence was not essential for the proper folding and transport of TPO produced in CHO cells. Moreover, the TPOΔpro protein is correctly posttranslationally modified except for heme fixation.

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OP28

ALCOHOL CONSUMPTION IS PROTECTIVE FOR DEVELOPMENT OF AUTOIMMUNE HYPOTHYROIDISM – A POPULATION-BASED STUDY

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Objectives: Alcohol consumption is an important (protective) risk factor for a number of autoimmune diseases, but virtually nothing is known on the possible association between alcohol consumption and overt autoimmune hypothyroidism. In order to answer this question, we performed a case control study of patients with incident autoimmune overt hypothyroidism (n=140) prospectively identified in a Danish population-based study, and of age- and sex-matched controls with normal thyroid function and no history of thyroid

disease (n=560) recruited simultaneously from the same population and undergoing the same investigational program.

Methods: Participants gave information on alcohol intake, smoking habits, and family history of hypothyroidism. We analyzed the association between various alcohol intake patterns and development of hypothyroidism in univariate and multivariate models.

Results: Hypothyroid cases had a lower reported alcohol consumption compared with the controls (median units of alcohol (12g) per week: 3 vs. 5 units, $p < 0.013$). Odds ratios (OR) (univariate model) for developing hypothyroidism were significantly lower among subjects who consumed alcohol compared to alcohol abstainers (abstainers: 0 units/week, reference, OR = 1.00): consumers of 1-10 units/week: OR (95% confidence interval): 0.58 (0.35-0.96); 11+ units/week: 0.40 (0.21-0.78)). Odds ratios were similar in multivariate models including smoking habits and family history of hypothyroidism: 1.00/0.59 (0.35-0.99)/0.41(0.21-0.79). No interaction was found with regards to sex or age, and neither did we find any interaction comparing type of alcohol (wine vs. beer).

Conclusions: Alcohol consumption seems to confer considerable protection against development of overt autoimmune hypothyroidism - in women and men, at all ages, and regardless of type of alcohol consumed.

OP29

THYROID AUTOIMMUNITY IN MALIGNANT AND BENIGN BREAST DISEASE BEFORE SURGERY

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Objectives: A high prevalence of thyreoperoxidase antibodies (TPOAb) and of autoimmune thyroid disorders (ATD) has been shown in patients with breast cancer (BC) after treatment (surgery, chemo and/or radiotherapy). The aim of this study was to evaluate the prevalence of ATD in patients with nodular breast disease before any treatment.

Patients: 61 women aged 52.8±10.2 yrs (mean age±s.d.) with breast diseases submitted surgery: 36 (59%) with BC and 25 with benign breast disease (BBD). Controls included 100 healthy age-matched women.

Methods: All patients and control subjects were submitted to clinical, thyroid ultrasound (US) and serum-free thyroxine (FT4), serum-free tri-iodothyronine (FT3), TSH, TPOAb and thyroglobulin antibodies (TgAb) determination.

Results: Serum FT3, FT4 and TSH were not significantly different between patients with BC, BBD and controls. The prevalence of TPOAb in BC patients (12/36:33.33%) was significantly higher than in BBD patients (5/25:20%) ($P< 0.01$) and in controls (8/100:8%) ($P< 0.01$). The prevalence of TgAb in BC patients (12/36:33.33%) was significantly higher than that detected in BBD patients (4/25:16%) ($P< 0.01$) and in controls (12/100:12%) ($P< 0.01$). A diffuse hypoechogenic pattern at US was present in 20/36 (55.5%) BC patients and in 7/25 (28%) BBD ($P=0.03$). An association of hypoechoic pattern at US and positive antithyroid antibodies (TAb) was present in10/20 (50%) BC patients and in 2/7 BBD patients (28.57%) ($P< 0.0001$). Signs of ATD (hypoechoic pattern associated or not with TAb) was present in 24/36 (66.7%) BC patients and in 9/25 (36%) BBD patients ($P=0.02$).

Conclusions: Our results confirm the strong relation between ATD and BC. This finding is independent of treatment of BC or BBD and underline the usefulness of screening for ATD in patients with nodular breast disease.

OP30

THYROID AUTOIMMUNITY AND HASHIMOTO'S THYROIDITIS AFTER UNIVERSAL IODINE PROPHYLAXIS: THE 2010 PESCOPAGANO SURVEY

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Objectives: The results of two surveys performed in 2010 and 1995 in a iodine-deficient community, (Pescopagano, Italy) were compared to investigate if iodine prophylaxis modified the prevalence of circulating thyroid autoantibodies (TAb) and Hashimoto's thyroiditis (HT).

Subjects: 1194 subjects (91 children and 1102 adults) in 2010 and 1411 subjects (419 children and 992 adults) in 1995 underwent to medical exam, thyroid ultrasound (US), measurement of serum FT4, FT3, TSH, TgAb, TPOAb and urinary iodine excretion (UIE).

Results: Median UIE was significantly higher in 2010 than in 1995 (95 µg/L vs 55 µg/L). Positive TAb were significantly more frequent in 2010 (232/1194, 19.4%) than in 1995 (178/1411, 12.6%, $p < 0.001$). On the whole, HT (defined as subjects with circulating TAb and/or hypothyroidism and/or hypoechoic pattern at US) was significantly more frequent in 2010 than in 1995 (153/1194, 12.8% vs 50/1411, 3.5% $p < 0.001$), both in young (15-45 yr) adults (64/507 12.6%, vs 19/591 3.2%, $p< 0.0001$) and in older (46-75 yr) adults (76/502, 15.1% vs 21/349, 6.0 %; $p< 0.0001$), but not in subjects older than 75 yr (7/52, 13.4% vs 7/86, 8.1%). Hypothyroidism was significantly more frequent in 2010 vs 1995 (58/1194, 4.8% vs 40/1411 2.8%; $p=0.006$). All hypothyroid subjects had HT.

Conclusions: A significant increase of the frequency of TAb and of HT was observed 15 years after iodine prophylaxis. In 2010 with respect 1995, an increased frequency of HT was found in both young and older adults and also the overall prevalence of hypothyroidism was significantly higher.

OP5 Thyroid Hormone Basic 1

OP31

EFFECT OF LACKING GPB5 ON DEIODINASE EXPRESSION IN PERIPHERAL TISSUES THAT EXPRESS THE THYROTROPIN RECEPTOR

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The putative glycoprotein hormone thyrostimulin, comprised of the GPA2 and GPB5 subunit, can activate the TSH receptor (TSHR), but its role in physiology has not been elucidated so far. As activation of the TSHR stimulates deiodinase expression in peripheral tissues we hypothesized that thyrostimulin may affect peripheral thyroid hormone metabolism.

We therefore studied the effects of lacking GPB5 on deiodinase expression in TSHR-expressing peripheral tissues during hypothyroidism, euthyroidism and hyperthyroidism in mice. We analyzed type 2 deiodinase (D2) and D3 expression and activity in muscle, white and brown adipose tissue (WAT and BAT) of $GPB5^{-/-}$ and wild type (WT) mice.

In muscle, D2 mRNA expression was higher in hypothyroid $GPB5^{-/-}$ compared to WT mice. Muscle D2 activity was not detectable during any of the conditions. Muscle D3 mRNA and activity decreased in hypothyroidism and increased in hyperthyroidism similarly in $GPB5^{-/-}$ and WT mice.

In WAT, D2 mRNA increased markedly during hyperthyroidism in $GPB5^{-/-}$ and WT mice. D2 activity was only detectable in WAT of hyperthyroid $GPB5^{-/-}$ and WT mice. D3 mRNA and activity decreased during hypothyroidism and increased during hyperthyroidism in $GPB5^{-/-}$ and WT mice to a similar extent.

In BAT, D2 mRNA and activity were higher in euthyroid $GPB5^{-/-}$ mice compared to WT. Hypothyroidism increased D2 mRNA and activity markedly in female - but not male - $GPB5^{-/-}$ mice while no differences were observed in WT mice. BAT D3 mRNA and activity increased during hyperthyroidism in both $GPB5^{-/-}$ and WT mice.

We conclude that lacking GPB5 results in altered D2 expression in muscle and BAT that are difficult to reconcile with TSHR activation by thyrostimulin. The results are in line with an inhibitory effect of GPB5 on D2 expression.

This work was supported by a grant from MSD and the $GPB5^{-/-}$ mice were generated by Lexicon Genetics Incorporated.

OP32

ANALYSIS OF MOUSE MUTANTS DEFICIENT IN THE THYROID HORMONE TRANSPORTER OATP1C1

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The organic anion transporting polypeptide 1c1 (Oatp1c1; Slco1c1) represents a high-affinity T4 transporter that is predominantly expressed in brain capillary endothelial cells as well as in astrocytes. Based on its substrate specificity and its restricted expression pattern Oatp1c1 may be critically involved in mediating the passage of T4 across the blood brain barrier (BBB). In order to gain further information about its physiological function, transgenic animals were generated which carry loxP sites (fl) flanking exon 3 of the Oatp1c1 gene. By breeding Oatpc1c1 fl/fl animals with mice carrying a germ-line deleter cre recombinase construct, we obtained animals that are globally deficient in Oatp1c1 as shown by southern blot analysis and immunohistochemistry. A preliminary analysis of these animals revealed that Oatp1c1 ko mice are born at a normal mendelian rate, are fertile and do not exhibit any overt neurological abnormalities. Serum thyroid hormone levels and D1 mRNA levels in liver and kidneys were indistinguishable between Oatp1c1 ko mice and wild type littermates. In contrast, tissue content of T4 in the brain was found to be significantly decreased and D2 activities were strongly increased in Oatp1c1-deficient animals. Moreover, qPCR analysis of brain homogenates revealed decreased mRNA levels of T3-regulated genes RC3, hairless, Aldh1a1 and Cbr2 indicating a hypothyroidal state of the CNS in the absence of Oatp1c1. Ongoing studies should reveal to which extent the transport of T4 via the BBB and/or into astrocytes is impaired in the absence of Oatp1c1.

OP33

CARDIAC INDUCTION OF THE THYROID-HORMONE DEGRADING ENZYME DEIODINASE TYPE III IN HUMAN ISCHEMIC HEART DISEASE

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Objective: Deiodinase type III (D3) activity is markedly and stably induced in the left ventricle (LV) following myocardial infarction in mice. The subsequent remodeling of the LV and the development of ischemic heart disease (ISHD) is associated with decreased LV tissue TH content and decreased TH-dependent transcription activity in cardiomyocytes. This local hypothyroid condition may contribute to the development of heart failure, given the known regulation by TH of cardiac genes implicated in contractile dysfunction in ISHD. Here, we investigated whether D3 is also induced in myocardium of heart-failure patients suffering from ISHD.

Methods: LV tissue samples from ISHD patients (n=23) were obtained during heart transplantation surgery. Non-failing heart tissue was obtained from donor hearts (n=55). Tissue micro-arrays of 120 individual 4 µm thick paraffin sections of duplicate LV cores of 1 mm diameter of patients and donors were stained with affinity-purified anti-human-D3-antibody. Staining intensity of the blinded samples was scored by three investigators using a visual grading score of 1 to 4 (no staining to strong staining) and the scores were averaged.

Results: Little or no D3 staining was found in donor samples, with 46 out of 55 scoring 1-2.5. In contrast, D3 staining in 14 out of 23 ISHD samples ranged from 3.5 to 4. In most of the D3-positive ISHD samples all cardiomyocytes showed high D3 expression, but in some samples both D3-positive and non-stained cardiomyocytes were intermixed, similar to what is found in ischemic mouse myocardium.

Conclusion: This study demonstrates for the first time that cardiac D3 activity is induced in human ischemic heart disease. This suggests that the D3-dependent local hypothyroid condition of the heart found in mice following myocardial infarction, may also apply to the human situation and contribute to the development of heart failure.

OP34

DIFFERENTIAL EXPRESSION PATTERN OF THYROID HORMONE TRANSPORTERS IN THE MOUSE CNS

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Thyroid hormone actions in the brain requires the presence of thyroid hormone transporters that not only mediate the transport across the blood- brain barrier (BBB) but also facilitate the uptake of thyroid hormone into neurons and glia cells. So far, only limited information is available about the cellular distribution pattern of thyroid hormone transporters that may play an important role particularly during critical stages of brain development. In our study, we determined the mRNA expression pattern of the transporters Mct8, Mct10, Lat1, Lat2, and Oatp1c1 in the mouse brain at the postnatal days P6, P12, P21 and P120 in wild-type and athyroid Pax8 ko mice by in situ hybridization histochemistry. In addition, we included mice in our studies that lack the thyroid hormone transporter Mct8 and, consequently, exhibit an impaired uptake of T3 into the brain. In agreement with previous data we observed a strong expression of Oatp1c1 and Lat1 at the blood-brain barrier and in astrocytes whereas Mct8 hybridization signals were restricted to larger capillaries, choroid plexus and to distinct neurons in the cerebral cortex, hippocampus, striatum, cerebellum and hypothalamus. For Lat2, specific mRNA signals were found in the cerebral cortex, hippocampus and cerebellar Purkinje cells indicating an overlapping expression pattern with Mct8. However, a strong expression for Lat2 was also found in neurons throughout the thalamus, an area devoid of any specific Mct8 labeling. During the first postnatal weeks, Mct10 specific hybridization signals were found in hippocampal granule cells, in the cerebellum as well in the cerebral cortex. Surprisingly, in the adult brain, Mct10 mRNA expression was restricted to white matter regions indicating age-dependent alterations in the localization. Based on our analysis, we propose distinct functions for these transporters in the mouse brain that may even change during postnatal development.

OP35

LIVER THYROID HORMONE CONCENTRATIONS IN RATS ON AMIODARONE OR DRONEDARONE TREATMENT CORRELATE WITH LIVER DEIODINASE ACTIVITIES AND ARE INDEPENDENT OF LIVER THYROID HORMONE TRANSPORTERS

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Background: The iodine-containing drug Amiodarone (AM) and its non-iodine containing analogue Dronedarone (Dron), are very potent antiarrhythmic drugs. AM acts as a thyroid hormone receptor (TR) a_1 and b_1 antagonist whereas Dron selectively inhibits binding of T_3 to TRa_1. AM treatment results in profound alterations in serum T_4 and T_3 levels as well as altered hepatic T_3 target gene expression, while Dron has only minor effects on these parameters. It is unknown at present to what extent AM and Dron affect liver thyroid hormone concentrations.

Objective and Methods: In this study, we investigate the effect of AM and Dron on liver T_4 and T_3 content, type 1 deiodinase (D1) and D3 activity as well as MCT8 and MCT10 mRNA expression. Three groups of male rats received either AM, Dron or vehicle by daily intragastric administration for two weeks. Serum T_3 and T_4 were measured by immunoassay. Tissue T_3 and T_4 concentrations were measured using liquid chromatography-tandem MS. Liver D1 and D3 activities were measured by Sephadex columns and HPLC, respectively, and mRNA expression was measured by qPCR.

Results: AM treatment decreased serum T_3 by 30% while serum T_4 increased by 50% compared to Dron treated and control rats. Liver T_3 content showed a substantial decrease compared to Dron and control rats upon AM treatment (50%, $p< 0.01$) but liver T_4 content was unaffected. Liver D1 activity and mRNA decreased while D3 activity and mRNA increased in AM-treated

rats compared to Dron and control rats. Of note, MCT8 and MCT10 mRNA expression were similar between the groups.

Conclusion: Profound alterations in liver D1 and D3 activities due to AM treatment are likely to cause a marked reduction in hepatic T3 content, which is unlikely to result from changes in thyroid hormone transporters in the liver.

OP36

SELENIUM AND THYROID HORMONES IN POSTMENOPAUSAL HEALTHY WOMEN

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Introduction: Thyroid Hormone (TH) activation and inactivation is controlled by the family of iodothyronine deiodinases (DIO). There are three DIO isozymes, all of which contain the trace element selenium (Se) in their active site belonging to the small family of selenoproteins. It is hypothesized that Se controls DIO biosynthesis and TH status.

Methods and Subjects: Serum samples from healthy women participating in the OPUS (Osteoporosis and Ultrasound Study) were analysed. Individuals with thyroid disease, chronic illness, or those receiving drugs affecting thyroid function were excluded. Values for fT4, fT3, TSH and fT4/fT3 ratio were determined on an automated analyzer. Se concentrations were assessed by total reflection X-ray fluorescence. Selenoprotein P (SePP) was determined by a luminometric assay. Normal distribution was tested by the Kolmogorov-Smirnov test. Se or SePP and thyroid status were compared by stepwise adjusted regression analysis.

Results: A total of 1565 women were analysed. Average Se concentrations were 98.6 ± 26.6 µg/L. Se and SePP correlated positively (Spearman's rho = 0.324; $P < 0.001$). After adjustment for age, BMI and smoking, higher levels of Se and SePP were associated with lower levels of fT4 *(Se:*β = -0,096; $P < 0,001$; SePP: β = -0,103; $P < 0,001$) and fT3 (Se: β = -0,085; $P = 0,001$; SePP: β = -0,171; $P < 0,001$). There were no associations of Se status with TSH ($\beta = 0,033$; $P = 0,196$).

Discussion and Conclusion: In our study, the majority of healthy postmenopausal European women were not Se deficient or hypothyroid. Their free TH concentrations and Se status were significantly interrelated. TSH as the major indicator of thyroid status appeared independent of the actual Se supply. These findings are indicative of modulating Se effects on thyroid gland functioning or biosynthesis of hepatic TH-binding proteins, which might be important during disease.

OP37

REGULATION OF BRAIN TH SIGNALLING DURING THE PERINATAL PERIOD IN EUTHYROID AND HYPOTHYROID PUPS

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Thyroid hormone (TH) regulation of perinatal neurogenesis exemplifies the many physiological process co-ordinated by these signals. In the adult, circulating TH availability is tightly controlled, both peripherally by local deiodinases and centrally by the Hypothalamic Pituitary Thyroid (HPT) axis. However, in the newborn mouse the HPT axis is developing and little is known about the establishment of negative feedback loops that control circulating TH levels at this stage. In the first two postnatal weeks circulating TH levels increase, ensuring proper brain maturation. TH deficiency, at this stage, affects brain development; the severity of the phenotype depending on timing and degree of hypothyroidism. Given the importance of TH signalling at this time, one can predict that TH availability must be tightly controlled both temporally and spatially. Impaired TH availability during axis maturation will also have consequences on the control of TH homeostasis in adult. T3 availability in the brain is result of T3 generation by type 2 deiodinase (D2) and TH degradation by type 3 deiodinase (D3). Clearly, T3 action also requires expression of the thyroid receptors (TR) and membrane TH transporters. Here, we addressed the differential expression of TR isoforms, D2, D3 and TH transporters in euthyroid *vs* hypothyroid pups. Two brain areas were compared: the hypothalamus and a neurogenic area, the tissues surrounding the lateral ventricule (VZ). We also investigated how the transcriptional regulation certain genes by T3 was affected by thyroid status. Our data show that as early as one day of post-natal life in mice, all the main elements of the transcriptional network governing the control of TH availability are expressed. Furthemore, thyroid status at birth differentially affects T3-responses, in a tissue and gene-dependent manner.

OP38

EFFECTS OF AMIODARONE (AMIO) ON THYROID HORMONE (TH) TRANSPORT AND METABOLISM

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Introduction: Amio is an anti-arrhythmic agent with major side effects on thyroid function and TH metabolism. The latter may be mediated by Amio itself or by metabolites such as compound L3373, which lacks the triethylamine side-chain and thus shows a high structural resemblance with TH. Benziodarone (Benz) is a vasodilator with a structure almost identical to L3373.

Aim of the study: To determine the effects of Amio and analogs on cellular TH transport and metabolism.

Materials & Methods: JEG3 cells where transfected with the TH transporters MCT8 or MCT10 with or without µ-crystallin (CRYM), a high-affinity cytoplasmic TH-binding protein. Uptake of T3 was studied in the presence of 0, 1, 10 or 100 µM Amio or Benz. We also studied 1) the effects of Amio on the uptake and metabolism of T3, T4 and Triac in HepG2 liver cells, and 2) the effects of Amio, L3373 and Benz on recombinant human D1, D2 and D3 activities.

Results: Amio had no direct effect on D1, D2 and D3, but all deiodinases were potently inhibited by L3373 and Benz. T3 uptake by MCT8 and MCT10 was 50% inhibited by both Amio and Benz at 100 µM. T4, T3 and Triac uptake by HepG2 cells was not inhibited by Amio. T4 and T3 were hardly metabolized by HepG2 cells, but Triac showed rapid D1-mediated metabolism, which was inhibited dose-dependently by Amio with complete inhibition at 100 µM.

Conclusion and Discussion: Our results suggest that TH transport by MCT8 and MCT10 is modestly inhibited by Amio. D1, D2 and D3 activities are unaffected by Amio but potently inhibited by the Amio metabolite L3373. The inhibition of Triac metabolism by D1 in HepG2 cells is probably mediated by an Amio metabolite such as L3373.

OP6 Graves' Disease

OP39

A NOVEL MECHANISM INVOLVED IN THE PATHOGENESIS OF GRAVES OPHTHALMOPATHY (GO) - CLATHRIN IS A POSSIBLE TARGETING MOLECULE FOR INHIBITING LOCAL IMMUNE RESPONSE IN THE ORBIT

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Introduction: Excessive orbital fibroblast (OF) proliferation and extracellular matrix production, as well as inflammation resulting in the expansion and remodeling of orbital tissue, are characteristic of Graves ophthalmopathy (GO). Our aim was to analyze and inhibit signaling pathways in resident OFs that are involved in GO.

Methods/Main Outcome Measures: Primary human OFs were obtained from 12 patients with active, severe GO and from 12 healthy control subjects. The cells were characterized by immunofluorescence assay and flow cytometry. Tyrosine phosphorylation of cellular proteins was determined by Western blot techniques, immunoprecipitation, and mass spectrometry. Cell proliferation was determined by BrdU incorporation, ELISA evaluation of hyaluronic acid (HA) production, and dichlorofluorescein assay of intracellular reactive oxygen species (ROS). Clathrin heavy chain (CHC) expression was inhibited with siRNA technology.

Results: Tyrosine phosphorylation of CHC is constitutively increased in vitro in GO-derived OFs, independent of serum or other stimulating factors. The proliferative and biosynthetic capabilities (production of HA, ROS) of GO-derived OFs are significantly higher than those of OFs from healthy control subjects. Downregulation of CHC expression leads to a normalization of pathologically increased proliferation and production of HA and ROS in GO-derived OFs in vitro.

Conclusions: Our findings strongly suggest that clathrin and clathrin-mediated signaling pathways are involved in the inflammatory signal transduction of OFs in GO. With the identification of clathrin, we report a new potential targeting molecule for specific pharmacological inhibition of the local inflammatory response characteristic of GO.

OP40

THE ECONOMIC BURDEN OF GRAVES' ORBITOPATHY

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Aims: Patients with Graves´ orbitopathy (GO) suffer from disfiguring proptosis, diplopia and/or sight loss. For the first time, the public health relevance of GO was investigated.

Methods: Within a Multidisciplinary University Orbital Center, 680 subjects (310 patients with GO and 370 controls) were prospectively enrolled. Complete endocrine and ophthalmic investigation of all GO-patients was performed. Subsequently, information pertaining to work disability, sick-leave, and the specific therapies were collected. Productivity losses were assessed by the human capital approach. Direct costs were gathered according to an official German code system.

Results: A higher prevalence of work disability was noted in patients with GO (n=77, 35%, p< 0.001) than in healthy subjects (n=5, 8%), patients with either Graves´ disease or Hashimoto´s thyroiditis without eye signs (n=15, 11%), patients with various non-thyroidal autoimmune diseases (e. g. rheumatoid arthritis; n=8, 20%) or benign thyroid nodules (n=2; 4%). Compared to the German average of 11.6 days/year, 22%, 21%, 6%, and 12% of patients with optic neuropathy, moderately severe, mild GO, and controls, respectively, were longer on sick-leave (p=0.026). Patients with optic neuropathy were twice as often work disabled than patients without optic nerve compression (64% vs. 32%, p=0.033). The rate of work disability was 71%, 41%, 41% and 22% in patients with constant, inconstant, intermittent and absent diplopia, respectively (p< 0.001). Non-smokers were less often work disabled than smokers (n=30, 27% vs. n=46, 41%; p=0.002). The total indirect costs averaged 6,568 Euros/year whereas the direct costs due to GO-specific therapies were 2,573 ± 336 Euros/patient. Estimates of total direct costs of GO in Germany were 2.5 billion Euros and the calculated direct costs were 6.4 billion Euros/year.

Conclusions: These data demonstrate the economic burden of GO, which incurs immense indirect and direct costs. Impaired earning capacity is mostly noted in patients with diplopia and/or optic neuropathy.

OP41

SERUM BAFF CONCENTRATIONS IN PATIENTS WITH GRAVES' DISEASE (GD) AND ORBITOPATHY (GO) BEFORE AND AFTER IMMUNOSUPPRESSIVE TREATMENT

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B cells are known to play a key role in the pathogenesis of autoimmune disease. B-lymphocyte activating factor (BAFF), a member of TNF family, promotes autoantibody production by increasing B cell survival and proliferation. Serum BAFF concentrations have been shown to be increased in systemic lupus erythematosus, rheumatoid arthritis and Sjogren syndrome.

Objective: Aim of the present study was to measure serum BAFF concentrations in patients with GD with or without GO in relation to immunosuppressive treatment.

Methods: Forty-three patients and 9 normal control subjects (C) were studied. Thirty-five patients had GO which was active in 23. Of these, 9 were treated with rituximab (RTX) and 14 were treated with i.v. steroids (IVGC). Serum BAFF concentrations were measured in all patients at baseline, at peripheral B cell depletion and repopulation after RTX and after therapy with IVGC.

Results: Mean±SD serum basal BAFF concentrations in GD patients were significantly higher when compared to C (P=0.001) and no difference was observed in those with or without active GO (P=NS). Serum BAFF concentrations were also significantly correlated with serum TgAb (P=0.04), but not with sex, age, smoking habits, therapy for thyroid disease and serum TPOAb and TRAb (P=NS). After RTX, there was a significant, four-fold increase of serum BAFF concentrations at the time of B cell depletion (P=0.02) but also at B cell repopulation (P=0.04). In patients treated with IVGC serum BAFF concentrations decreased significantly after therapy (P=0.001).

Conclusion: We report, for the first time, that BAFF concentrations are increased in the serum of patients with GO and they increase further after B cell depletion with RTX. The decrease of serum BAFF after IVGC may be due to the steroid-induced inhibition of BAFF production. These data further underscore the importance of B cells involvement in the pathophysiology of GD and GO.

OP42

CIRCULATING CXCL10 AND CCL2 CHEMOKINES IN PATIENTS WITH GRAVES' OPHTHALMOPATHY WITH PREVALENT EXTRAOCULAR MUSCLE INVOLVEMENT: MODULATION BY CYTOKINES AND BY PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ALPHA AGONISTS IN PRIMARY MYOBLASTS

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Objective: The Th1 and Th2 chemokines are expressed in muscle during the course of inflammatory myopathies. However, until now, no study has evaluated the involvement of these chemokines in extraocular muscle myopathy in Graves' ophthalmopathy (GO).

Methods: We have compared serum CXCL10 and CCL2 levels in active GO patients with prevalent extraocular muscle (EOM) involvement with respect to those with prevalent orbital fat (OF) expansion.

Furthermore, the effects of IFN-gamma and TNF-alpha stimulation, and of increasing concentrations of PPAR-alpha agonists (ciprofibrate, fenofibarte, gemfibrozil; 10, 100, 400 mcM), on Th1-chemokine (CXCL10) and Th2-chemokine (CCL2) secretion in primary cultures of myoblasts from eye muscle of GO patients were tested.

Results: Serum CXCL10 levels were higher in both OF and EOM patients, than in controls, however no significant difference was observed between OF and EOM patients. Serum CCL2 levels were not significantly different in controls, or in both OF and EOM patients.

In primary myoblasts cultures (EOM-c) from patients with GO, CXCL10 was undetectable in the supernatant. IFN-gamma dose-dependently induced CXCL10 release, whereas TNF-alpha alone had no effect. The combination of TNF-alpha and IFN-gamma had a significant synergistic effect on CXCL10 secretion. EOM-c produced in basal condition low amounts of CCL2. TNF-alpha dose-dependently induced CCL2 release, whereas IFN-gamma alone had no effect. However, the combination of TNF-alpha and IFN-gamma had a significant synergistic effect on CCL2 secretion.

Treatment of EOM-c cultures with PPAR-alpha agonists (ciprofibrate, fenofibarte, gemfibrozil), added at the time of IFN-gamma and TNF-alpha stimulation, dose-dependently inhibited CXCL10 and CCL2 release.

Conclusion: High levels of CXCL10 are present in EOM and OF patients. Extraocular muscles in GO participate in the self-perpetuation of inflammation by releasing both Th1 (CXCL10) and Th2 (CCL2) chemokines under the influence of cytokines. PPAR-alpha activation plays an inhibitory role both on Th1 and Th2 chemokines.

OP43

SERUM SELENIUM IS LOW IN NEWLY DIAGNOSED GRAVES`DISEASE AND AUTOIMMUNE HYPOTHYROIDISM. A POPULATION BASED STUDY

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Selenium (Se) is an essential trace element required for thyroid hormone biosynthesis and metabolism. Studies have suggested that Se deficiency plays an important role in initiation and progression of autoimmune thyroid disease in genetically predisposed individuals.

Aim: To compare s-Se values in patients with newly diagnosed autoimmune thyroid disease and controls from the Danish population.

Methods: S-Se was measured (in triplicate by a fluorimetric method) in patients with newly diagnosed Graves`disease (GD) (n = 97) and autoimmune overt hypothyroidism (AIH) (n = 96), and for comparison, in euthyroid subjects with high serum levels of TPO-Ab (TPO-Ab > 1500 U/ml, n = 92) and in random controls (n = 830). Patients and controls were consecutively included from two population based surveys. Data were analysed in univariate and multiple linear regression models to adjust for possible confounders.

Results: S-Se was lower in patients with GD than in controls (mean (SD), GD: 89.9 µg/l (18.4); controls: 98.8 µg/l (19.7), $p < 0.01$). This was confirmed in a multivariate linear regression model adjusting for age, sex, mineral supplements, smoking, geographical region and time of sampling ($p < 0.01$). In a univariate model, s-Se was similar in patients with AIH (mean (SD): 98.4 µg/l (24.9)) and in controls ($p = 0.86$). In the multivariate model however, s-Se was lower in patients with AIH compared to controls ($p = 0.04$). There was no significant difference in s-Se between euthyroid participants with high TPO-Ab and controls (univariate: $p = 0.97$; multivariate: $p = 0.27$).

Conclusion: In a carefully controlled, population based study, patients with newly diagnosed GD and AIH had significantly lower s-Se compared with random controls. This observation supports the postulated link between inadequate Se supply and overt autoimmune thyroid disease.

OP44

HYPERTHYROIDISM, RATHER THAN AUTOIMMUNITY, SEEMS TO DETERMINE QUALITY OF LIFE IN PATIENTS WITH GRAVES´ DISEASE

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Purpose: To evaluate relationships between clinical variables and thyroid-specific quality of life (QoL) in Graves´ hyperthyroidism.

Methods: The thyroid-specific QoL-questionnaire ThyPRO was completed by 168 cross-sectional outpatients with Graves´ hyperthyroidism. Blood samples were drawn and an ultrasound and a clinical examination performed at time of completion of the questionnaire. ThyPRO measures thyroid-related QoL in 13 scales: 6 physical and psychological symptom scales (Goitre-, Hyperthyroid-, Hypothyroid-, and Eye symptoms, Depressivity and Anxiety), 3 function and well-being scales (Tiredness, Cognitive problems and Emotional susceptibility) and 4 scales measuring participation (Imparied Social life, Daily life, Sex life and Cosmetic concern). Data were analyzed within a QoL framework, both univariately and multivariately. The clinical variables entered were thyroid volume, low TSH, high fT_4, high fT_3, high TSH, low fT_4, low fT_3, CAS, NOSPECS, TPO-Ab and TSHR-Ab.

Results: In initial pairwise analyses, all clinical variables were related to one or more QoL scales. However, in the path analysis multivariate model only hyperthyroid function, i.e. lower TSH and higher fT_3 was related to QoL scales. Low TSH and high fT_3 both affected Hyperthyroid Symptoms (standardized partial regression coefficient r=-0.28 and 0.28 respectively, $p< 0.01$ for both), which in turn was related to all three well-being scales (Tiredness r=0.45, $p< 0.0001$, Cognition r=0.32, p=0.003, Susceptibility r=0.26, $p< 0.0001$) as well as Impaired Daily life (r=0.41, $p< 0.0001$). FT_3 also had a direct relationship with Tiredness (r=0.16, p=0.029), Impaired Daily life (r=0.16, p=0.026) and Impaired Sex life (r=0.38, $p< 0.0001$).

Conclusion: When analyzed univariately, many clinical measures were related to impact on thyroid-related QoL. However, when analyzed multivariately, QoL was related solely to thyroid hyperfunction through hyperthyroid symptoms. QoL was not associated to TSHR-Ab or TPO-Ab levels indicating only minor influence of autoimmunity *per se* on QoL in patients with Graves' disease.

OP45

COMPARISON OF EARLY TOTAL THYROIDECTOMY WITH ANTITHYROID TREATMENT IN PATIENTS WITH MODERATE TO SEVERELY ACTIVE GRAVES' ORBITOPATHY, A RANDOMIZED PROSPECTIVE TRIAL

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Objectives: We aimed to compare early total thyroidectomy with the anti-thyroid treatment regimens, in patients with moderate to severely active Graves' orbitopathy (GO) prospectively.

Methods: The inclusion criteria: Hyperthyroidism and GO developed in the last six months, thyroid volume ≥15 mL, no previous treatment except local interventions for GO. GO activity has been defined as clinical activity score (CAS) ≥3 and carrying at least one of the following criteria; Proptosis ≥21 mm in one eye, ≥2 mm difference between two eyes, presence of diplopia, lid aperture ≥9 mm. Initially, all the patients were made euthyroid (TSH 0.4-1 mIU/L). Pulse methylprednisolone of total 4.5 gr were given intravenously to all patients before randomization. In the first group, patients were sent to total thyroidectomy and TSH levels were kept within 0.4-1 mIU/L with levothyroxine. Second group of patients were followed with anti-thyroid drugs and with the addition of levothyroxine, when necessary, to keep TSH within 0.4-1 mIU/L.

Results: 12 patients were randomized to total thyroidectomy (TT) group and 11 patients were randomized to medical antihyroid treatment (AT) group. There were no difference between the two groups with respect to age, gender, smoking habit, duration of hyperthyroidism and GO, thyroid volume, TSH, free T4, anti-TPO, anti-Tg and TRAb levels initially. When the TT group was compared with AT group, thyroid antibodies were significantly decreased in TT group while there was no significant difference with respect to proptosis, lid aperture, CAS and diplopia between groups. However in TT group additional pulse methylprednisolone treatment was given to 3 (25%) patients and urgent orbital decompression was applied to 2 (17%) of those patients.

Conclusion: Although the significant decrease of thyroid autoantibodies were achieved in TT group, this was not reflected as an beneficial effect on the course of GO during the 15 months follow-up period.

OP46

IS THE ASSOCIATION BETWEEN OVERT HYPERTHYROIDISM AND MORTALITY CAUSAL? CRITICAL REVIEW AND META-ANALYSIS

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Background: Overt hyperthyroidism has been associated with e.g. cardiac arrhythmias, hypercoagulopathy, stroke and pulmonary embolism, which all may increase mortality. Some, but not all studies show an increased mortality in patients with hyperthyroidism. This inconsistency may be due to differences in study design, characteristics of participants, or confounding. In order to test whether hyperthyroidism influences mortality, we performed a critical review and statistical meta-analysis.

Methods: Based on an electronic PubMed search, using the MeSH-words hyperthyroidism, thyrotoxicosis and mortality or survival, case-control and cohort studies were selected and reviewed. Using meta-analysis an overall Relative Risk (RR) of mortality was calculated. In order to test consistency, the analyses were repeated using different study-combinations.

Results: Eight studies fulfilled the inclusion criteria, six of which showed an increased all-cause mortality. Seven studies, including 31138 patients and 400.000 person years at risk, allowed calculation of mortality. Based on this, the RR of overall mortality was 1.21 (95% CI: 1.05-1.38). Analyses including studies considering setting and control for co-morbidity did not significantly alter this finding. Six studies, reporting cardiovascular mortality were pooled and showed an increase in cardiovascular mortality (RR 1.19; 95% CI 1.00-1.29). An increased, but statistically non-significant, mortality risk remained when pooling the four studies where patients received radioiodine treatment, (1.17; 95% CI 0.98-1.39). As the squared-I ranges from 89.1% to 98.3%, which is much higher than the 50% generally viewed upon as a threshold, the statistical heterogeneity is very pronounced in the included studies.

Conclusion: In patients diagnosed with hyperthyroidism mortality is increased by approximately 20%. Future studies need to address the cause of hyperthyroidism, impact of choice of therapy, time dependency, as well as the potential influence of confounding or genetic susceptibility before the question of causality can be answered.

OP7 Thyroid Cancer Basic

OP47

THE TARGETED INACTIVATION OF THE TRβ GENE INCREASES RET-PTC$_3$-INDUCED GROWTH AND NEOPLASTIC TRANSFORMATION OF THE THYROID GLAND

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Besides their role in development and metabolism, thyroid hormone receptors (TR) might have a function in the control of cell growth. TRβ acts as an inhibitor of growth of transplanted tumors in nude mice and an inactivating TRβ mutation (TRβ$^{PV/PV}$) leads to the development of carcinoma in the thyroid. To further explore the tumor suppressor function of TRβ, we analyzed whether thyroid-selective inactivation of *TRβ* gene affects Ret/PTC$_3$-driven growth and neoplastic transformation of the gland. Mice devoid of functional TRβ (Thyr-TRβ$^{-/-}$mice) were generated by crossing transgenic Thyr-Cre mice (expressing the Cre recombinase selectively in the thyroid) with mice carrying TRβ^{flox} alleles. Thyr-TRβ$^{-/-}$mice were then crossed with mice expressing the Ret-PTC$_3$ oncogene selectively in the thyroid (RP3 mice). At 4 months of age, the size and functional state of thyroid of Thyr-TRβ$^{-/-}$mice did not differ from that of wild-type mice. RP3 mice were characterized by a 15-fold increase in thyroid weight as compared to normal mice (74 *versus* 4.8 mg) and a reduction of activity revealed by the decrease of plasma T4 concentration. Thyroid parameters of Thyr-TRβ$^{-/-}$/RP3 mice did not differ from those of RP3 mice. At 8 months of age, Thyr-TRβ$^{-/-}$ mice exhibited a 30% increase in thyroid weight (7.2 *versus* 4.8 mg in control mice) without change in plasma T4 and TSH concentrations and RP3 mice showed a further rise in thyroid size and maintained a low plasma T4 level. Interestingly, as compared to RP3 mice, Thyr-TRβ$^{-/-}$/RP3 mice showed an additional increase of thyroid mass (234 *versus* 162 mg) and the thyroid enlargement was accompanied by a decrease of plasma T4 and an increase of plasma TSH concentrations. In conclusion, we show that TRβ exerts a negative control on growth of normal thyroid and acts as a down regulator of oncogene-driven growth and neoplastic transformation of the gland.

OP48

TRANSCRIPTOME PROFILING OF LASER-MICRODISSECTED PAPILLARY THYROID CANCER CELLS

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Introduction: Transcriptome profiling of bulk tumor tissue gives the gene expression data for the mixture of cancer, stromal and infiltrating cells. Papillary thyroid cancer (PTC) has a very distinct gene expression profile (Jarzab, Cancer Res 2005). It is a matter of debate whether it depends mainly on the inherent gene expression changes in the thyrocyte or is the result of different cellular content.

Aim of the study: The aim of our analysis was to compare the gene expression profiles of isolated PTC thyrocyte populations and compare it to the profile of bulk PTC tissue.

Material and Methods: In the study we analyzed the transcriptome of 15 laser-microdissected PTC thyrocyte samples, 11 normal thyrocyte samples and compared it to bulk tissue samples (15 PTC and 15 normal thyroid). From microdissection we collected approx. 500.000 μm^2 of cells, 10-50 ng of RNA was taken for microarray analysis (HG-U133 Plus 2.0 Affymetrix).

Results: Genes were divided into 4 groups: (A) differentially expressed in microdissected and bulk samples ($p< 0.001$ = FDR< 2%, fold change > 4) - 559 probesets, (B) differentially expressed in bulk and not changed in microdissected samples - 160 probesets, (C) differentially expressed in microdissected and not changed in bulk tissues - 107 probesets, (D) remaining genes. No change was defined as $p>0.01$ (FDR>5%). All data will be presented, of special interest were the genes from group C, characteristic only for PTC microdissected samples. Among these 107 transcripts there were genes involved in MAPK signaling pathway and non-specific immune response, one of them was described as candidate susceptibility gene for PTC.

Conclusions: At least 100 transcripts are specific for the transformed PTC thyrocyte but their expression change is slight and could be detected only in pure cell population. These potential driver genes shall be further analyzed.

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OP49

IGF-I PROLIFERATIVE EFFECTS ARE INHIBITED BY TARGETING PKC IN HUMAN MEDULLARY THYROID CARCINOMA CELLS

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Insulin-like Growth Factor I (IGF-I) is a well known stimulator of cell proliferation also in the settings of neuroendocrine tumors. Previous evidence has shown that IGF-I stimulates cell proliferation and resistance to pro-apoptotic stimuli in medullary thyroid carcinoma (MTC) cell lines and primary cultures. IGF-I signals through many pathways, including protein kinase C (PKC). We here investigate whether PKC may mediate IGF-I proliferative stimuli in the in vitro models represented by MTC primary cultures and the TT cell line, by using a novel PKC inhibitor, Enzastaurin. We found that Enzastaurin inhibits IGF-I stimulated cell proliferation at 5 and 10 μM (concentrations reached also at plasma level in human clinical trials) by inducing caspase-mediated apoptosis both in MTC-derived cells. We found that Enzastaurin also reduces IGF-I stimulated phosphorylation of glycogen synthetase kinase 3 beta (GSK3-β), a downstream target of PKC pathway and a pharmacodynamic marker for Enzastaurin in TT cells. These data indicate that in MTC cells Enzastaurin blocks IGF-I induced proliferative stimuli inducing apoptosis, with a mechanism likely involving GSK3β signaling, indicating that PKC plays a crucial role in the control of human MTC proliferation and survival and that PKC inhibitors may represent a new pharmacological target in MTC.

OP50

CAMP ANALOGS: A NEW PERSPECTIVE IN THE TREATMENT OF POORLY DIFFERENTIATED THYROID CANCER

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Aims: Thyroid cancer is the most common endocrine malignancy. Most of the cases are well-differentiated and have a good prognosis, but there is a group of poorly differentiated thyroid carcinomas (PDTC) highly aggressive and scarcely responsive to currently available therapies. The aim of our study was to evaluate the effects of a PKA I-selective cAMP analogs association and of another well known analog (8-Cl-cAMP) on different cellular models of PDTC.

Methods: We performed our studies on a cell line derived from a PDTC of follicular origin (WRO) and on two cell lines derived from poorly differentiated human epithelial carcinomas (ARO and NPA) carrying the $BRAF^{V600E}$ mutation. We analyzed the effects of our treatments on proliferation, cell cycle, apoptosis and on key signaling pathways involved in regulation of cell fate as cAMP/PKA, Ras/Raf/ERK, p38MAPK, PI3K/Akt and AMPK pathways.

Results: Our results show that both treatments have antiproliferative effects, and these are only partially dependent of PKA´s activity modulation. In particular the PKA I selective analogs are cytostatic for the cell lines carrying the $BRAF^{V600E}$ mutation and this is due to the inhibition of ERK pathway, here directly involved in the process of malignant transformation. Differently, 8-Cl-cAMP is able to induce apoptosis in all cell lines after intracellular transformation in its metabolite 8-Cl-Ado, through the activation of AMPK, the subsequent activation of p38MAPK and finally of caspases 3/7.

Conclusions: These data show that site-selective cAMP analogs are promising anticancer agents for PDTCs. In the end 8-Cl-cAMP is able to induce apoptosis through p38-dependent pathway in all cell lines examined, while the action of the pair of PKA I selective analogs appears specific for epithelial tumors carrying the $BRAF^{V600E}$ mutation, which is a particularly frequent genetic alteration in papillary thyroid cancer with a low degree of differentiation.

OP51

PODOPLANIN AND PROX 1 IN DIFFERENTIATED THYROID TUMORS

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Background: Differentiated thyroid tumors (DTC) metastasize via different pathways: the papillary carcinoma (PTC) usually via lymphatic spread whereas follicular thyroid cancers (FTC) mainly hematogenously. These peculiarities in the metastatic features are not fully understood.

The Aim of the study: To examine the expression of lymphatic endothelial markers: podoplanin (PDPL), a small membrane mucine-type glycoprotein I and Prox 1, a lymphatic endothelial nuclear transcription factor in the PTC and FTC derived cell lines and in a series of DTC.

Methods: PDPL and Prox 1 expression was assessed in BcPAP, TPC1, FTC-133, CGTH-W-1, ML-1 cell lines using quantitative RT-PCR (Q-RT-PCR), Western blot and immunofluorescence methods and in 120 PTCs and 27 FTCs using immunohistochemical (IHC) staining.

Results: PDPL gene was highly expressed in BcPAP and TPC1 whereas FTC-133, CGTH-W-1 and ML-1 cells were negative. The transcript level was paralleled by the protein level in a PDPL positive cell lines. Prox 1 gene was highly expressed in FTC-133, CGTH-W-1 and ML-1, while BcPAP and TPC1 showed trace level of mRNA. The PDPL protein was negative in 72/120 of PTC and all FTCs. In 40% of PTCs PDPL was expressed in tumor cells

with heterogonous intensity. Normal thyroid (NT) and normal peritumoral tissues (NPT) as an inner control were totally negative. High intensity stained lymphatic vessels were used as internal positive control. Prox 1 protein was strongly expressed in the cytoplasm, weakly in some nuclei of PDPL positive PTCs and clearly in the nuclei of NT.

Conclusions: Our study is the first to demonstrate the difference in the expression of lymphatic specific markers podoplanin and nuclear transcription factor Prox 1 in DTCs, and that Prox 1 protein is misslocalized in PTCs. This might suggest different spreading pathways of PTC and FTC. Further ongoing studies will define the mechanisms and their potential implications.

OP52

FUNCTIONAL ANALYSIS OF MOLECULAR PROFILE OF CHILDHOOD/ADOLESCENTS RADIATION INDUCED THYROID CANCER

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Radiation exposure at a young age is known to trigger of thyroid cancer, predominantly papillary type. However, the problem whether the molecular background of radiation-induced thyroid cancer is different than in the sporadic childhood cancer is still a matter of debate. We applied gene expression profiling to compare these two groups.

Methods: We analyzed 65 childhood/young adult PTC samples by oligonucleotide microarray (HGU133 2.0Plus, Affymetrix). All patients were residents of Ukraine, but were born either before Chernobyl accident and were Exposed to Chernobyl Radiation fallout (33 ECR cases) or at least 9 months after (32 non-ECR cases). Groups were matched according to histology and disease stage, however, the patients in ECR group were slightly older then non-ECR ones (17,7 v. 16,3; $p< 0,05$). Gene ontology and gene set analysis were used to searched for molecular background of ECR cancers.

Results: Comparison of expression profile between ECR and non-ECR PTC revealed 300 differently expressed probesets ($p< 0,001$) with a fold change ranging from 0,48 to 3,42. The overall difference in gene expression was significant in global Goeman test ($p< 0,001$). Within these genes, cell communication, differentiation and response to stimulus were the most significantly changed biological processes. There were 71 gene sets showing concordant significance in four tests used for gene sets analysis ($p< 0,05$), associated with the activation of MAP3K and protein phosphatase type 2A regulator activity (crucial in pathway activation), RAR/RXR pathway and pathways related to phospholipase A2 activity. Radiation response-related gene sets were insignificant.

Conclusions: These results provide the suggestion of presence of the specific gene signature in patients with papillary thyroid cancers and the history of low-dose radiation in childhood.

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OP53

RET SOMATIC MUTATIONS ARE NOT AN EARLY EVENT IN THE TUMORAL TRANSFORMATION OF SPORADIC MEDULLARY THYROID CANCER

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The reported prevalence of RET somatic mutations in sporadic MTC is about 40-50% and the most frequent somatic mutation is Met918Thr in exon 16. MTC harboring a somatic RET mutation have been demonstrated to have a more advanced stage at diagnosis and a worse outcome. Although RET mutations are believed to be driving events in the MTC tumorigenesis only the finding of somatic mutations in microMTC can confirm this hypothesis.

Aim of the present work was to search for RET somatic mutations in sporadic microMTC (< 1 cm) and to compare their prevalence between microMTC and MTC of bigger size.

We selected a group of 148 MTC cases in which RET exon 16 point mutation was analyzed by direct sequencing. Tumors were classified according to the size of the nodule as follows: group A, < 1 cm; group B, >1 and < 2 cm; group C, > 2 and < 3 cm; group D, >3 cm.

The overall prevalence of RET mutation was 18.24% (27/148). RET mutations were differently distributed in the four groups. In particular it was 4.6% (2/43) in group A, 12.5% (8/64) in group B, 40% (8/20) in group C and 42.8% (9/21) in group D, thus showing an increasing rate according to the increase of the tumor size. Furthermore, when comparing the prevalence of mutations in the four groups we found a lower prevalence in microMTC ($p< 0.0001$).

In conclusion these data indicate that: a) the overall prevalence of RET somatic mutations is lower than expected; b) the prevalence of RET somatic mutations is very low (4.5%) in microMTC suggesting that they are not an early event in MTC tumorigenesis. As an alternative to this hypothesis we have to suppose that microMTC could be caused by other oncogene(s) with a lower transforming activity.

OP54

MEK INHIBITION REDUCES THE DEDIFFERENTIATION INDUCED BY EPIDERMAL GROWTH FACTOR, RESTORING THE EXPRESSION OF AND THE IODIDE TRANSPORT MEDIATED BY THE SODIUM IODIDE SYMPORTER (NIS) IN CULTURED THYROCYTES

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Objectives: Efficient radiotherapy of thyroid cancer with I-131 is dependent on functional expression of the sodium iodide symporter (NIS). Means to enhance this in tumours with poor uptake and retention of radioiodine is therefore a great concern. Epidermal growth factor (EGF) has been described as a dedifferentiating factor for cultured thyrocytes and constitutive activation of the MAPK signaling pathway is recognized in thyroid cancer. In this study we investigated whether EGF-induced down-regulation of NIS-mediated iodide uptake can be reversed pharmacologically.

Methods: Porcine thyrocytes grown as a monolayer in a bicameral system were stimulated with thyroid stimulating hormone (TSH, 1 mU/ml) alone or in combination EGF (10 ng/ml). NIS mRNA expression was quantified by real time RT-PCR and the basal-to-apical $^{125}I^-$ transport was monitored after 24-72 h. The MEK1/2 inhibitor U0126 was added to cultures (10μM or 25μM) at different time points for evaluation of possible prevention and recovery effects.

Results: U0126 blocked EGF-induced phosphorylation of Erk, indicating full inhibition of MEK. EGF reduced TSH-stimulated NIS expression as well as $^{125}I^-$ transport by more than 90 %. U0126 added simultaneously with hormones nearly completely prevented the repressing effect of EGF on NIS-mediated $^{125}I^-$ transport. Likewise, MEK inhibition significantly restored the $^{125}I^-$ transport when U0126 was added to cultures pre-stimulated with TSH+EGF. U0126 also prevented the deterioration of epithelial barrier function observed after prolonged EGF stimulation.

Conclusions: The findings demonstrate that EGF-induced dedifferentiation of thyroid function in cultured cells is largely attenuated by inhibition of MEK kinase activity. The restored NIS expression and iodide uptake in EGF-stimulated cells suggests that MEK inhibition may be a potentially interesting strategy to re-differentiate thyroid cancer cells and improve I-131 radiotherapy of tumours with poor radioiodine uptake.

OP8 Hypothyroidism, Goitre and Nodules

OP55

THYROID HORMONES, ANDROGEN RECEPTORS AND TESTICULAR DEVELOPMENT

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Chronic dietary induced fetal-postnatal hypothyroidism results in a transient delay in testis development. In the present study we have investigated the mechanism behind this delay. Hypothyroidism was induced in rats during fetal development by feeding an iodide-poor diet supplemented with 0.5% sodium-perchlorate. Euthyroid controls received AIN-93-based rat chow.

Sertoli cells are targets for thyroid hormone as they express TRα1. Q-PCR analysis revealed that under hypothyroid conditions the expression of TRα1 is transiently increased until day 35 postpartum (pp). We observed that the phase of Sertoli cell proliferation was prolonged under hypothyroid conditions up to day 35pp, since the presence of Anti Müllarian Hormone, a specific marker for early Sertoli cell development, was prolonged. Moreover, under euthyroid conditions the androgen receptor (AR) is first detected in Sertoli cells around day 6pp, versus day 35pp in the hypothyroid group. These observations indicate a delay in Sertoli cell differentiation.

Activation of tissue-specific transcription requires decondensation of chromatin and a subsequent change in chromatin structure. Histone acetylation and methylation at distinct lysine residues influence this gene activation and repression. Monomethylation of histone 3 at lysine 9 (H3K9me1) has been linked to transcriptional repression and is normally absent in Sertoli cells. However, in hypothyroid animals we observed H3K9me1 up to day 28pp in Sertoli cell nuclei, a period when AR expression is inhibited. Demethylases specific for H3K9me1 can counteract this repression. The demethylase LSD1/KDM1, present in Sertoli cells acts as co-activator of the AR, facilitating transcriptional activation, but was absent in these cells up to day 16pp of hypothyroid rats.

Conclusion: Chronic hypothyroidism delays testicular development. The delay in the progression of spermatogenesis seems to be due to a postponement in AR expression in Sertoli cells and concomitant hypermethylation of the transcriptional suppressor H3K9me1 and the absence of the AR co-activator LSD1/KDM1.

OP56

MICRORNAS EXPRESSION FOR DIFFERENTIATION OF BENIGN AND MALIGNANT THYROID NODULES STARTING FROM CELLS OF FINE NEEDLE ASPIRATION

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MicroRNAs (miRNAs) constitute a recently identified class of small endogenous non-coding RNAs that pair with target mRNAs regulating gene expression. They are involved in central biological processes including development, organogenesis, tissue differentiation, cell cycle and metabolism, and changes in miRNA levels occur in human cancers, including thyroid cancer.

Fine needle aspiration (FNA) with cytologic evaluation is the most reliable tool for preoperative diagnosis of thyroid nodules, but diagnosis remains indeterminate for 20% of nodules. The aim of this study was to evaluate the expression of 7 miRNAs to distinguish benign and malignant thyroid nodules. The prospective study included 88 samples obtained by FNA of thyroid nodules from 87 patients (45 benign, 43 malignant). miRNA expression was evaluated by quantitative RT-PCR and levels were calculated relative to normal thyroid tissue; statistical analysis of data was performed.

An increase in miR-224, miR-146b and miR-187 expression was observed in malignant nodules with respect to benign ones (Mann-Whitney U test, p-value< 0.001), while the expression of miR-221, miR-222, miR-155 and miR-197 were similar in both types of nodules. By using data mining techniques we obtained a criterion able to classify a nodule as benign or malignant on the basis of the values of expression of microRNAs. The decision model obtained was based on the expression of only three miRNAs (miR-146b, miR-221 and miR-155) and was valid for 86/88 nodules (97.73%). In order to evaluate how much general is the criterion in correctly classifying a nodule not present in our study group, we adopted cross-validation techniques, obtaining a reliability of 78.41% (Sensitivity=79.07% and Specificity=77.77%).

In conclusion, the expression profiles of three miRNAs allowed a good prediction for distinguish benign from malignant thyroid lesions starting from FNA. Future studies will be performed to verify if nodules with indeterminate cytology may be classify by this criterion.

OP57

DIAGNOSTIC VALUE OF ULTRASONOGRAPHY TO DISTINGUISH BETWEEN BENIGN AND MALIGNANT THYROID NODULES. A PROSPECTIVE STUDY WITH 13902 PATIENTS

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Objectives: It is well-known that the prevalence of goiter, the distribution of various thyroid disorders, the diagnostic potential of FNAC differ significantly according to iodine intake. Therefore we aimed to evaluate the diagnostic power of various sonographic (US) features in the differential diagnostic of thyroid nodules (TN) in our iodine deficient area.

Methods: In a 12-year period we analysed the various US properties of 24102 TN in 13902 consecutive patients of whom 2645 underwent surgery.

Results: 268 patients had malignant nodule.

Table. Sonographic fatures and the risk of malignancy

Sonographic feature	No. of nodules	Malignant	OR (95% confidence interval)
Hypoechogenic	9625	187	3,54 (2,73-4,60)
Moderately hypoechogenic	4665	36	0,65 (0,46-0,93)
Mixed cystic-solid	4408	26	0,48 (0,32-0,73)
Hyperechogenic	2986	18	0,51 (0,32-0,83)
Echonormal	1898	1	0,04 (0,01-0,31)
Halo sign (all)	3295	21	0.54 (0,35-0,84)
Halo sign in hypoechogenic nodule	314	0	0
Halo sign in moderately hypoechogenic nodule	508	14	2,63 (1,53-4,54)
Halo sign in hyperechogenic nodule	744	6	0,72 (0,32-1,63)

The most important features favouring malignancy were the following: blurred border of the nodule and microcalcification with OR 15.7 and 5.71, respectively.

Conclusions: We demonstrated that the US signs of a malignant TN are in general the same in iodine deficient region than in iodine sufficient areas. The interpretation of halo sign as a benign sign seems equivocal: the absence of halo sign decreases the risk of malignancy only therefore, because in the most frequent type of malignant nodules, in hypoechogenic nodules we are not able to demonstrate halo sign. Therefore it is not surprising that in the case of moderately hypoechogenic nodules, the presence of halo sign significantly increases the risk of malignancy.

OP58

CURRENT PRACTICE TO DIAGNOSE AND TREAT THYROID NODULES IN GERMANY

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The diagnosis and management of thyroid nodules according to current evidence is described in recently revised guidelines. However, the current practice to deal with this clinical problem is unknown. We therefore retrospectively investigated the insurance claim and prescription data for diagnostic and therapeutic measures of 29080 patients who were first diagnosed with nodular goiter or single thyroid nodule in the second quarter of the year 2006 in Germany.

We analyzed the diagnostic examinations during the 9 months before the diagnosis nodular goiter or single thyroid nodule was first made and all further diagnostic or therapeutic measures and treatments (including surgery or radioiodine) during the succeeding two years.

The diagnoses were made by general practitioners (31%), internists (37%), nuclear medicine (16%) and others with ultrasound (94%) szintigraphy (55%), TSH determination (98%), FNAB (5%). During the 2 years after diagnosis 5,4% / 0,3% of the patients treated by general practicioners, 4,6% / 0,3% by internists, 6,3% / 0,4% by nuclear medicine, 26,2% / 0% by surgeons underwent thyroid surgery or radioiodine respectively. Only 16,5% of all patients who underwent surgery had a FNAB. Medical treatment consisted of L-thyroxine therapy for 19% and L-thyroxine - iodine combination for 8%. Iodine therapy could not be evaluated since its use does not necessarily require a prescription.

Contrary to the guidelines these data demonstrate a very infrequent use of FNAB for the diagnostic work up of thyroid nodules. The different specialists use different diagnostic and therapeutic options with different frequencies. Whereas most patients with thyroid nodules are iodine deficient in Germany current prescription regulations in Germany render it difficult to treat this iodine deficiency appropriately. The reasons for the variations and discrepancies need further elucidation. However, the need for a change of regulations, guideline dissemination and training appears obvious.

OP59

INTRODUCTION OF THE DANISH IODINE FORTIFICATION PROGRAM: IMPACT ON DRUG AND TREATMENT COSTS

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Objectives: Initiation of iodine fortification (IF) is associated with clear benefits such as a reduced occurrence of thyroid disorders. IF is therefore expected to be associated with reduced costs in relation to treatment. Treatment activity can be readily monitored in Denmark by use of existing nationwide registers. In Denmark IF was initiated in 1998 because of mild-to-moderate iodine deficiency. The aim of this study was to analyze the impact of introducing IF on the costs related to treatment of thyroid disorders.

Methods: Every Dane is given a personal identification number at birth or immigration. The ID number is used in all contacts with public services and is used in the compilation of data in nationwide registers on dispensed prescription drugs and hospital contacts. We extracted data on all dispensing of thyroid medication, operations for thyroid disorders, and treatments with radioiodine from these nationwide registers between 1995 and 2008. Costs were adjusted to the age-and sex composition of the Danish population in year 2000.

Results: Treatment costs increased in the first years following initiation of IF (max. 22% in the previously moderately deficient region) and remained 14% higher in 2008 - 11 years after the initiation of IF (1997:404,434€/100,000 inhabitants; 2008:461,144€/100,000 inhabitants). The costs for radioiodine increased only temporarily and ended up lower than before initiation of IF. Cost for antithyroid medication also declined after an early increase, but costs were still higher than before initiation of IF. Costs of surgery remained almost constant, while costs of thyroid replacement therapy increased throughout the period.

Conclusions: Even though iodization of salt in Denmark has had a beneficial effect on the occurrence of thyroid disease, such as goitre and autonomous hyperthyroidism, treatment costs are still above the pre-iodization level. The full beneficial effect of IF may only become apparent decades after initiation.

OP60

IODINE DEFICIENCY DISORDERS IN THE SO-CALLED HIMALAYAN GOITRE BELT: A TWO DECADE PROFILE

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A so-called Himalayan Goitre Belt passing through various regions of Northwest to Eastern Himalaya including the state of Uttarakhand in the west ($28^0 43'$ to $31^0 27'$ N & $77^0 34'$ to $81^0 02'$ E). But despite IDD having been adjudged a major health problem and salt iodation programs having been introduced following a legislation surprisingly very little scientific database is available.

Here we report results of work carried out in four districts of Uttarakhand state i.e. Chamoli, Rudraprayag, Pauri & Tehri Garhwal in two phases(1988-94 and2004-08) in association with State Government Health Directorate. Village chiefs were contacted and health camps were organized. Questionnaire-based & visual observations on IDD were collected from individuals of randomly selected 65 villages (between 500-3400m altitude). Systematic goitre grading (0, Ia, Ib, II & III) was carried out using PAHO1986 method. Visual observations were made on other IDD symptoms.

Circulating T_4, T_3 were determined using Radioimmunoassay, TSH was determined by commercial IRMA kit. Household salt samples were tested for Iodine content, quantitatively using WHO recommended titri-metric method. Urinary iodine was determined spectrophotometrically.

Results indicate:

- the incidence of IDD is unexpectedly low(adjudged 'non-existent' to 'mildly iodine deficient' as per WHO/ICCMOD criterion)despite severe iodine
- there has been a decline in the overall incidence of visible goitre and cretinism, since 1934 to 1989 (without iodine prophylaxis)
- comparison of current results with data obtained in 1988-1989 reveal a significant decline in the incidence of total goitre, visible goitre and cretinism despite continued severe iodine deficiency and absence of iodine prophylactic programs.
- most areas 60-80% population consume un-iodised salt, purchased under a barter scheme once in a year and stored in exchange with the local produce *amaranthus*
- there is no difference in the incidence of IDD between populations from severely iodine deficient (judged by iodine content in the salt consumed 0-07ppm) and iodine sufficient populations (15-25ppm).

OP61

LEVOTHYROXINE MONOTHERAPY CANNOT GUARANTEE EUTHYROIDISM IN ALL ATHYREOTIC PATIENTS

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Background: Levothyroxine monotherapy is the treatment of choice for hypothyroid patients because peripheral T4 to T3 conversion is believed to account for the overall tissue requirement for thyroid hormones. However, levothyroxine-treated patients require higher FT4 concentrations to normalize TSH levels, thereby exposing peripheral tissues to an imbalanced ratio of circulating FT4 and FT3 levels. In spite of normal serum TSH, some hypothyroid patients under levothyroxine monotherapy suffer an unsatisfactory well-being condition.

Methods: To evaluate whether levothyroxine monotherapy can normalize serum thyroid hormones and thyroid-pituitary feedback, a seven-year retrospective, observational study, was carried out using the measurement of TSH, FT4, FT3 serum concentrations and individual FT3/FT4 ratio. A large series (1,811) of levothyroxine-treated athyreotic patients with normal TSH levels (0.4-4.0 mU/L) and 3,875 euthyroid controls were studied.

Results: FT4 levels were significantly higher and FT3 levels significantly lower in levothyroxine-treated athyreotic patients than in matched euthyroid controls ($p < 0.001$ in both cases). Among the levothyroxine-treated patients 15.2% had lower serum FT3, 7.2 % had higher serum FT4 and 29.6% had FT3/FT4 ratios lower than the reference range. The correlation between thyroid hormones and serum TSH levels indicated a less sensitive response of thyrotropic cells to thyroid hormones in levothyroxine-treated patients.

Conclusions: More than 20% of levothyroxine-treated athyreotic patients, despite normal TSH levels, do not maintain FT3 or FT4 values in the reference range. Altered T3/T4 ratio of circulating thyroid hormones affects tissue response in the pituitary. Measurement of TSH alone may be, therefore, misleading in these patients. The long-term effects of chronic tissue exposure to abnormal T3/T4 ratio are unknown. The question whether a subgroup of hypothyroid patients requires a more physiological treatment, using a combined therapy with levothyroxine and a sustained-release T3 preparation is still not answered and requires further studies.

OP62

NEWBORN SEX RATIO IS ASSOCIATED WITH MATERNAL TSH

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Aim: Several environmental and medical factors have been documented to influence the sex ratio historically established at 1.06. Our aim was to analyze the sex ratio in offspring of mothers with hypothyroidism and the association of maternal autoimmunity and first trimester TSH with newborn sex.

Methods: We studied women with pregestational hypothyroidism or differentiated thyroid carcinoma treated with levothyroxine since before pregnancy in whom autoimmunity status and first trimester TSH levels were known. Women with pregestational diabetes mellitus were excluded. Autoimmunity was defined as present/absent and mean first trimester TSH (mUI/L) was arbitrarily classified in four groups: I: TSH £0.29, II TSH 0.3-2.49, III TSH 2.5- 4.99 and IV TSH ³ 5 mUI/l (cut-offs corresponding to the normal limits outside pregnancy and the recommended upper cut-off for TSH in the first trimester of pregnancy). Statistical analyses: Chi-square tests and logistic regression analysis.

Results: 129 women were studied. Autoimmunity was present in 74.2% and median TSH was 3.04 mUI/l. Newborn sex ratio was 0.877, not significantly different from expected. Median TSH levels in different groups of TSH were 0.02, 1.53, 3.85 and 7.31 mUI/L and percentage of patients with positive autoimmunity was 15.4%, 72.1%, 90.2% and 81.3%, in groups I, II, III and IV respectively. The percentages of male births according to TSH category were 61.5%, 50%, 56.8% and 24.2% (p=0.02), respectively. The logistic regression demonstrated TSH category as the single predictor of newborn sex (OR 0.625, 0.846 and 0.217 for categories II, III and IV respectively).

Conclusion: Sex ratio in offspring of women receiving levothyroxine treatment since before pregnancy is not significantly different from the expected. The percentage of male newborns is decreased when maternal TSH in first trimester is ³ 5 mUI/l.

OP9 Thyroid Cell Biology and Genetics

OP63

TSH COMPENSATES THYROID SPECIFIC IGFI RECEPTOR KNOCKOUT AND CAUSES PAPILLARY THYROID TUMOURS

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Although TSH stimulates all aspects of thyroid physiology insulin-like growth factor (IGF) I signaling through a tyrosine kinase-containing transmembrane receptor exhibits a permissive impact on TSH action. To better understand the importance of the IGFIR in the thyroid in vivo, we inactivated the *Igf1r* with a Tg promoter driven Cre-lox system in mice. We studied male and female mice with thyroidal wild type, $Igf1r^{+/-}$ and $Igf1r^{-/-}$ genotypes. Targeted *Igf1r* inactivation did not significantly change thyroid hormone levels but significantly increased TSH levels in both heterozygous and homozygous mice without affecting thyroid weight. Histological analysis of thyroid tissue with *Igf1r* inactivation revealed hyperplasia and heterogeneous follicle structure. From 4 month of age, we detected a papillary thyroid architecture in heterozygous and homozygous mice. We also noted increased body weight of male mice with a homozygous thyroidal null mutation in the *Igf1r* locus, compared to WT mice, respectively. A decrease of mRNA for thyroid peroxidase and increased mRNA for insulin-like growth factor II receptor but no significant mRNA changes for the insulin receptor, the thyroid-stimulating hormone receptor and the sodium-iodide-symporter in both $Igf1r^{+/-}$ and $Igf1r^{-/-}$ mice were detected. Our results suggest that the strong increase of TSH benefits papillary thyroid carcinoma (PTC) growth and completely compensates the loss of IGFI receptor signaling at the level of thyroid hormones without significant increase in thyroid weight. This could indicate that the IGFI receptor signaling is less essential for thyroid hormone synthesis but maintains homeostasis that prevents thyroid tumourigenesis.

OP64

MICRORNAS REGULATE THYROID CELL PROLIFERATION INDUCED BY TSH AND THYROGLOBULIN

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Objectives: microRNAs (miRNAs) are endogenous short RNAs that bind 3'-UTR of multiple target mRNAs and usually result in gene silencing. More than fifteen thousand miRNAs are identified to date, however, most of their function as well as the target genes are yet to be determined. In the present study, we tried to identify miRNAs whose expression were modulated by TSH or thyroglobulin (Tg), two major factors that stimulate thyroid cell growth using a miRNA microarray analysis to determine the miRNAs.

Methods: Rat thyroid FRTL-5 cells were treated with TSH after maintaining with no TSH for one week. Alternatively, FRTL-5 cells maintained with no TSH, no insulin, and 0.2% rather than 5% serum were treated with Tg. Total cellular RNA was extracted and the expression of miRNA was determined using miRNA microarray analysis. The agonistic RNA of some detected miRNAs were transfected before TSH or Tg stimulation, and bromodeoxyuridine (BrdU) incorporation assay, cell count, and RT-PCR of miRNA target genes were performed.

Results: We have identified 47 miRNAs whose expression were suppressed over two fold by TSH, 21 miRNAs downregulated by Tg, and 19 miRNAs modulated by both TSH and Tg. We next evaluated cell proliferation by (BrdU) incorporation and cell count after transfecting miRNA agonist in FRTL-5 cells. Consequently, we have successfully identified several miRNAs, such as miR-16 and miR-195, which seem to be the major mediator of the action of TSH or Tg to stimulate thyroid cell growth.

Conclusion: Although several miRNAs were reported in relation to thyroid carcinogenesis, miR-16 and miR-195 have not been reported in thyroid carcinomas. Therefore it is plausible to speculate that these miRNAs are involved in the physiological and/or non-neoplastic growth of the thyroid cells. Our results also indicated that miRNAs are involved in the regulation of thyroid physiology.

OP65

EXPRESSION, MATURATION AND TURNOVER STUDIES OF PENDRIN VARIANTS WITH NORMAL OR SLIGHTLY REDUCED FUNCTION

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Biallelic mutations of the SLC26A4 gene are associated with the autosomal recessive Pendred syndrome (PS) which includes sensorineural hearing loss (SNHL) due to inner ear malformations and goiter due to partial iodide organification defect, whereas monoallelic mutations associate with the large vestibular aqueduct syndrome (LVAS). Nevertheless, the reports of PS patients with heterozygous mutations and of normally or slightly hypofunctioning variants are not infrequent. It has thus been suggested that other genetic factors could be involved and 2 additional genes (FOXI-I and KCNJ10) have been candidated. These genes, together with SLC26A4 and the binding domain for FOXI-I, have been tested in a series of PS/LVAS patients. The SLC26A4 gene was mutated in 5/19 patients (26.3%), whereas no mutations were found in the other genes. Among mutated patients, 2 were identified with novel missense variants harbouring, at the fluorimetric method, a normal pendrin Cl^-/I^- transport. In one case, the variant (E29D) was associated with an already described splice site mutation and the phenotype was PS, whereas in the other patient the substitution was monoallelic (R185T) and associated with LVAS. Interestingly, the analysis of the protein expression revealed a significant heterogeneity in the processing of mutant molecules, while WT-pendrin reached the plasma membrane. Moreover, the incubation with the protein-synthesis inhibitor cycloheximide showed an impaired maturation of the mutant proteins with respect to WT-pendrin.

In conclusion, present findings strengthen the crucial role of SLC26A4 in PS and LVAS, indicating that these syndromes can be associated with monoallelic variants with a normal or only slightly reduced ability to transport chloride and iodide, but with an anomalous localization in the cell and with an impaired maturation. These variants, even if monoallelic, associate with LVAS and, when combined with a complete loss of function mutation, lead to a full PS phenotype.

OP66

A "CUSTOMIZED" CGH-ARRAY THYROARRAY® IDENTIFIES GENETIC DEFECTS IN CONGENITAL HYPOTHYROIDISM NOT DETECTABLE BY PCR AND SEQUENCING

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Background: Currently 26 gene defects are known to cause congenital hypothyroidism (CH). However, only a small percentage of patients harbour mutations which fully explain their thyroid phenotype. This could indicate the existence of still unidentified thyroidal genes that cannot be yet studied and/or that classical mutation screening by PCR and Sanger sequencing has technical limitations.

Objective: To test the capacity of comparative genomic hybridization (CGH) arrays to identify small deletions/duplications in CH patients without defects in classical screening.

Methods: A "customized" Agilent-based CGH-array (8x60K oligos) was designed to study copy number alterations in thyroid-specific genes (e.g. TG, TPO, DUOX2, NIS, TSHR) and their transcription factors. Average resolution in the areas of interest was 1 oligo per 150 bp and 125 kb for the rest of the genome. Eight patients with thyroid dyshormonogenesis without mutations in TPO, DUOX2 or DUOXA2 genes were studied.

Results: We identified a heterozygous deletion of around 10 kb in the TG gene in a non-goitrous CH patient with a positive perchlorate discharge of 42 %. The deletion includes exon 45 and was confirmed by PCR-sequencing from flanking primers, comprising 9,908 bp. This defect is not a copy number variation (CNV) present in the population. The resulting TG mRNA lacks 108 bp and 36 amino acids encoding part of the ACHE motif and the acceptor hormonogenic tyrosine Y2554. Other defects identified are under detailed characterization.

Conclusions: We present the proof of principle that a genome-wide, thyroid-customized array (THYROARRAY®) is capable to detect genetic defects that escape the classical mutation analysis. Our high density design allowed identification of small deletions/duplications that even commercial arrays (Agilent 44K and 244K) would have not detected. Novel genomic techniques are useful in case of failed detection of mutations in human thyroid hormone synthesis genes by classical means.

OP67

FUNCTIONAL CHARACTERIZATION OF TSHR HINGE REGION RESIDUES IDENTIFIED FURTHER TEN TSH INTERACTION SITES OUTSIDE OF THE LRR

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Objectives: The exact binding properties between TSH and the thyroid stimulating hormone receptor (TSHR) subsequently leading to its activation are only incompletely understood. TSH binding to the TSHR is mainly mediated by the LRR, influenced by sulfation at Y385 and in case of bTSH also by three negatively charged positions in the receptor hinge region (HinR). However, there is a lack of structural data for the HinR, which links the LRR with the serpentine domain. After identification of the first TSH binding sensitive residues in the HinR it was apparent that multiple positions in this particular structure remained to be characterized. The goal of this study was therefore, to clarify if further contact points for initial TSHR activation by TSH exist in the structurally undefined HinR.

Methods: Therefore, we systematically analyzed 41 so far uncharacterized residues of the TSHR HinR outsite of the C-peptide as single mutants regarding differences between cell surface expression measured by FACS and bTSH binding. Moreover, TSHR hinge mutants with influence on bTSH binding were also analyzed for binding of the superagonistic hTSH analog TR1401 and side chain variations were performed to identify the potential amino acid characteristic, which is necessary to maintain the hormone-TSHR hinge interaction.

Results & Conclusion: Indeed, we identified further 10 residues of the HinR with a strong decrease in bTSH and TR1401 binding compared to the respective cell surface expression. Our data show that multiple interaction sites for bTSH and TR1401 e.g. four negatively charged, two hydrophilic and four hydrophobic residues exist in the HinR. This knowledge is not only important for the further elucidation of the precise molecular interactions of the hormone with its receptor but also for the receptor driven approach to generate and optimize orthosteric TSHR antagonists, inverse agonists and also improved TSH analogs.

OP68

BIALLELIC DUOX2 VARIANTS APPEAR INVARIABLY ASSOCIATED WITH PERMANENT CONGENITAL HYPOTHYROIDISM

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Since the first identification of DUOX2 as an actor in the pathogenesis of congenital hypothyroidism (CH), monoallelic and biallelic mutations have been associated with transient and permanent forms, respectively. Nevertheless, following data questioned this paradigm since monoallelic permanent cases and biallelic transient patients have been described. This topic has been thus considered in our series of patients, which includes 8 unrelated children and two siblings with CH and partial iodide organification defect (PIOD). In this cohort, 9 novel and 4 previously reported DUOX2 mutations (6 missense, 6 stop codon -3 nonsense and 3 frameshift- and 1 splice site mutations) have been identified by means of PCR amplifications with different primers pairs, in order to distinguish between the two highly homologous DUOX1 and DUOX2 sequences.

The missense variants involve conserved aminoacids and are located in the peroxidase-like domain and in the first intracellular loop nearby the EF-hands motif, all critical regions for protein function. In 2 patients with a stop codon mutation, the amplification of the cDNAs allowed to detect only the wild-type allele, indicating the occurrence of nonsense-mediated RNA decay, whereas the skipping of the mutated exon was observed in 1 case.

The 5 patients with compound heterozygous variations had a permanent hypothyroidism, but without evident correlations between the mutation type and the severity of the disease in terms of TSH levels and iodide discharge after perchlorate. On the other hand, among the 3 patients harbouring monoallelic mutations, 1 had transient and 2 permanent CH.

In conclusion, DUOX2 biallelic pathogenic variants appear as invariably associated with permanent CH. Cryptic DUOX2 variations or alterations involving other thyroid mechanisms may account for the discrepant monoallelic cases with permanent CH.

OP69

SUBCELLULAR LOCALIZATION OF S6K1 AND S6K2 IS RELATED TO FUNCTIONAL ACTIVITY OF RAT THYROCYTES *IN VITRO*

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The kinase of ribosomal protein S6 is an important member of PI3K signal transduction pathway involved in control of protein synthesis and G1/S transition of the cell cycle. There are two forms of this kinase S6K1 and S6K2. Previously we have shown that in normal thyroid tissue they are detected predominantly in the cytoplasm of thyrocytes whereas in monolayer culture in course of follicle outspreading S6K1 and S6K2 appeared in nuclei as well. The goal of presented work was to detect which processes involved in follicle transformation from 3D structure to monolayer colony (migration, proliferation, loss of follicle organization) is related to S6K subcellular redistribution. The cultivation of thyrocytes resulted in activation of cell proliferation. But there was not the correlation between S6K1/2 subcellular relocalization and Ki-67 appearance in proliferating cells. To study possible effect of migration on subcellular localization of S6K1 and S6K2, cultured thyrocytes were stimulated to penetrate a porous membrane of Transwell. But immunocytochemical analysis revealed predominantly cytoplasmic localization S6K1/2 as well. Detection of the content of these kinases in thyrocytes in 3 D culture with retention of follicle structure shown that in thyroglobulin-positive cells from follicle like structures S6K1/2 localized in cytoplasm, but in thyroglobulin-negative cells from solid areas of cultured aggregates of follicles S6K1/2 were observed in nuclei as well (like in monolayer cultures). Thus, the change of subcellular localization of S6K1/2 in cultured thyrocytes is directly related to change of level of functional activity, unlike the processes of proliferation and migration.

OP70

REGULATION OF H_2O_2 GENERATION BY THYROGLOBULIN IN FRTL-5

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Objective: Thyroglobulin (Tg) is a macromolecular precursor of thyroid hormone synthesis and also a potent regulator of thyroid follicle function. We have reported that Tg suppresses the expression and the function of several thyroid-specific genes such as the sodium/iodide symporter (NIS), thyroglobulin (Tg) and thyroid peroxidase (TPO). Dual oxidases (DUOXs) are members of NADPH oxidases essential for iodide organification by producing H_2O_2. In this study we have investigated the possible effects of Tg on the expression and functions of DUOXs.

Methods: Rat thyroid FRTL-5 cells were treated with Tg, and the mRNA expression of DUOX1 and DUOX2 and their corresponding maturation factors DUOXA1 and DUOXA2 were evaluated by real-time PCR. Protein levels of DUOX2 were also examined by Western blot analysis. Intracellular H_2O_2 generation was quantified in FRTL-5 cells by a fluorescent dye, 5-(and-

6)-chloromethyl 2',7'-dichlorodihydrofluorescein diacetate, acetyl ester (CM-H_2DCFDA).

Results: Tg significantly reduced mRNA levels of DUOX2 and DUOXA2 in dose- and time-dependent manner, while expression of DUOX1 and DUOXA1 was not affected by Tg. DUOX2 protein levels were decreased by Tg. Generation of H_2O_2 in FRTL-5 cells was also significantly reduced by Tg treatment.

Conclusion: Our results demonstrated that Tg reduces the expression and function of DUOX2 and DUOXA2 in accordance with the reduction of other thyroid-specific genes. Such a reduction will contribute to the suppression of follicular function where Tg concentration is high, which explains the nature of follicular heterogeneity.

OP10 Thyroid Cancer Clinical

OP71

TI-RADS SCORE: CLINICAL EFFICIENCY EVALUATED WITH THE BETHESDA SYSTEM IN A ONE-YEAR PROSPECTIVE STUDY ON 2480 NODULES

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Objectives: To evaluate the accuracy and impact of the thyroid imaging-reporting and data system (TI-RADS) for the diagnosis of thyroid carcinomas on a population encountered in day-to-day practice in a thyroid clinic.

Methods: We conducted a prospective study on a modified TI-RADS score developed to estimate the individual risk of thyroid carcinoma with ultrasound. We evaluated 2480 consecutive nodules in 1904 patients seen in one year, all referred for fine-needle aspiration biopsy of at least one thyroid nodule. Using a simple flow-chart during ultrasound examination, each nodule was attributed a grade ranging from 1 to 5 (1 : normal, 2 : benign, 3 : very probably benign, 4A and 4B : respectively low and high risk of carcinoma, 5 : carcinoma). Then all nodules were submitted for FNAB and the results read according to the Bethesda system.

Results: Prevalence of carcinoma in the studied population was 4%. Sensitivity, specificity, negative predictive value (NPV) and accuracy of TI-RADS score were respectively 94%, 53%, 99.6%, 44%. NPV is very high for TI-RADS scores 2 and 3 : thyroid carcinoma is very unlikely in those cases. Biopsying only nodules scored 4 and 5 would lead to a 45% decrease of the total number of FNABs. However lesions initially scored 2 and 3 whose size increases should be biopsied. Positive predictive value is low if one includes all suspicious TI-RADS scores between 4A to 5 (7%), but rises up to 67% if only scores 4B and 5 are taken into account.

Conclusions: TI-RADS score is a simple and useful tool that can be used to decide whether or not to make FNAB of thyroid nodules and decrease unnecessary biopsies. It is applicable to the population encoutered in real clinical practice with low prevalence of thyroid carcinoma.

OP72

FOSBRETABULIN TROMETHAMINE (CA4P), A TUBULIN-BINDING VASCULAR DISRUPTING AGENT (VDA), IS ASSOCIATED WITH IMPROVED 1-YEAR SURVIVAL IN ANAPLASTIC THYROID CANCER (ATC) PATIENTS TREATED IN 5 INDEPENDENT PROSPECTIVE STUDIES COMPARED TO A LARGE SINGLE INSTITUTION HISTORICAL SERIES

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Background: ATC is a rare, highly vascular, and rapidly progressive malignancy, with a high mortality rate, no effective therapeutic options and a median survival of 3 to 4 months. CA4P selectively disrupts tumor blood vessels by destabilizing endothelial cell microtubules. Preclinical studies have shown that CA4P has activity either as monotherapy or in combination with chemotherapy in ATC cell lines and animal models. CA4P has been tested in five Phase 1 and Phase 2/3 clinical trials.

Objective: To compare the 1-year survival rate of ATC patients treated with CA4P in these clinical trials to the 1-year survival rate from a historical cohort of ATC patients.

Methods: Between November 1998 and February 2011, 84 ATC patients received CA4P in five independent Phase 1 and 2/3 clinical trials. Twenty-nine patients received 18 to 90 mg/m^2 CA4P monotherapy in two studies. Fifty-five patients received 27 to 60 mg/m2 CA4P + chemotherapy in three studies. Chemotherapy included carboplatin (AUC 5) alone or carboplatin (AUC 6) in combination with paclitaxel (200 mg/m^2). CA4P was administered once every 3 weeks or on Days 1, 8, and 15 every 21 days. Survival data from these trials were combined and compared to survival data from the largest historical series of 134 ATC patients managed over 50-years at the Mayo Clinic, Rochester, Minnesota.

Results: Irrespective of disease stage, the 1-year survival rate of ATC patients treated with CA4P was 24% as compared to 9.7% for the historical dataset. The improved 1-year survival rate appears clinically meaningful in this otherwise near-universally fatal disease.

Conclusions: CA4P alone or in combination with chemotherapy may improve the 1-year survival rate of ATC to 24% from the < 10% reported in historical series.

OP73

MIRNA EXPRESSION PATTERNS DIFFERENTIATE BETWEEN FOLLICULAR THYROID CARCINOMA (FTC) AND FOLLICULAR THYROID ADENOMA (FA)

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Fine-needle aspiration cytology is a very sensitive and specific tool for the differential diagnosis of thyroid nodules. However, it reveals the inconclusive result of follicular proliferation (characteristic for both FTC and FA) in up to 20%. Since miRNA profiles are promising markers for the differential diagnosis of tumor types that cannot be determined on the basis of tumor cytology, the goal was to determine the predictive value of miRNAs and to select the most significant miRNAs for the distinction between FTC and FA.

We analyzed 10 FTC and 5 FA frozen tissue samples and 12 FTC and 12 FA FFPE tissues. The data were analyzed using both classical and novel approaches (unsupervised Random Forests) within the R/Bioconductor environment. Features differentiating between classes were selected, appropriate SVM classifiers have been suggested.

Unsupervised analyses results of the frozen and FFPE data sets were compared and both sets showed a strong difference in the miRNA profiles of FTC and FA. The predictive value of the data was investigated using leave-one-out cross-validation. Accuracy of classification varied in a range between 70% and 90% depending on the number of features selected for the classifier. Minimization of the predictive miRNA list was performed. The best cross-validation classification accuracies with linear SVM were obtained for 61 miRNAs (frozen) and 2 miRNAs (FFPE). However, there was a discrepancy between the top significant miRNA sets obtained from snap frozen and FFPE derived material. This resulted in poor predictive accuracy when the classifier obtained in the frozen set was applied to the FFPE set and vice versa.

High accuracy miRNA based classifiers of FTC and FA for frozen and FFPE samples were found. Validation of proposed classifiers might further improve the differential diagnosis of FNA results with the diagnosis "follicular proliferation".

OP74

COMPARISON OF FOUR STRATEGIES OF RADIOIODINE ABLATION: FINAL RESULTS OF THE RANDOMIZED, PROSPECTIVE ESTIMABL STUDY ON 752 LOW-RISK THYROID CANCER PATIENTS

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Purpose: This multicentric randomized, controlled, phase III trial, compared 4 strategies for postoperative ablation (RAI) in a 2*2 factorial design, each strategy combining a TSH stimulation method (either thyroid hormone withdrawal (THW) or rhTSH (Thyrogen®, Genzyme)) and radioiodine activity (either 1.1 GBq or 3.7GBq).

Patients and Methods: Study patients met the following criteria: age>18 yrs; total thyroidectomy for differentiated papillary or follicular (no aggressive histology) thyroid carcinoma between 30 and 120 days before randomization, TNM stage pT1< 1cm, N1 or Nx, pT1>1cm (any N) or pT2, N0; absence of distant metastasis. The primary endpoint is the rate of thyroid ablation at 6-10 months, which was assessed by neck-US and rhTSH-stimulated Tg determination or whole-body scan (WBS) if Tg antibodies (TgAb) were present. The comparison between the four strategies was based on equivalence framework, with two-side α=0.05.

Results: 752 patients were included between April 2007 and February 2010: 79% were female, mean age was 49 years, 90% had papillary cancer; 30% of tumors were pT1N0, 17% were pT1N1, 39% were pT1,Nx and 12% were pT2,N0. 27 patients were excluded for abnormal post-ablation WBS, 20 patients withdrew their consent and 20 patients had incomplete follow-up. Among the remaining 685 patients, neck-US was normal in 652 patients (95%) and stimulated Tg level was ≤1.0 ng/mL in 650 (95%) patients. Thyroid ablation was complete in 629 patients (92%). Results showed the equivalence of ablation rate both for I31I activity ($D_{1.1\ GBq\ /\ 3.7\ GBq}$ = - 2.1%, IC_D= [- 5.5%; 1.4%]) and for TSH stimulation method ($D_{rhTSH\ /\ THW}$ = - 2.1%, IC_D= [- 5.5%; 1.4%]).

Conclusion: These results validated the use of rhTSH and 1.1 GBq for ablation in low-risk patients.

OP75

HILO: MULTICENTRE RANDOMISED PHASE III CLINICAL TRIAL OF HIGH VS LOW DOSE RADIOIODINE, WITH OR WITHOUT RECOMBINANT HUMAN THYROID STIMULATING HORMONE (RHTSH), FOR REMNANT ABLATION FOR DIFFERENTIATED THYROID CANCER

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Background: Recommended treatment for most patients with differentiated thyroid cancer is surgery followed by a high administered activity of 3.7 GBq (100mCi) radioiodine ablation. However, a lower activity (1.1 GBq or 30 mCi) has advantages including a shorter stay in hospital isolation and lower risk of side effects, including the risk of a second cancer. Also, Thyrogen (rhTSH) allows patients to continue thyroid hormone replacement during ablation, avoiding symptoms of hypothyroidism. We conducted a large randomised factorial multicentre trial to simultaneously address whether ablation success rates are similar using (i) either 1.1 GBq or 3.7 GBq, and (ii) either Thyrogen or thyroid hormone withdrawal. It is the first ever UK national prospective trial in thyroid cancer.

Methods: Eligible patients had: tumour stage pT1-T3, and NX, N0 or N1, M0 (TNM 6th edition); total thyroidectomy (R0 resection), with or without lymph node dissection. Patients were randomised to one of four arms: 1.1 or 3.7 GBq, each with Thyrogen (given on each of the two days before ablation) or thyroid hormone withdrawal. All patients were put on a low iodine diet and had a pre-ablation scan using Technetium 99m (to assess remnant size). Ablation success was determined 6-9 months later using an I-131 iodide diagnostic scan (uptake < 0.1%), and undetectable serum thyroglobulin (Tg). Toxicities and QoL were recorded.

Results: 438 patients were recruited from 31 UK centres from the National Cancer Research Network; January 2007-April 2010. Median age 44 years;

77% female; 23% T3; 16% N1. Final results on ablation success rates and toxicities will be available in May 2011.

Conclusions: Preliminary results indicate that 1.1 GBq could be used instead of 3.7 GBq, and this was the conclusion in subgroups based on T and N stage. Patients could have Thyrogen to allow them to continue thyroid hormone replacement during ablation.

OP76

NOT ALL NEW RET MUTATIONS SHOW TRANSFORMING ACTIVITY WHEN ANALYZED BY IN SILICO AND IN VITRO ASSAYS

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Germline RET proto-oncogene point mutations are virtually causative of all hereditary medullary thyroid carcinomas (MTC) and somatic RET point mutations have been described in about 40% of sporadic MTC.

Aim of this study was to analyze the biologic features of 6 new RET mutations (T338I, V648I, M918V, A883T, S904F, M848T) by "*in silico*" and *"in vitro"* methods. Six well known *RET* mutations were used as controls in this study.

The *"in silico"* analysis showed that S904F, M848T, M918T and C634R had the highest scores, M918V, V804M, Y791F, and A883T had an intermediate score whereas L790F, G691S, T338I, and V648I had a 0 score.

The *"in vitro"* focus formation assay showed that cells transfected with S904F, M918T, M848T or C634R generated the highest number of focus formation units (FFU). Intermediate numbers of FFU were observed in cells transfected with M918V, V804M, Y791F or A883T, while cells transfected with L790F, G691S T338I or V648 showed a number of FFU similar to control cells. Only cells transfected with M918T or C634R grew faster than control cells. Moreover, cells transfected with M918T or C634R generated the highest number of colonies in soft agar, whereas the cells transfected with the other mutations produced a number of colonies similar to control cells; however, the cells that were transfected with V804M produced an intermediate number of colonies.

In conclusion, 2 of our 6 new *RET* mutations, S904F and M848T showed a relatively high transforming activity but a low aggressiveness. At variance the other 4 mutations, T338I, V648I, M918V and A883T showed a low or non-transforming activity and their ability to induce tumoral transformation might be related to particular genetic conditions.

OP77

THYROID AUTOIMMUNITY AND THYROID CANCER: PATHOLOGICAL AND MOLECULAR STUDY IN A LONGITUDINAL SERIES OF UNSELECTED NODULES

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Aim: To confirm the potential association between autoimmune thyroid diseases (AITD) and papillary thyroid carcinoma (PTC) in a prospective study in unselected thyroid nodules (TN).

Patients and Methods: One-hundred-eighty-four patients (235 TN) consecutively submitted to fine-needle aspiration cytology (FNAC), fully evaluated for associated AITD. In most FNAC samples, $BRAF^{V600E}$ mutation was evaluated by PCR and RET-PTC rearrangements by PCR and interphase fluorescence in situ hybridization (I-FISH), using a newly developed homebrew dual-color-breakpart RET probe. In 61 operated patients (75 TN), histology and lymphocytic thyroid infiltration (LTI) description were available.

Results: Higher prevalence of suspicious/malignant cytology was found in AITD+ TN (22.6% *vs* 9.8% in AITD-, $p< 0.01$). Prevalence of PTC in operated TN was higher in AITD+ (68.8%) than in AITD- (44.2%, $p< 0.05$) and LTI was found in 66% of malignant *vs* 34% of benign TN ($p < 0.05$). $BRAF^{V600E}$ mutation was found in 11/93 (11.8%) AITD+ *vs* 2/142 (1.4%) AITD- TN ($p< 0.001$), all PTC. $BRAF^{V600E}$ mutation was found in 11/22 (50%) AITD+ and in 2/17 (11.8%; $p< 0.02$) AITD- PTC. RET-PTC rearrangements were found by PCR only in 3 FNAC (one AITD+ and two AITD-) all showing a separate breakapart I-FISH signal in ≥ 6.8% nuclei. When compared to normal thyroid, broken signal (cutoff ≥3%, mean±3DS), was found in a larger number of FNAC distributed along the whole cytological spectrum, with higher prevalence in indeterminate to suspicious/malignant (13.6%) *vs* benign (3.1%) cytology, but no correlation was observed between broken I-FISH signal and AITD.

Conclusions: A significant association between AITD and PTC was confirmed in a prospective study of TN submitted to FNAC. This association does not appear to be mediated by RET-PTC rearrangements. The higher prevalence of $BRAF^{V600E}$ mutation in PTC associated with AITD will deserve further investigation.

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OP78

CLINICAL SIGNIFICANCE OF ANTI-THYROID ANTIBODIES (AT-AB) TITER TREND IN A LONG-TERM FOLLOW-UP OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA (DTC)

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AT-Ab are present in about 25% of patients with DTC at the time of diagnosis. While it is known that the diseappearance of AT-Ab is correlated with the complete ablation of thyroid tissue, it is still not defined if the persistence of a positive titer of AT-Ab correlates with the persistence of thyroid cancer tissue.

Objective: To evaluate the trend of AT-Ab titer in a group of DTC patients who were positive for AT-Ab at diagnosis (n=178) both in those who became negative (n=137) and in those who were still positive (n=41) after a first follow-up of 18 years. We followed these patients for other 15 years.

Results: All 137 negative patients remained AT-Ab negative at the end of second follow-up. Furthemore 29/41 (71%) positive cases became negative, while 12/41 (29%) remained positive for anti-thyroglobulin antibodies (Tg-Ab). Of this last group, 7 died (4 for thyroid cancer and 3 for other causes). Of the 5 alive patients positive for Tg-Ab, 3 patients had lung or mediastinal lymph nodes metastasis identified by CT scan and/or ^{131}I therapeutic whole body scan (WBS), while 2 patients had a stable titer of Tg-Ab without evidence of disease at neck ultrasound and/or at WBS.

Conclusions:

1) AT-Ab negativity may also occur after more than 20 years;

2) no patients who became negative for AT-Ab at the end of first follow-up returned to be positive within further 15 years;

3) patients still positive for AT-Ab, also 30 years after thyroidectomy, should be considered still affected by DTC and should be investigated with all available methods.

OP11 Thyroid Hormone Basic 2

OP79

NOVEL TRANSGENIC TOOLS ILLUMINATE THE COORDINATED DEVELOPMENT OF THE THYROID GLAND AND THE CARDIOVASCULAR SYSTEM IN ZEBRAFISH EMBRYOS

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In the recent past, zebrafish has gained much attention as a genetically tractable vertebrate model for studies on organ morphogenesis. We recently developed a novel transgenic fluorescent reporter line, *tg(tg:mCherry)*, that offers visualization of thyroid morphogenesis in live zebrafish embryos. In this study, we used a panel of new double transgenic lines, including *tg(cmlc2:EGFP;tg:mCherry)* and *tg(kdrl:EGFP;tg:mCherry)* to study the role of cardiovascular development for thyroid organogenesis in zebrafish. Time-lapse imaging of live embryos and three-dimensional reconstruction of confocal microscopy images were used to generate a dynamic atlas of zebrafish thyroid development with a special focus on the spatio-temporal relationship between thyroid and cardiovascular morphogenesis. For example, by tracking thyroid and cardiovascular development in *tg(cmlc2:EGFP;tg:mCherry)* embryos, a close association of the thyroid anlage with the arterial pole of the developing heart was evident as well as a tight coordination of the descend of the heart with thyroid budding and subsequent thyroid migration. At later stages, we observed that thyroid cells cluster around the distal portion of the *bulbus arteriosus*, the main component of the zebrafish heart outflow tract. Growth expansion of the thyroid along the pharyngeal midline occurs concurrent with a remodeling of the pharyngeal vasculature. In a first phase, the thyroid tissue expands rostrally adjacent to the paired first and third aortic arch arteries. During a second phase, follicles begin to disperse over the dorsolateral surface of the now rostrally extending midline ventral aorta. In addition to the morphological characterization, a vital role of cardiovascular development for normal thyroid morphogenesis became evident from the observation of defective thyroid development in various zebrafish models with cardiovascular anomalies. In summary, we show that transgenic zebrafish models provide novel tools to illuminate the role of the cardiovascular system for thyroid gland organogenesis.

OP80

THE THYROID HORMONES INHIBIT TRANSCRIPTIONAL RESPONSES TO THE TRANSFORMING GROWTH FACTOR β

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The thyroid hormone receptors (TRs) regulate transcription by binding to thyroid hormone response elements (TREs) or by cross-talk with other transcription factors and signalling pathways. We have analyzed the regulation of Transforming Growth Factor β (TGF-β) responses by the thyroid hormone in pituitary GH4C1 cells. TGF-β plays a key role in proliferation, differentiation and cancer. TGF-β stimulates transcription of its target genes by phosphorylation of Smad2/3 that heterodimerize with Smad4 and are transported to the nuclei where they bind to SBEs (Smad binding sites). TGF-β can also stimulate the ERK/MAPK pathway. We have found that T3 reduces phosphorylation of Smad 2 and ERK by TGF-β in GH4C1 cells, suggesting that T3 can repress TGF-β-dependent transcription. This was confirmed in transfection assays with a luciferase reporter containing SBEs, where T3 reduced the response to TGF-β. Furthermore, T3 inhibited transactivation by Smad3 and Smad4 in the absence of TGF-β. Antagonism can be mediated by TRα and TRβ, since expression of both isoforms abolished induction of luciferase activity by TGF-β in HaCaT cells, which express low endogenous TR levels. T3 also repressed transcription of endogenous genes by TGF-β in GH4C1 cells. TGF-β increased the mRNA levels of the well-known transcriptional targets of this growth factor, the inhibitory Smad7 and the cyclin kinase inhibitor p15, and T3 reduced this response. In chromatin immunoprecipitation assays, we observed that TGF-β caused the recruitment of Smad4 to the Smad7 and p15 promoters and that T3 inhibited this recruitment, demonstrating the existence of a novel mechanism by which the thyroid hormones can regulate transcription of TGF-β target genes independently of receptor binding to a TRE. These findings provide evidence of the existence of a cross-talk between the thyroid hormone and TGF-β signalling pathways, which may have important implications in different physiological and pathological conditions.

OP81

EFFECTS OF MCT8 AND MCT10 ON THE BIOLOGICAL ACTIVITY OF T3

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Objectives: Transport of thyroid hormone (TH) across the plasma membrane is necessary for the genomic action of T3 mediated by nuclear T3 receptor (TRs). Several TH transporters are known, such as MCT8 and MCT10. Mutations in MCT8 are associated with severe psychomotor retardation. The aim of this study was to investigate the effects of MCT8 and MCT10 on the biological activity of T3.

Methods: Jeg3 cells were transiently transfected with TRβ1 and a construct containing a T3 response element (TRE)-dependent luciferase reporter and a control renilla reporter (pdV-L1; gift from Dr. W.S. Simonides, VUMC, The Netherlands). In addition, cells were transfected with MCT8, MCT10 and/or μ-crystallin (CRYM). CRYM is a high-affinity intracellular TH binding protein which inhibits TH efflux. Two days after transfection, cells were incubated for 0.5, 1, 2, 6 or 24 h with 1 nM T3. After removal of T3, incubations were continued for a total time of 24 h, and the luciferase/renilla activities were determined.

Results: Cells co-transfected with CRYM and MCT8 or MCT10 showed a significantly higher fold change in response to T3 than cells transfected with CRYM alone (e.g. 60 min 1.87±0.13 and 1.80±0.19 vs 0.96±0.08, P< 0.004). Without CRYM, transfection of MCT8 or MCT10 did not clearly enhance the T3 response. Combining all data, the cellular T3 concentration and the T3 response were highly correlated in the absence or presence of CRYM.

Conclusions: We demonstrate that TH transporters, such as MCT8 and MCT10, increase not only the cellular T3 concentration but also the biological availability of T3 for the nuclear receptor. However, the effect is not seen in the absence of CRYM, probably due to the rapid equilibrium of T3 influx and efflux.

OP82

TYPE 3 DEIODINASE IS HIGHLY EXPRESSED IN PROLIFERATING MYOBLASTS AND DURING THE EARLY PHASE OF MUSCLE REGENERATION

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Thyroid hormone (TH) is a critical mediator of cellular metabolism and differentiation and has long been known to play important roles in skeletal muscle physiology. Its action is initiated by the activation of T4 to T3, catalyzed by the type 1 or the type 2 selenodeiodinases (D1 or D2). Inactivation of T4 and T3 is catalyzed by the type 3 iodothyronine selenodeiodinases (D3).

The presence and function of D2 and D3 in skeletal muscle have been investigated for many years. We recently demonstrated that D2 is expressed in muscle precursor cells, and its over-expression is essential for myoblast differentiation and to allow a normal regeneration process. D3 mRNA is also present in adult muscle and its function in this context is completely unknown.

To investigate the role of D3 in skeletal muscle physiology, we used the primary muscle cells (pp6) that can be cultured in proliferative or differentiating conditions. D3 mRNA is expressed in proliferative pp6 cells and its expression declines during differentiation. We also evaluated D3 expression during the regeneration of muscle fibers by injecting cardiotoxin into muscles of C57 mice and the corresponding untreated muscles used as controls. D3 mRNA expression was evaluated by real time PCR at different time points, revealing that D3 is strongly induced in the early phase of the regeneration

process, with peak D3 expression at around 4 days after the injury, declining thereafter. This precedes the peak of D2 activity at 9-12 days.

These results demonstrate a highly dynamic expression pattern for the deiodinases during differentiation and regeneration of muscle cells. Even though circulating TH concentrations are not altered after muscle injury, our data indicate that the sequential changes in D3 and D2 can induce complex pattern of changes in intracellular T3 levels to facilitate the repair of injured skeletal muscle.

OP83

TISSUE 3-IODOTHYRONAMINE UPTAKE IN VIVO: COMPARISON WITH EXPRESSION OF TRACE AMINE ASSOCIATED RECEPTORS

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Objectives: 3-iodothyronamine (T1AM) is a novel endogenous chemical messenger which has been detected in most tissues. Since T1AM is able to interact with G protein-coupled receptors known as trace amine-associated receptors (TAARs), we evaluated the uptake of blood-born T1AM in different mouse tissues, and compared it to TAAR expression.

Methods: [^{125}I]-T1AM was injected in the tail vein at physiological concentration (about 0.3 nM). T1AM uptake in different organs was determined by measuring tissue radioactivity at 30-1440 min. In parallel experiments, the expression of the 9 known TAAR subtypes was evaluated by quantitative real-time PCR.

Results: [^{125}I]-T1AM preferentially distributed to the gastrointestinal tract, liver and kidney. At 30 min radioactivity concentration was highest in gallbladder, stomach, intestine, liver and kidney, where it was significantly higher than in blood. Tissue radioactivity decreased exponentially over time with an overall half life of 25 min, but different time constants were observed in different tissues, and after 24 hours 70% of the residual radioactivity was detected in liver and adipose tissue. In most tissues [^{125}I]-T1AM uptake was blocked by 1000-fold excess of unlabeled T1AM, suggesting the presence of specific and saturable binding sites. Most radioactivity underwent urinary excretion and most urine radioactivity was still associated with T1AM, as shown by thin layer chromatography. PCR experiments showed that TAARs were expressed only at trace amounts (< 10 copies per mg mRNA) in most tissues, the exceptions being TAAR1 (stomach and testis) and TAAR8 (intestine, spleen and testis). In all cases expression was however < 100 copies per mg mRNA.

Conclusions: exogenous [^{125}I]-T1AM distributed to all mouse tissues. Tissue distribution was consistent with biliary and urinary excretion, and long term accumulation occurred in liver and adipose tissue. TAAR expression seemed unable to account for T1AM distribution, suggesting the existence of other high affinity binding sites.

OP84

UPTAKE AND METABOLIC EFFECTS OF 3-IODOTHYRONAMINE IN RAT LIVER

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Objectives: 3-iodothyronamine (T1AM) is an endogenous thyroid hormone derivative able to interact with trace amine associated receptors, a family of G protein-coupled receptors, and possibly with other specific molecular targets. Since T1AM has been suggested to produce metabolic effects, in the present work we investigated whether T1AM is taken up by hepatocytes and whether it is able to affect liver metabolism.

Methods: Human hepatocellular carcinoma cells (HepG2) were exposed to exogenous T1AM (1μM) for 5-300 min, then T1AM and its putative catabolites, namely thyronamine (T0AM), 3-iodothyroacetic acid (TA1) and thyroacetic acid (TA0), were assayed in the incubation medium and in cell lysate by HPLC coupled to tandem mass spectrometry. In other experiments T1AM was infused in an isolated rat liver preparation perfused with Krebs-Henseleit buffer. The effluent perfusate was then collected for 60 min at 5 min intervals to measure the release of glucose, lactate, pyruvate and ketone bodies (acetoacetate and beta-hydroxybutyrate).

Results: T1AM was taken up by HepG2 cells, and since 5 min lysate concentration exceeded medium concentration by over 5-fold. After 300 min, about 80% of total T1AM was recovered unchanged, while less than 10% was converted into TA1. Minimum amounts of T0AM were observed while TA0 was undetectable. Similar results were observed in perfused rat liver, since tissue T1AM concentration exceeded 100 pmol/g after a 60 min infusion of 50 nM T1AM. In this model, infusion of 1 μM T1AM did not produce any significant change in glucose, lactate and pyruvate release, while acetoacetate and beta-hydroxybutyrate release increased significantly (0.027±0.003 vs 0.015±0.002 μmol/min per g, and 0.075±0.001 vs 0.031±0.001 μmol/min per g, $P < 0.01$ in both cases).

Conclusions: We conclude that exogenous T1AM is taken up by hepatocytes, where it is partly deaminated to TA1 and stimulates ketogenesis.

OP85

THE ROLE OF MICRORNA AND PROMOTER METHYLATION IN REGULATION OF THYROID HORMONE RECEPTOR BETA EXPRESSION IN RENAL CANCER

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Objectives: TRbeta, nuclear receptor for triiodothyronine, mediates biological activities of hormone. THRB is a tumor-suppressor, exhibiting decreased expression in malignancies. In our previous studies on clear cell Renal Cell Carcinoma (ccRCC), downregulation of THRB was linked with aberrant alternative splicing of the gene's untranslated regions (UTRs). To elucidate pathways of THRB expression regulation, in this work we focused on analyses of THRB promoter methylation and identification of microRNAs that bind TRbeta 3'UTR. microRNAs, non-coding RNAs, inhibit gene expression and their upregulation could result in suppression of TRbeta in ccRCC.

Methods: Methylation analysis was performed on bisulfite converted DNA. THRB promoter was cloned from 12 paired ccRCC tumor-control samples and sequenced. miRNAs putatively binding THRB 3'UTR were identified *in silico* and their functionality was confirmed using reporter vector, containing THRB 3'UTR cloned downstream of luciferase. Effect of microRNAs on native THRB expression was analyzed in UOK171 ccRCC cell line, transfected with microRNA precursors. microRNA and THRB levels were measured in 26 paired-tissue samples using SQ-PCR.

Results: No differences in THRB methylation were found between ccRCC and control samples. miR-155 and miR-425 were confirmed to directly bind the THRB 3'UTR. 1.5-fold and 3.5-fold decrease in THRB mRNA was observed after transfection of UOK171 with pre-miR-155 and pre-miR-425, respectively. In tissue samples, 2.1-fold *THRB* reduction in tumor was concomitant with 10-fold upregulation of miR-155 and 1.5-fold upregulation of miR-425.

Conclusions: Investigating factors potentially involved in regulation of THRB expression, we identified miR-155 and miR-425 as its direct interactors. TRbeta downregulation in ccRCC does not result from hypermethylation of gene promoter but is possibly caused by overexpression of both microRNAs. Importantly, upregulation of both microRNAs is observed in other cancers and diseases, therefore it can be hypothesized that their pathogenic and oncogenic role is partially exerted via silencing of TRbeta.

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OP86

DISTURBED ALTERNATIVE SPLICING OF TYPE 2 DEIODINASE IN PITUITARY TUMORS

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Objectives: Type 2 deiodinase (D2) plays a particular role in physiology of the pituitary where it provides locally synthesized T3 and this way contributes directly to the regulation of TSH secretion. Pituitary tumors belong to the most common intracranial neoplasms. Previous studies revealed that D2 mRNA expression and activity do not correlate in pituitary tumors, suggesting possible posttranscriptional regulation. The aim of this study was to analyze alternative splicing of D2 in pituitary tumors.

Methods: 36 pituitary tumors and 5 control non-neoplastic pituitary samples were used for isolation of RNA which was reversely transcribed. The resulted cDNA was used for AT-cloning of D2 transcript variants in pGEM-T vector. D2 pre-mRNA sequence was used for prediction of binding motifs for splicing factors with ESE Finder software. Expression of splicing factors was analyzed with real-time PCR.

Results: Cloning of D2 mRNA isoforms from non-neoplastic pituitary samples revealed wild type D2 (consisting of exon 1 and 2) and new mRNA variants, not previously reported. Transcript variants cloned from pituitary tumors included transcripts present in control samples and 8 other new transcripts. In one tumor sample wild type D2 was missing and instead a new short mRNA variant, consisting of exon 1 and 2 fragments was present. Translation prediction showed that the cloned transcript variants code for proteins devoid of the most essential regions, e.g. catalytically active centre or a region involved in protein ubiquitination. Computed analysis revealed that D2 pre-mRNA contains potential binding sites for splicing factors SF2/ASF, SC35, SRp40, and SRp55. The expression of all these splicing factors was statistically significantly upregulated in tumor samples in comparison with control pituitaries.

Conclusions: D2 alternative splicing is disturbed in pituitary tumors which may possibly result from upregulated expression of splicing factors.

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P01

PATIENTS WITH DIFFERENTIATED THYROID CANCER (DTC) WHO UNDERWENT RADIOIODINE REMNANT ABLATION (RRA) WITH LOW ACTIVITY OF ^{131}I EITHER RECOMBINANT HUMAN TSH (RHTSH) OR AFTER THYROID HORMONE THERAPY WITHDRAWAL (THW) SHOW THE SAME OUTCOME AFTER 10 YEARS OF FOLLOW UP

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Objectives: RRA requires TSH stimulation that can be obtained either after THW or rhTSH administration. Two are the issues which still need to be clarified: 1)if the outcome of patients prepared with rhTSH or THW for RRA is similar in a long term follow-up; 2) if the RRA rate obtained with low ^{131}I activity (30 mCi) is similar when stimulation is performed with rhTSH or after THW or both. We compared the outcome of patients who underwent RRA with 30 mCi of ^{131}I either after rhTSH or THW or both [EU+rhTSH, HYPO and HYPO+rhTSH groups in a previous study] and followed-up for 10 years.

Methods: The outcome of 159/162 patients enrolled in our previous study was evaluated. They were divided into 2 groups: ablated (n=115) and not ablated (n=44) at the 6 month control after RRA. In all ablated patients serum thyroglobulin (Tg), anti-thyroglobulin antibodies (Tg-Ab) and neck ultrasound were performed on LT4. Not ablated patients also performed a rhTSH-stimulation Tg test and a diagnostic whole body scan if Tg-Ab were positive.

Results: 111/115(96.5%) ablated patients [35/37(94.6%) HYPO, 30/31(97%) HYPO+rhTSH and 46/47(98%) EU+rhTSH] remained ablated and cured while 4/115(3.5%) showed a DTC recurrence [2/37(5.4 %) HYPO, 1/31(3%) HYPO+rhTSH and 1/47(2%) EU+rhTSH]. In the not ablated patients 16/44(36.4%) were still affected [4/13(30%) HYPO, 6/8(75%) HYPO+rhTSH and 6/23(26.1%) EU+rhTSH] while 28/44(63.6%) were cured during follow-up [9/13(70%) HYPO, 2/8(25%) HYPO+rhTSH and 17/23(74%) EU+rhTSH]. No differences were observed in the outcome of the 3 groups of patients.

Conclusions: This study indicates that the outcome of DTC patients who underwent RRA 10 years ago with 30 mCi either after rhTSH or THW or both is similar in a long term follow up. Furthermore, if new criteria of ablation are used, the percentage of ablated and not ablated patients in the 3 groups is similar.

P02

INCREASED INCIDENCE OF DIFFERENTIATED THYROID CANCER IN DENMARK 1943–2008. IS IT INFLUENCED BY IODINE SUPPLEMENTATION?

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Objectives: Thyroid cancer is the most frequent endocrine malignancy, and during the previous decades the incidence has increased worldwide. The aetiology has been described to include iodine intake, previous irradiation, particularly in childhood, genetic factors and endocrine disrupting chemicals. The aim of the present study was to asses the overall trend in incidence of thyroid cancer from 1943-2008.

Methods: Data were obtained from The Danish Cancer Registry which contains information on all newly diagnosed cancers ocurring in the population since January 1st 1943, including topography, morphology (after 1978), date of diagnosis and Personal identification number of each patient. It is linked to The National Patient Registry and The Causes of Death Registry. Coverage is considered close to 100%. During most of this period the eastern part of the country had mild and the western part moderate iodine deficiency, while compulsory iodine fortification was established in 2000.

Results: Overall, 1925 men (30%) and 4599 women (70%) were diagnosed with invasive thyroid cancer at a median age of 59 years. The age standardised incidence, constituted mainly of papillary cancers and in younger people, rose from 0.22 to 1.73 per 100,000 in men and from 0.57 to 4.3 per 100,000 in women, with an estimated annual percentage change of 1.3 (95% CI, 1.1-1.6) and 1.4 (95% CI, 1.2-1.6) respectively. Divided into shorter periods the increase was particularly present at the end of the study period after iodine supplementation (not significant), but without a significant difference between the eastern and western parts.

Conclusions: In this nationwide and globally longest study differentiated thyroid cancer increased over 66 years, and more so during the last decade coinciding with commencement of iodine supplementation. However, both more prevalent use of thyroid imaging discovering very small tumours and other factors might be responsible for the increase rather than iodine.

P03

SORAFENIB IN THE TREATMENT OF RADIOIODINE REFRACTORY THYROID CANCER. A MULTICENTER PHASE II STUDY

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Background: Patients with progressive disease (PD) of differentiated thyroid carcinomas (DTC) refractory to radioiodine (RAI) treatment have a poor outcome due to ineffectiveness of chemotherapy and should be considered for treatment with tyrosine kinase inhibitors (TKIs).

Methods and Patients: A phase II clinical trial was performed with sorafenib, a multikinase tyrosine inhibitor, in 11 patients (> 20 years old, 7 women, 4 men) with advanced, locally progressive or metastatic, unresectable and RAI resistant DTC. All patients were treated for a minimum of 4 months and up to 9 months and received sorafenib 200 mg tabl.2× 2/daily. Responses were measured radiologically according to RECIST criteria, by 18FDG-PET imaging and Tg measurements.

Results: Two patients (18%) had PD, 3 patients (27%) registered a partial response (PR) and 6 (55%) had stable disease. Tg was variably decreased by up to 85%. The most frequently reported side effects were hand-foot syndrome, fatigue, diarrhea and, in 3 patients arterial hypertension. Due to side effects all patients had to reduce the daily dosage. Two PD pat. and 2/3 with PR were withdrawn from the study after 5-7 months of treatment. None was rendered positive to RAI. Cervical metastases were more resistant to treatment than lung lesions.

Conclusion: Despite the limited number of patients this further confirms the efficacy of Sorafenib in advanced RAI refractory DTC and therefore should be available as a potential therapeutic tool. However, the aggressiveness of disease in some patients implies that targeted therapy should take into

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account biomarkers and consider combinations with other TKIs or with mTOR inhibitors, adapting the dose, to enhance tolerability and response.

P04

FOLLOW-UP OF DIFERENTIATED THYROID CANCER (DTC) PATIENTS DEFINED FREE OF DISEASE WITH A SINGLE NEGATIVE RECOMBINANT HUMAN THYROTROPINE (RHTSH) THYROGLOBULIN (TG) STIMULATION TEST

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Objectives: To evaluate: 1) the capability of a single negative rhTSH-Tg test in establishing the clinical remission of DTC patients after total thyroidectomy and therapeutic 131-I treatments; 2) the opportunity to repeat the rhTSH-Tg test during follow-up.

Methods: We studied 138 DTC patients with a negative rhTSH-Tg test (basal and stimulated Tg< 0.5ng/ml) performed between 1999 and 2001, at any time of their clinical history. These patients were negative for anti-Tg antibodies and without clinical evidence of disease (i.e. free of disease). We yearly followed these patients with neck US and basal-Tg measurement on LT4 therapy. We repeated a second rhTSH-Tg test 10 years later.

Results: 128/138(92.7%) patients are still free of disease. In 10/138(7.2%) patients a DTC recurrence was observed during the follow-up. In 4/10(40%) the recurrence was discovered because of a rising of basal-Tg (>0.5ng/ml), in 3/10(30%) we found both lymphnode metastasis at the neck US and detectable basal-Tg, while in 2/10(20%) neck US showed lymphnode metastasis with undetectable basal and stimulated-Tg. In 1/10(10%) only the stimulated-Tg was detectable (>2ng/ml) with negative neck US. Dividing patients in low, intermediate and high risk we found the majority of recurrences in intermediate and high risk groups (7/66,10.6%) while only 2/65(3%) were in the low risk group.

Conclusions: A single negative rhTSH-Tg test can predict a 10 years disease free follow up in 92.7% of cases. We found that the percentage of recurrence is significantly higher than that reported in studies in which the remission of DTC was defined by hypothyroidism-Tg measurement. Furthermore, we confirm that the association of neck US and serum Tg measurement has the best predictive positive value (90%) to discover DTC recurrence which can reach 100% by adding a rhTSH-Tg stimulation test. The cost-benefit of repeating this test to find out 1/138(0.7%) DTC recurrence should be considered.

P05

EXTRATHYROID EXTENSION AS A PREDICTING FACTOR OF PROGNOSIS IN PAPILLARY THYROID MICROCARCINOMA PATIENTS

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Objectives: The pathologic extrathyroid extension is known as one of the risk factors affecting the extent of surgery and prognosis in papillary thyroid carcinoma. However, the validity is not well established in papillary thyroid microcarcinoma (PTMC). We studied the extrathyroid extension as a predicting factor of prognosis in PTMC patients.

Methods: We analyzed the disease-free survival (DFS) and the recurrence rate of 184 patients who underwent thyroidectomy for PTMC between 1996 and 2001, and compared them according to the pathologic reports (extrathyroid extension status) and intraoperative gross findings (intrathyroidal confined cases and beyond capsular involvement cases).

Results: The mean age was 44.9 years old and the mean tumor size was 0.8 cm. About half of them received less than total thyroidectomy. Overall DFS was 92.7 ± 42.8 (months) and the recurrence rate was 3.8 % (n, 7). Recurrences were five after hemithyroidectomy and two after total thyroidectomy. There were no significant differences in the DFS compared within the two variables of extrathyroid extension. Among the intrathyroidal confined cases (n, 119) of gross findings, the DFS was not affected by the pathologic extrathyroid extension status.

Conclusions: In PTMC, the pathologic reports of extrathyroid extension status had no affect on the DFS. Also, with such low recurrence rate, aggressive surgery with radioiodine ablative therapy for pathologic extrathyroid extension seems to be an overtreatment regimen in PTMC since the intraoperative gross findings were useful enough to predict the initial extent of surgery.

P06

ROBOT-ASSISTED GASLESS TRANS-AXILLARY THYROIDECTOMY: SINGLE SURGEON'S EXPERIENCE OF 300 CASES

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Objectives: Since the introduction of robot-assisted gasless trans-axillary thyroidectomy, the procedure has been getting the spotlight more than ever. To share the updated surgical procedure, we report our experience of robot-assisted gasless trans-axillary thyroidectomy.

Methods: From December 2008 to November 2010, three-hundred patients underwent robot-assisted gasless trans-axillary thyroidectomy in Asan Medical Center,. We analyzed patients' clinicopathologic characteristics, type of surgery, operative time, postoperative course and complications.

Results: The mean age was 41.5±8.5 years. Among 300 patients, 297 patients received thyroidectomy under the diagnosis of papillary thyroid carcinoma and 3 patients for follicular neoplasm. The mean operative time was 139.2±27.7 minutes for less-than total thyroidectomy and 185.7±38.5 minutes for total or near-total thyroidectomy with or without central compartment node dissection (p< 0.05). The mean length of hospital stay was 3.6±1.9 days. The mean tumor size of carcinoma cases was 0.8±0.5cm and the mean number of retrieved lymph nodes was 6.6±4.7. Lymph node metastasis was found in 103 (34.7%) patients and perithyroidal soft tissue invasion in 158 (53.2%) patients. Multiplicity and bilaterality were 20.9 % and 10.4%, respectively. There were 3 (1.0%) cases of recurrent laryngeal nerve injury and 8 (2.7%) cases of airway problems. Patients with complications were recovered by conservative treatments. Among 107 patients who underwent total thyroidectomy, 95 patients received postoperative radioactive iodine treatment and the mean level of pre-ablation stimulated thyroglobulin was 2.4±5.9 ng/mL.

Conclusions: Robot-assisted gasless trans-axillary approach is feasible, safe and promising for the selected patients with thyroid carcinoma. In the near future, this procedure will carry an important role even in the patients with more advanced disease status.

P07

COMPARISON OF 800MBQ AND 3700 MBQ IODINE-131 FOR THE POST-OPERATIVE ABLATION OF THYROID REMNANT IN PATIENTS WITH LOW RISK DIFFERENTIATED THYROID CANCER

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The aim of the study is to compare the success rate of low and high activities of I-131 for postoperative remnant ablation.

Patients and Methods: 108 non-metastatic low risk patients (mean age: 46, 85% female) with papillary and follicular carcinoma had I-131 ablation (RAIA). Fifty-three and 55 patients received low (L) (800 MBq) and high dose (H) (3700MBq) respectively. After total thyroidectomy, thyroid bed I-131 uptake (RAIU) and neck ultrasonography (USG) was performed to determine remnant volume and iodine avidity which were used to calculate the dose delivered to remnant tissue. The success rate of I-131 ablation was assessed with 4 different criteria.;1) three test strict criteria: a) USG negative, b) no tracer uptake or less than twice background activity in the thyroid bed on DxWBS and/or ≤ 0,2% RAIU, c)Tg < 0,2ng/ml, 2) three test lax criteria: a) USG negative, b) no tracer uptake or less than twice background activity in the

thyroid bed on DxWBS and/or ≤ 0,2% RAIU, c) Tg< 2ng/ml, 3) two test strict criteria: a) USG negative, b)Tg < 0,2ng/ml, 4) two test lax criteria a) USG negative, b) Tg < 2ng/ml).

Results: When 3 tests were used to define successful ablation, in group L, 32 out of 53 (60 %) and 43 out of 53 (81 %) patients were successfully treated versus 35 out of 55 (64 %) and 42 out of 55 (76 %) for group H based on strict and lax criteria respectively. (*P*=n.s). The differences were not statistically significant between two groups when only two test were used to define ablation success (62% vs. 69% with strict and 89% vs. 87% with lax criteria respectively). Our findings suggest that remnant thyroid tissue in patients with low risk, well differentiated thyroid cancer after total thyroidectomy can be ablated with 800MBq of I-131.

P08

SIGNIFICANCE OF MICROSCOPIC CENTRAL COMPARTMENT LYMPH NODE METASTASIS IN PAPILLARY THYROID CARCINOMA

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Objectives: Cervical lymph node metastasis is a risk factor for the recurrence in papillary thyroid carcinoma (PTC). However, the risk of recurrence by microscopic central compartment lymph node (CLN) metastasis has not been well evaluated and we studied the significance of microscopic CLN metastasis in PTC patients.

Methods: From 1996 to 2000, six-hundred and forty-eight patients received thyroidectomy with CLN dissection (curative or prophylactic) for PTC. The recurrence rate was compared between group I (no CLN metastasis), group II (microscopic CLN metastasis), and group III (clinical CLN metastasis). Also, pathological metastases of intraoperative CLN positive findings were evaluated.

Results: Number of cases for each group were 272 (42.0 %), 175 (27.0 %), and 201 (31.0 %), respectively. Lymph node recurrence was found in 52 (8.0 %), 1 in CLN and 51 in lateral lymph nodes. The recurrence rate between group I (3.7 %) and CLN metastasis group II and III (11.2 %) had statistical difference (P< 0.05). However, group I (3.7%) and group II (5.2%) showed no difference, and group II (5.2 %) and group III (17.4 %) showed difference (P< 0.05). Intraoperative CLN positive findings were seen in 236 cases and 201 had pathologically proven metastasis, showing positive prediction at 85.1 % and sensitivity at 53.5 %.

Conclusions: In our study, microscopic CLN metastasis was not a risk factor for recurrence suggesting that pathological positivity is different from clinical metastasis. Also, these suggest that the patients with intraoperative CLN positive findings might benefit from prophylactic CLN dissection. However, due to low sensitivity, the CLN dissection is still a routine procedure in our institution.

P09

DIAGNOSTIC IMPACT OF ^{18}F-DOPA-PET/CT IN RESIDUAL OR RECURRENT MEDULLARY THYROID CANCER

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Background: After initial therapy of medullary thyroid cancer (MTC), serum calcitonin (Ct) and/or carcinoembryonic antigen (CEA) concentration serve as markers of recurrent disease but conventional imaging often fails to localize the metastases. It is unclear which imaging technique is best for localizing metastases and whether this is affected by Ct/CEA doubling time (DT) and histology. The aim was to compare fluorine-labelled dihydroxyphenylalanine (^{18}F-DOPA) PET/CT, fluorodeoxyglucose (^{18}F-FDG) PET/CT, multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) in detection of metastases in MTC and relate the findings to Ct/CEA concentrations and histology.

Material and Methods: Nineteen MTC patients who after total thyroidectomy demonstrated increased Ct and/or CEA on follow-up were prospectively imaged by ^{18}F-DOPA and ^{18}F-FDG PET/CT, MDCT and MRI. Independent experts analyzed images provided by each method to detect pathologic lesions, which then were surgically removed if possible. The diagnostic sensitivity of the different imaging methods was related to current Ct and CEA concentrations and histopathological findings.

Results: In 63 % (12/19) of patients, one or more imaging method was positive for tumor lesion. The sensitivity of ^{18}F-DOPA PET/CT for disease detection was 58% (11/19) and that of ^{18}F-FDG PET/CT, MDCT, and MRI were 53% (10/19), 47% (9/19) and 63% (10/16), respectively, based on histological evaluation of surgically removed metastases (n= 11) and follow-up (n= 8). There were significant correlations between Ct and CEA concentrations and sensitivity of ^{18}F-DOPA PET/CT imaging (P=0.0007 and P=0.0263, respectively), this held true also for ^{18}F-FDG PET/CT (both P< 0.0001). In patients with unstable (< 24 mo) Ct DT, ^{18}F-DOPA and ^{18}F-FDG PET/CT were equally sensitive. In contrast, for patients with unstable (< 24 mo) CEA DT, ^{18}F-FDG PET/CT seems to be more sensitive.

Conclusion: ^{18}F-DOPA PET/CT accurately detected metastases in most patients. In patients with unstable CEA DT, ^{18}F-FDG PET/CT may be more feasible.

P10

PATHOLOGICAL REEVALUATION OF DOUBTFUL CASES OF THYROID CANCER

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Background: Microscopic pathology of thyroid carcinoma remains difficult and inter-observer differences occur in up to 20% of pathology reports. The objective of this study was to reassess diagnostically doubtful cases of thyroid tumors based on the results of consultations provided by the expert panel of pathologists.

Material and Methods: A prospective analysis of our institutional register of thyroid surgery data revealed 2366 thyroid operations performed between 01/2008 and 12/2010. The diagnosis of thyroid cancer was made in 263 (11.1%) of these patients. However, 115 (43.73%) cases were considered

to be diagnostically complex and were subject to reassessment by expert panel of pathologists. Standard hematoxylin-stained microscopic tissue sections collected from primary tumor foci and lymph node metastases were reevaluated, and in selected patients, histopathology was supplemented by immunohistochemistry. The primary outcome measure was number of cases with change in initial diagnosis following revision of the expert panel. The data were analyzed statistically.

Results: Among 115 cases with initial diagnosis of thyroid cancer the change of final diagnosis provided by an expert panel was made in 23 (20%) cases (χ^2-test; $p< 0.001$).

Conclusion: A high degree of differentiation of morphological types of thyroid tumors is a source of considerable diagnostics considerations, even in tertiary referral centers of thyroid surgery. Any diagnostic doubts should be consulted by an expert panel of specialists who take into consideration the clinical symptoms and course of the disease, as well as additional histological and immunohistochemical test results. Strict adherence to such a management strategy allows for appropriate post-surgical treatment.

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P11

INCREASED LONG TERM MORTALITY IN PATIENTS WITH DIFFERENTIATED THYROID CANCER AND CONCOMITANT GRAVES' DISEASE

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It has been reported that differentiated thyroid cancers (DTCs) concomitant to Graves' disease may have increased aggressiveness as compared to DTCs occurring in matched euthyroid controls. However, studies on this subject are scanty and have not reached univocal conclusions. Differences in genetic and environmental factors, as well as lack of appropriate controls and/or inadequate patient follow-up in some studies may account for these discrepancies.

Objectives and Methods: We compared the long-term outcome in a cohort of non-occult DTCs occurring in Graves' patients (n=21) as compared to the outcome of DTCs occurring in euthyroid controls (n=70) matched for age, sex and tumor size. All patients were enrolled at a single institution during the 1982-94 period and were subjected to total thyroidectomy and followed-up according to a standardized protocol. A previous study of these cohorts carried out approximately 15 years ago had shown increased aggressiveness of DTCs in the Graves' group.

Results: Patients follow-up ranged 50-394 months (median 165.6 months). Patients with DTC and concomitant Graves' disease showed a significantly higher disease-specific mortality (6 deaths in 21 patients = 28.6%) as compared to the euthyroid group (2 deaths in 70 patients = 2.9%) (P=0.043). Persistent/recurrent disease also tended to be more frequent in the Graves' group than in control group (14.3% vs. 10.0%, respectively, NS). At last follow-up visit, 12 patients (57.1%) remained disease-free in the Graves' group as compared to 61 (87.1%) in the control group (P=0.005).

Conclusions: Long-term disease-specific mortality of patients with DTC and concomitant Graves' disease is significantly higher as compared with that of matched euthyroid DTC patients. These findings emphasize the need for early diagnosis and treatment of DTCs in Graves' patients.

P12

LOBECTOMY FOR PAPILLARY THYROID CANCER: PROGNOSIS AND INDICATIONS

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Introduction: Though total thyroidectomy is, generally, the standard procedure of initial surgery for papillary thyroid cancer (PTC), lobectomy is, in Japan, the mainstay of the primary surgeries for PTCs and total thyroidectomy is an option for an advanced case. To validate this therapeutic strategy, we conducted a long term follow-up survey on PTC patients treated by lobectomy.

Patients and Methods: Among 2036 consecutive PTC patients who had initial surgeries at our hospital between 1986 and 1995, 1226 patients treated by lobectomy were included. Patients' characteristics and clinical outcomes were collected retrospectively from medical records. The median follow-up period was 17.1 years. Prognoses were evaluated and risk factors of disease free survival (DFS) and cause specific survival (CSS) were analyzed by univariate and multivariate analyses using the Cox proportional hazard model.

Results: There were 127 males and 1099 females with a median age of 46.5 year-old. Median tumor size was 22 mm. Pathologically confirmed lymph node metastases and extra-thyroidal invasions were found in 861 and 104 patients, respectively. Recurrences in residual grand, lymph nodes, and distant organs were 53 (4%), 100 (8.2%), and 42 (3%) cases, respectively. Twenty-nine patients were died of this disease. The 25-year DFS and CSS rates were 84.0 and 94.6 %. Preoperative lymphadenopathy (HR: 3.2, $p< 0.0001$) and extrathyroidal invasion (HR: 3.4, $p< 0.0001$) were significant risk factors for DFS. Older age than 45 year-old (HR: 8.6, $p=0.0001$), preoperative lymphadenopathy (HR: 3.3, $p=0.0088$), extrathyroidal invasion (HR: 15.1, $p< 0.0001$), and distant metastasis (HR: 11.4, $p=0.0200$) were significant factors for CSS by multivariate analysis.

Conclusion: Though most of studied were not well recognized "low risk patients", prognosis was excellent. Patients older than 45 year-old, with preoperative lymphadenopathy, extrathyroidal invasion, or distant metastasis, were possible candidates for total thyroidectomy and postoperative iodine ablation.

P13

PREVALENCE OF LEVEL VI LYMPH NODES INVOLVEMENT IN PATIENTS WITH PAPILLARY THYROID CANCER STAGED PREOPERATIVELY AS NODE NEGATIVE

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Objectives: Clinical involvement of regional lymph nodes is usually found preoperatively in not more than 10% of patients with papillary thyroid cancer (PTC). Unfortunately, preoperative and intraoperative staging based on combination of palpation and ultrasound may results in underestimation of lymphatic spread in patients with subclinical nodal disease. These patients may experience future nodal recurrence having an impact on quality of life and prognosis. The aim of this study was to evaluate the actual prevalence of lymph nodes involvement within cervical level VI among patients with PTC staged preoperatively as cT1-3N0Mx.

Methods: Prospective analysis of clinical register of thyroid cancer including 147 patients undergoing surgery between 2009 and 2010. 116 (78,9%) patients with PTC were identified, who were not suspected for level VI lymph nodes involvement („staging": T1 - 67.2%, T2 - 12.6%, T3 - 19.8%, including Tm - 20.7%). In all patients total extracapsular thyroidectomy was performed together with elective level VI lymph node clearance. Pathological reports were reviewed to identify number of resected and metastatic lymph nodes.

Results: Level VI metastases were identified in 22 (20%) patients. Mean number of lymph nodes found in the specimen was 4.7±3.5 nodes (1-18, median 4). On average 1±2 metastatic lymph nodes were found (0-8, median 1).

Conclusions: Level VI lymph node involvement in patients with PTC and clinically negative preoperative node staging can be encountered in one fifth of patients following systematic histopatological staging after elective lymph node clearance.

P14

A COMPARISON OF SURGICAL OUTCOMES BETWEEN ENDOSCOPIC AND ROBOTIC THYROIDECTOMY

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Objectives: The gasless, transaxillary endoscopic thyroidectomy offers a distinct advantage over the conventional open operation by leaving no visible neck scar, and in attempt to improve surgical outcomes, the robotic thyroidectomy was introduced. Excellent results for robotic thyroidectomy has been reported, but it remains unclear whether robotic thyroidectomy offers any potential benefits over endoscopic thyroidectomy. This present study compared endoscopic and robotic thyroidectomy in terms of surgical outcomes.

Methods: Between May 2009 and February 2011, 165 patients underwent endoscopic thyroidectomy (endoscopy group) and 46 patiens underwent robotic thyroidectomy (robot group). A gasless transaxillary approach was used in both group. The 2 groups were compared in terms of patient characteristics, perioperative clinical results, pathologic findings and postoperative complication.

Results: Both patient groups were similar in terms of patient characteristics, the mean number of retrieved central lymph node, pathological features, length of hospital stays, postoperative complication rate and serum Tg level. However, the mean total operation time for thyroidectomy was 126.2±37.84 min in the endoscopy group and 179.6±44.34 min in the robot group (P< 0.001). Amount of postoperative total drainage for lobectomy was 153.3±45.64 for the endoscopy group and 179.9±49.15 for the robot group (P=0.031). Cost effectiveness is also an important consideration when evidence for predominance of two surgical technique is lacking. The mean cost of robotic thyroidectomy was $6655, compared with $829 for endoscopic thyroidectomy (P< 0.001). There was no difference in postoperative complications as hypocalcemia, RLN injury, chyle leakage, tracheal injury in the two groups (p=0.332).

Conclusions: In our experience, Surgical outcomes as complication rate and length of hospital stays were similar for 2 procedures. Robotic thyroidectomy was found not to be superior to endoscopic thyroidectomy in terms of operation time, amount of postoperative total drainage and operation cost.

P15

FAMILIAL HISTORY OF THYROID GLAND DISEASES, MALIGNANT TUMOURS AND RISK OF DIFFERENTIATED THYROID CANCER

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Background: Apart from two well - established environmental risk factors of differentiated thyroid cancer (DTC): iodine deficiency and ionising radiation it seems that there are biological risk factors like hereditary disposition towards thyroid diseases and different malignant tumours.

The aim of the study was to assess the influence of family history of thyroid diseases and cancer on the risk of DTC.

Material and Methods: The "case-controll" study was performed in 232 patients with DTC: 31 men (mean age 55,3±14 years) and in 201 women (mean age 50,7±13,1 years) and 342 healthy subjects: 58 men (mean age 60,2±12 years) and 285 women (mean age 53,4±14,3 years). Based on the same questionnaire there was an interview conducted concerning information of thyroid diseases and different malignant neoplasms in first degree relatives.To assess the relative risk of DTC and influence of mentioned factors the logistic regression adjusted to age was used.

Results: The thyroid diseases were more common in families of DTC patients than in control group and increased the risk of DTC: in one of parents: 18,5% v.s 9,6% (OR=2,12), in siblings: 16,8% v.s. 7,7% (OR=2,27), in children: 13,2% v.s.7,9% (OR=1,75). The malignant tumours were diagnosed in 31,9% families of DTC patients and in 29,7% families of control group. Renal cancer, breast cancer, female reproductive organs cancer and thyroid cancer were two times more frequent in DTC patients families. Breast cancer and female reproductive organs cancer increased over three times the risk of follicular thyroid cancer (FTC), while the renal cancer almost four times increased the risk of papillary thyroid cancer (PTC).

Conclusions: Thyroid diseases in families increase the risk of DTC. Renal cancer in families is connected with increased risk of PTC. Breast cancer and female reproductive organs cancer could be connected with increased risk of FTC.

P16

NO INFLUENCE OF MULTIFOCALITY/ BILATERALITY ON RECURRENCE-FREE SURVIVAL IN PATIENTS WITH PAPILLARY THYROID CARCINOMA

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Background: Papillary thyroid carcinoma (PTC) often present as multifocal or bilateral tumors. It has been reported that discrete tumor foci in multifocal PTC can arise independently. Whether multifocality or bilaterality is associated with increased risk of recurrence is still controversial. We retrospectively studied to evaluate the impact of multifocality or bilaterality of PTC on the disease recurrence.

Methods: We reviewed the medical records of 2095 patients who underwent total thyroidectomy for PTC. Patients were classified as solitary vs. multifocal and unilateral vs. bilateral groups according to the number and location of tumors. We analyzed the clinico-pathological features and outcome of each groups.

Results: Multifocal PTC were found in 672 of 2095 patients (32%). Extrathyroidal invasion, cervical lymph node metastasis and advanced T stage were more frequent in multifocal PTC than solitary PTC.

Among 2059 patients with PTC, 479 patients (23%) had bilateral PTC. Old age more than 45 years, extrathyroidal invasion, advanced T stage and advanced N stage were more frequent in bilateral PTC than unilateral PTC. Overall recurrence was detected in 44 patients (2.1%) at a median 2.8 years after remission. Overall recurrence-free survival rates at 5, 10 and 15 years after remission were 98.1, 96.5, and 95.4%, respectively. The rate of recurrence and recurrence-free survival did not differ between solitary and multifocal PTC group, and between unilateral and bilateral PTC group.

Conclusions: Although Multifocality and bilaterality of PTC had aggressive pathologic factors, they were not associated with increased risk of recurrence.

P17

TIMING OF PROPHYLACTIC THYROIDECTOMY IN PATIENTS WITH FAMILIAL MEDULLARY THYROID CARCINOMA

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Background: Recommendations on the timing of prophylactic thyroidectomy in patients with familial medullary thyroid carcinoma (FMTC) are based on classification of *RET* mutations into four risk levels according to genotype - phenotype correlations. From various reasons in the past it was not always possible to fulfill the recommended timing.

Objectives: To study the clinical course of FMTC patients with various *RET* mutations who were operated with a time delay.

Methods: Retrospective analysis of clinical course in 34 *RET* mutation carriers from 8 FMTC families.

Results: In all 23 patients with high risk mutation (codone 634) operated after the recommended time limit (age range 13 - 48 years) MTC was histologically confirmed. Thirty percents of them suffered from persistend disease. One patient operated after 40 years died from the progression of MTC. Eight carriers of low risk mutations (codone 618, 620) were operated at the age of 27 - 51 years. In all of them FMTC was revealed. Seven patients reached full remission of the disease. One man with very low risk mutation (codone 791) was operated at the age of 61 years. The operation indicated after possitive stimulation test in his two sons aged 40 and 36 years was completelly prophylactic, only C-cell hyperplasia was revealed.

Conclusions: Our data confirm the necessity to fulfill the guidelines on the timing of prophylactic thyroidectomy at the age of 5 years for high risk mutation (codone 634) carriers, while in low risk mutation carriers surgery may be postponed until an abnormal stimulation test result is observed.

P18

THE RISING INCIDENCE OF THYROID CANCER IS MAINLY DUE TO AN INCREASE IN CLINICAL CANCERS: A 40-YEAR STUDY IN 1778 PATIENTS

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Objectives: The aims of the present study were: (a) to identify a changing trend in the incidence of thyroid cancer in Northern Greece, (b) to investigate the incidence of microcarcinomas and that of clinical cancers and (c) to examine patients' and tumoral characteristics.

Methods: Medical records of 1778 patients diagnosed with thyroid cancer between January 1971 and December 2010 were reviewed. The study period was divided in 4 decades i.e. 1971-1980, 1981-1990, 1991-2000 and 2001-2010. The following characteristics were evaluated for each patient: year of diagnosis, age at diagnosis, gender, histology, tumor size, number of tumor foci (unifocal/multifocal), lymph node metastases, nodule capsule or thyroid capsule invasion, vascular invasion, infiltration of the thyroid parenchyma and extrathyroidal extension. Microcarcinomas (WHO) were defined as unifocal cancers ≤ 10mm in diameter found incidentally after thyroidectomy for other indications.

Results: Patients diagnosed with thyroid cancer per decade increased substantially. Age at diagnosis (mean±SD) significantly increased during the 4 decades of the study (37.6±11.3, 45.6±12.9, 45.3±14.9 and 46.9±15.0 years; p=0.032). Most cancers occurred in women (81.0%). Papillary cancers increased (60.0%, 71.8%, 77.6% and 84.6% during 1971-1980, 1981-1990, 1991-2000 and 2001-2010, respectively) whereas follicular cancers declined significantly (40.0%, 23.5%, 20.0% and 11.6%, respectively; p< 0.001). Cancer size (mean±SD) declined during the study period (39.6±18.3, 24.1±16.4, 24.2±19.2 and 18.1±16.2mm during 1971-1980, 1981-1990, 1991-2000 and 2001-2010, respectively; p< 0.001). Microcarcinomas increased during the study period but constituted only a small minority of total cancers (0%, 6.4%, 13.1% and 19.3%; p< 0.001). The increase in the number of cancers during the study period was mainly due to the increase in clinical cancers (15, 80, 361 and 1018 cases during 1971-1980, 1981-1990, 1991-2000 and 2001-2010, respectively).

Conclusions: The increase in the number of cancers during the study period was mainly due to the increase in clinical cancers rather than microcarcinomas.

P19

DISTRIBUTION OF PERIPHERAL BLOOD MONOCYTE SUBPOPULATIONS IN MALIGNANT AND NON-MALIGNANT THYROID TUMOURS

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Objective: Immune processes may exert both beneficial and detrimental effects on tumour development and spreading. Recently, on the basis of CD16 expression, peripheral blood monocytes have been divided into subpopulations characterized by diverse functional properties. Interestingly, CD16 positive monocytes were suggested to be an independent prognostic factor in inflammatory and malignant diseases. However, little is known about their role in thyroid disorders. The aim of this study was a prospective analysis of the distribution of peripheral blood monocyte subpopulations in patients with thyroid tumours.

Methods: Peripheral blood was obtained from 67 patients with thyroid tumours, subjected to surgical treatment. One day before surgery, distribution and costimulatory phenotype (CD86) of monocyte subpopulations (classical CD16 negative monocytes and two CD16 positive subpopulations: CD14highCD16+ and CD14lowCD16+) were assessed *ex vivo* by flow cytometry with the use of appropriate monoclonal antibodies. The results were then correlated with histopathological findings.

Results: In our study we observed an increase of CD16+ monocyte fraction in peripheral blood obtained from patients with thyroid cancer (TC, n=8), as compared to patients with non-malignant thyroid tumours (NMT, n=59). The altered structure of monocyte population in TC patients was predominantly dependent on an elevated percentage of CD14highCD16+ monocytes. Also the absolute numbers of CD16 positive monocytes in peripheral blood of TC patients were increased. On the contrary, the costimulatory phenotype of investigated monocyte subpopulations showed no differences between TC and NMT patients.

Conclusions: Results of our study demonstrate an increase of the proinflammatory CD16+ monocyte fraction in peripheral blood of TC patients. This observation may be of potential importance for the development of new diagnostic and therapeutic attempts at thyroid disorders.

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P20

METASTATIC THYROID CANCER UNRESPONSIVE TO CONVENTIONAL THERAPY TREATED WITH SORAFENIB "OFF-LABEL": AN UPDATE OF OUR EXPERIENCE

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Objective: We evaluated the clinical benefits of Sorafenib in patients (pts) with aggressive thyroid cancer (TC). We enrolled 26 pts with advanced and documented progressive metastatic TC with no other therapeutic options and not eligible for clinical trials: 7 de-differentiated papillary TC, 5 follicular/Hurthle TC, 6 poorly differentiated TC, 5 medullary TC and 3 anaplastic TC. They were followed from 15 days to 28 months after the beginning of the treatment. To evaluate the response to the therapy we performed a CT scan after 1 month and every 3 months, biochemical evaluation of disease (tireoglobulin or calcitonin) and performance status of pts.

Results: In 4 cases the treatment was discontinued after less than 2 weeks and these pts were not evaluated for the drug response (3 of them died because of poor clinical conditions and 1 discontinued the drug for sever neurological side effects). 4 pts showed a stabilization of the disease progression during a treatment period varying from 1 to >6 months. In 14 cases we observed a partial remission according to mRECIST criteria (5 pts >30%, 9 pts between 10 and 30%). In 4 cases a progression of disease was observed during the treatment. The best responders appeared to be the follicular/Hurthle TC (5/5) and the anaplastic (3/3). Unfortunately the progression of the disease was observed in 3/14 responders; furthermore 4/14 pts had severe side effects that caused the discontinuation of treatment; 5/14 are still successfully continuing the drug while 2/14 died for deteriorated clinical conditions.

Conclusions: We observed an overall clinical benefit in 18/22 pts (81.8%) but the escape phenomenon and the severe side effects are the two major limiting factors for the long term disease control operated by the drug.

P21

DO WE NEED TO PERFORM STIMULATED THYROGLOBULIN (TG) ASSAY AND I-131 SCINTIGRAPHY IN TREATED THYROID CANCER PATIENTS WHO HAVE UNDETECTABLE TG ON THYROXIN?

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After initial therapy of differentiated thyroid carcinoma with thyroidectomy and radioidine ablation (RAIA), follow-up is generally carried out by serum thyroglobulin (Tg) measurement and whole body scanning (WBS) after thyroxine withdrawal.

Objective: The aim of this study is to determine the value of TSH stimulation in patients with undetectable Tg on thyroid hormone replacement and negative anti Tg antibodies.

Patients: 177 studies were evaluated who were treated with total thyroidectomy, RAIA and were classified as low risk. Patients had a normal clinical exam, Tg < 0.2ng/ml while on T4 where tg was measured with highly sensitive assay with a functional sensitivity of 0.2ng/ml.

Results: The mean age of patients was 46±12 yrs (17-77). After T4 withdrawal and elevation of TSH (>30mIU/l), 48 (27 %) and 16 (9 %) converted Tg levels to ≥0.2ng/ml and ≥1ng/ml respectively. Out of 48 patients who had Tg ≥0.2ng/ml, 31 (65 %) had uptake in the thyroid bed and only 1 had extrathyroidal uptake on I-131 WBS. Out of 48 patients who converted Tg ≥0.2ng/ml, 2 patients were diagnosed with cervical lymph node metastases with USG. No uptake was seen in the metastatic lymph nodes on WBS. Two patients who had Tg ≥5ng/ml, normal USG and WBS were submitted to FDG-PET but no metastatic lesions were found. Undetectable Tg on T4 showed a high negative predictive value (98%) which increased to 99% when combined with neck USG. In this study, only one patient was diagnosed with metastases who had serum Tg levels < 0.2 ng/ml during suppressive therapy and normal USG.

Conclusion: Undetectable Tg on T4 in the absence of antibody interference and normal USG has a high NPV in low risk thyroid cancer patients and further testing can be omitted.

P22

^{99M}TC-EDDA-HYNIC-TOC SCINTIGRAPHY FOR THE EVALUATION OF MEDULLARY THYROID CANCER IN PERSISTENT HYPERCALCITONINEMIA

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Introduction: Numerous radionuclide imaging modalities are used to detect foci of recurrence or metastases of medullary thyroid carcinoma (MTC). Radiolabelled somatostatin analogue, ^{99m}Tc-EDDA/HYNIC-TOC, shows high utility in the imaging of NET. Its role in the diagnosis of MTC has not been investigated on a larger scale.

Aim of the study: The aim of the study was to evaluate the utility of peptide receptor scintigraphy with the use of ^{99m}Tc-EDDA/HYNIC-TOC in the diagnosis of MTC in patients with elevated calcitonin (CT).

Methods: ^{99m}Tc-EDDA/HYNIC-TOC scans (SRS) were performed 3 and 24 hours after i.v. administration of the tracer (20 mCi, 740 MBq). The obtained images were compared to other radionuclide and radiological imaging methods.

Material: 70 patients in different stages of MTC were included: 14 patients who were diagnosed before surgery (group A), 47 patients with persistent elevation of CT after surgery (group B) and 13 patients in complete remission (group C). Patients' age: 14 to 83 yrs. (mean 49,6 ± 16,9 yrs.).

Results: Based on the comparison of SRS with the results of other diagnostic modalities sensitivity and specificity of SRS was 63,4% and specificity 61,1%.Positive SRS was found in pts. with higher CT (992 ± 1663 vs. 204 ± 263 pg/ml) and CEA (103 ± 151 vs. 8,1 ± 10,6 ng/ml) concentrations. The highest sensitivity and specificity of SRS was obtained when cut-off values were: CT>210 pg/ml and CEA>9 ng/ml. In 20 pts. (32,8%), SRS showed impact on the management (surgical or radiation therapy treatment, peptide-receptor radionuclide therapy).

Conclusions: Scintigraphy with the use ^{99m}Tc-EDDA/HYNIC-TOC is useful in the evaluation of patients with advanced forms MTC. Its advantage is a relatively high impact on management. It shows slightly higher sensitivity and specificity than majority of radionuclide imaging methods, but not high enough to be recommended as a sole imaging method.

P23

RADIOIODINE ABLATION AFTER RECOMBINANT HUMAN TSH OR THYROID HORMONE WITHDRAWAL IN PATIENTS WITH T3/T4 (TNM STAGE) THYROID TUMORS

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Recent studies have confirmed that radioiodine (RAI) therapy after recombinant human TSH (rhTSH) stimulation is effective for thyroid remnant ablation (TRA) in low risk patients with thyroid cancer.

Objective: To evaluate efficacy of TRA RAI-aided ablation in patients with T3/T4 (TNM stage, AJCC6) and to determine the frequency of disease recurrence or persistence (R/P) in the follow-up.

Methods: Forty five consecutive patients with T3/T4 thyroid tumors (N0/N1 and M0) and negative anti thyroglobulin (Tg) antibodies received rhTSH-assisted TRA (n=18, G 1) or TRA after thyroid hormone withdrawal (THW: (n=27, G 2). Considering baseline characteristics, age and therefore, the TNM stage were the only statistically different variables between G1 and G2. *Recurrence*: evidence of disease after considering the patient free of disease (FD: suppressed Tg level of less than 1 ng/mL and a stimulated Tg level of less than 2 ng/mL one year after TRA); *Persistence*: the patient could never be considered FD (detectable Tg level/ FNAB guided by ultrasound or other imaging studies showing metastatic disease). Data are expressed as mean ± SD. Disease R/P was retrospectively assessed at 40 ± 16 months after TRA in G1 and after 54 ± 40 months in G2 (P=0.02). TRA RAI dose was 150 ± 38 mCi 131-I in G1 and 128 ± 30 mCi 131-I in G2 (P=NS).

Results: Similar rates of clinically evident disease recurrence (6% G1 vs. 7% G2, P = NS) were observed. Persistence was more frequently seen in G2 (22% rhTSH vs. 33% THW, P = 0.03). The FD status was obtained more frequently in G1 (73%) than in G2 (60%), P = 0.03).

Conclusion: rhTSH-aided TRA seems to be effective for ablating high risk thyroid cancer patients.

P24

THYROID LESIONS PREVALENCE IN INDIVIDUALS SUBMITTED TO CHILDHOOD X-RAY EPILATION FOR TINEA CAPITIS TREATMENT

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Introduction: Scalp irradiation to induce epilation for tinea capitis treatment was applied to a 5356 children cohort in northern Portugal in the 50's. In previous studies of similar cohorts, conducted in other countries, subjects were not clinically observed.

Objective: Due to the well-known carcinogenic effect of ionizing radiation our goal was to evaluate the prevalence of thyroid lesions and to identify the major risk factors for thyroid pathology in these individuals.

Material and Methods: We clinically observed 1338 individuals; 69 had been previously submitted to thyroidectomy. A thyroid ultrasound scan was advised to 1314 individuals. FNAB was suggested for thyroid nodules ≤ 15 mm with suspicious scan characteristics, and to all nodules > 15 mm. A second

clinical observation is being proposed for follow-up, 4-5 years after the first one.

Results: The 1338 individuals did not differ significantly from the original cohort regarding irradiation dose, however, the study group was composed of more individuals with younger age at time of irradiation and more women. Nodules were found in 534 out of 988 scans (54.0%) and thyroid carcinoma in 35 out of 1338 cases (2.6%).Clinical characteristics, ultrasound and FNAB reports of the nodules led to 45 thyroidectomy proposal; 31 thyroidectomies were actually performed, allowing the resection of 16 papillary carcinomas. Thyroiditis, carcinoma and nodules were significantly more frequent in women.Younger irradiated individuals were significantly more prone to have benign or malignant lesions surgically removed. In the second ongoing clinical observation, growing nodules with suspicious characteristics were observed in 5 of 45 cases, one of such cases suspicious for thyroid cancer.

Conclusion: The high prevalence of thyroid lesions found, namely papillary carcinoma, fits with the reported higher risk of papillary carcinoma in irradiated patients and justifies their continuous follow-up in order to be able to identify thyroid lesions at an early phase.

P25

LACK OF THRESHOLD VALUES OF CALCITONIN AND CARCINOEMBRYOGENIC ANTIGEN DOUBLING-TIMES IN RISK PREDICTION IN MEDULLARY THYROID CANCER

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Objectives: In patients with medullary thyroid cancer (MTC), after initial surgical treatment, the dynamics of the increase in it's tumor-markers' concentrations is strong predictor for patients´ outcome. In our previous study we showed that CT and CEA doubling times (DT) of less than two years are negative prognostic factors for MTC recurrence-free and overall survival. The aim of present study was to test whether continuous or the threshold method is better for patient outcome prediction.

Methods: We retrospectively analyzed the data from 110 surgically treated patients, followed-up during the years 2004-2005. The patients were screened at least twice yearly for a median time of 8.2 years. In 70 (46 women and 24 men) with elevated concentrations of serum markers we calculated CT and CEA doubling times and correlated it with the risk of disease recurrence (confirmed in cytological or radiological examinations) or death of any cause. We found log(x/DT+1) as the best transformation of doubling-time values to be linear hazard predictors appropriate for Cox analysis, where x was a coefficient separately optimized for each marker and endpoint. We used the uni- and multivariate Cox proportional hazard model to compare the value of threshold-based hazard stratification (threshold value = 2 years) with continuous hazard estimation.

Results: The risk of disease recurrence or death in MTC patients increased with any decrease of tumor-marker´s doubling time. In two-variate model the threshold-based classification was no-longer significant hazard predictor (for calcitonin p=0.22; p=0.54 and for carcinoembryonic antigen p=0.26; p=0.58, respectively for recurrence or death). The hazard was still significant and almost invariably linearly dependent on transformed DT value within high- and low-risk group based on our previous threshold classification.

Conclusion: We proved that continuous estimation using transformed DT values is significantly better than threshold-based prediction for MTC outcome in patients with biochemically overt disease.

P26

LOW RISK THYROID CARCINOMA: DOING MORE GOOD THAN HARM

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The study aim was to investigate the prognosis of patients with T1N0M0 papillary thyroid carcinoma (PTC) in order to define the appropriate strategy for their management and long-term surveillance. We retrospectively reviewed the medical data of 117 consecutive patients who underwent surgery for the treatment of PTC at a tertiary oncologic referral centre between January 2000 and December 2007. Patients had the following characteristics: T1 tumours (≤2cm) without clinically apparent lymph node or distant metastasis at diagnosis and complete resection of all macroscopic tumour. None of the patients had history of head-neck irradiation. Periodic follow-up included clinical and ultrasound examination and serum Tg, TSH and antithyroglobulin antibodies measurements. Other imaging modalities were used as required. There were 98 (83.8%) female patients. Mean age at diagnosis was 51.7 years (range, 22-79 years). The majority of the patients (94.9%) were treated with total or near-total thyroidectomy. Twenty-seven patients (23.1%) underwent a variety of lymph node dissections. The rate of permanent hypoparathyroidism was 15.3% and was highest for patients who underwent total thyroidectomy with lymph node dissection (p=0.0011). Radioiodine ablation therapy was administered to 34 patients (29.1%). Patients were followed for a median of 6.3 years after thyroidectomy. Residual/recurrent disease was identified in two patients (1.7%). A PTC in the remnant contralateral lobe was found in one patient and another had regional lymph node metastases detected during follow-up. None of the patients developed distant metastases and there was no disease-specific mortality. All patients were considered free of disease at the last follow-up. This study shows that T1N0M0 PTC patients have a very low-risk of recurrence. Our results suggest that these very low-risk patients may be effectively treated with a conservative management strategy in terms of surgical treatment (extent of thyroidectomy and prophylactic lymph node dissections), radioiodine ablation therapy and levothyroxine therapy.

P27

PREPARATION WITH ENDOGENOUS AND EXOGENOUS TSH STIMULATION FOR RAI TREATMENT GIVES COMPARABLE RESULTS IN PATIENTS WITH METASTATIC DIFFERENTIATED THYROID CANCER

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Background: Radioiodine therapy (RAI) for differentiated thyroid cancer (DTC) requires endogenous (thyroid hormone withdrawal THW) or exogenous (rhTSH) TSH stimulation. There is a controversy regarding the relative efficacy of rhTSH vs THW-aided RAI treatment of the patients with distant metastases of DTC.

Aim: To compare the relative efficacy and side effect profile of rhTSH vs. THW preparation for RAI therapy of metastatic DTC.

Methods: 56 patients (31 women, 25 men) with RAI-avid distant metastases of DTC treated with rhTSH-aided (n=15) or THW-aided RAI (n=41) and followed for 72+/-193 months were retrospectively analyzed. The groups were comparable in regard to the baseline tumor burden, as documented by mean size of target lesions (rhTSH vs THW 6.4vs4.8 cm, p=0.41), mean baseline thyroglobulin level (6995vs5544 ng/ml, p=0.83), distribution of micro-nodular and macro-nodular pulmonary metastases (67%vs63%, p=0.54, 13%vs15% p=0.64, respectively), osseous (53%vs29%, p=0.09), brain (0%vs2%, p=0.73), and liver/kidney metastases (13%vs2%, p=0.61). Patients from rhTSH group were older (rhTSH vs THW mean 62vs49 years, p= 0.01), received lower cumulative RAI dose (256vs416 mCi, p=0.03), which was more frequently based on dosimetric calculations (80%vs46%, p=0.024). Response to treatment was based on RECIST 1.1 criteria.

Results: Rates of complete response (CR), partial response (PR), stable disease (SD) progressive disease (PD) and progression free survival (PFS) were not different between the groups (rhTSH vs THW CR 7% vs 12%, p=0.48, PR 0% vs 0%, p=n/a, SD 73% vs 56%, p=0.20, PD 20% vs 32%, p=0.31, PFS 20 vs 24 months, p=0.55). Rates of leukopenia, thrombocytopenia, xerostomia and restrictive pulmonary disease were not significantly different (rhTSH vs THW 30% vs 28%, p=0.61, 10% vs 0%, p=0.37, 0% vs 12%, p=0.20, 0% vs 2%, p=0.73, respectively).

Conclusions: Our results suggest comparable effectiveness and adverse effects of rhTSH and THW preparation for radioiodine therapy of metastatic DTC.

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MEDULLARY THYROID CARCINOMA (MTC): TRENDS IN CLINICAL CHARACTERISTICS AND OUTCOME IN A REFERRAL CENTRE IN GREECE

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Objectives: MTC has varying clinical course. In recent years there is increased awareness for MTC. The purpose of this study was to assess possible trends in the clinical presentation during the last 34 yrs.

Methods: 128 MTC cases (39.2% males) presented in the Endocrine Unit of our department. Patients were classified according to year of diagnosis: group 1:1977-2004 (n=66), group 2:2005-2010 (n=62). The extent of disease at diagnosis and during follow up, the number of surgeries performed and pre and postoperative calcitonin levels were recorded.

Results: Mean age at diagnosis was 43.94 yrs (range 5-78); 48% of patients reported a family history of MTC. 114 patients were followed up for 0.6-30 years (mean 5.86±5.6 yrs, median 4.5 yrs). Age at diagnosis and sex distribution did not differ. Group 1 had larger tumor size at diagnosis compared to Group 2 (1.83±1.15 vs 1.32±0.99 cm, p=0.021), more frequently multifocality (44.4% vs 27.3%, p=0.05), less frequently micro MTCs (≤1cm) (27.7% vs 52.8%, p=0.01) and underwent more multiple surgeries (≥2) (p=0.001). At diagnosis, cervical lymph node invasion (53.4% vs 40.7%, p=0.12), capsular invasion (52.8% vs 35.3%, p=0.08), soft tissue involvement (23.5% vs 14.5%, p=0.18) tended to be more frequent in group 1, while distant metastasis was similar (13.3% vs 11.1%, p=0.47). Group 1 had less frequently remission of disease (45.6% vs 61.5%) and more frequently progressive disease (33.3% vs 13.5%) at follow up compared to Group 2 (p=0.025). The frequency of familial disease did not differ. No significant differences in preoperative calcitonin levels were found.

Conclusions: During recent years an increase in micro MTCs and smaller size tumors are observed, while indices of invasiveness and persistence of disease are better, similar to what has been observed in other series. This might be due to increased awareness and routine calcitonin measurements.

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THYROID CANCER NECK METASTASES: ULTRASONOGRAPHIC DIFFERENTIATION

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Objectives: Enlarged neck lymph nodes appear in many diseases and they are echographicaly presented with high accuracy. Benign lymph nodes seems to have typical sonomorphology as well as malignant. The aim of study was to compare possibilities of palpation and ultrasound in detection of metastatic neck lymph nodes. Our intention was to find out if ultrasound itself was able to distinguish benign from malignant nodes.

Methods: A total of 631 patients with thyroid cancer underwent neck palpation and ultrasound examination. The study included 578 enlarged nodes in which ultrasound (US) guided fine needle aspiration biopsy (FNAB) was performed and their echographic appearance like size, shape, echogenicity (the presence of hilum, calcification, cystic portions) and position in the neck were noted. All citologically verified malignant nodes were confirmed histologically after surgical removal.

Results: In majority of cases metastases were roundly shaped and of different echostructure with predomination of hypoechogenic nodes, without hilum. Nodal size alone has been shown to be unreliable criterion for differentiation of benign from malignant lymphadenopathy. Although there were statistical differences in size among metastatic and benign nodes in terms of maximum, minimum diameter and volume, among them, minimum diameter and shape of the nodes (longitudinal/transversal ratio) seems to be far more reliable in suggesting of malignancy. Cystic portions and calcifications in nodes are also suspicious on malignancy. In addition to morphological criteria it is necessary to consider the position of nodes when diagnosing them ultrasonically. Most metastatic nodes were situated in lower third of neck. Reactively enlarged nodes occure more frequently in upper part of neck.

Conclusion: The morphologic criteria of size, shape, internal architecture and localization of nodes in the neck are helpful in selection of the correct node to aspirate with US-guided FNAB that is crucial for final diagnosis.

PO4 Thyroid Cancer (basic/ translational) 1

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IL-32 PROMOTER POLYMORPHISM MODULATES IL-32 EXPRESSION AND INFLUENCES THE RISK AND THE OUTCOME OF EPITHELIAL CELL DERIVED THYROID CARCINOMA

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Objectives: IL-32 is reported as an intracellular cytokine capable of inhibiting cancer cell growth. Here, we aimed to elucidate whether genetic variation in the IL-32 promoter modulates IL-32 expression and influences susceptibility and/or outcome of epithelial cell-derived thyroid carcinoma (TC).

Methods: Apoptosis assays were performed in transfected HEK293T cells to overexpress the IL-32 isoforms alpha, beta and gamma. Immunohistochemical staining for IL-32 was conducted on TC tumor tissue. PBMCs from healthy donors with different genotypes for IL-32 T/A promoter polymorphism rs28372698 were assessed for mRNA expression of IL-32 isoforms. Furthermore, a cohort of TC patients (N=139) was genotyped for this SNP and compared to a cohort of healthy controls (N=138).

Results: After transfection of HEK293T cells with IL-32 isoform constructs, apoptosis rate was severely increased upon overexpression of IL-32beta and IL-32gamma, but not upon IL-32alpha and mock overexpression. Immunohistochemistry on TC tumor tissue revealed positive staining for IL-32 in tumor cells. Detection of mRNA expression of IL-32 isoforms in primary cells from healthy volunteers, unstimulated or TNFα-stimulated, revealed 75% lower expression of IL-32beta and IL-32gamma in cells homozygous for the wild-type T allele of the IL-32 promoter polymorphism ($p< 0.05$). Genetic analysis for the IL-32 promoter polymorphism revealed a different distribution of frequencies between TC patients and controls; the wild-type T allele is overrepresented in TC patients with OR (95%CI) = 1.71 (1.06-2.75). Accordingly, the cumulative radioactive iodine dose required to eradicate the tumor after total thyroidectomy was higher in TC patients bearing the wild-type T allele ($p< 0.05$).

Conclusions: IL-32 beta and gamma, but not alpha, isoforms induce apoptosis. Genetic variation in IL-32, that is expressed in TC tissue, leads to decreased IL-32 gene expression and was associated with increased risk for developing epithelial cell-derived TC and a lower dose of radioactive iodine required to achieve successful tumor ablation.

P31

ENDOGENOUS REGULATORS OF MITOCHONDRIAL BIOGENESIS IN FOLLICULAR THYROID CARCINOMA CELLS

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Follicular thyroid carcinoma cell lines present significantly different numbers of mitochondria, metabolic mechanisms and expression levels of key regulators of mitochondrial biogenesis and function. Mediators between environmental or endogenous signals and the transcriptional machinery governing mitochondrial biogenesis and cell cycle were associated to the peroxisome proliferator-activated receptor γ coactivator-1 family, i.e. PGC-1α, PGC-1β and the PGC-1-related coactivator (PRC). Endogenous factors as Nitric oxide (NO) and calcium have been hypothesized to participate in this signaling pathway. Identifying their role in the control of mitochondrial biogenesis during cell proliferation may lead to propose new therapeutic targets for follicular thyroid tumors.

We investigated the effects of the SNAP-NO donor, on the expression of genes involved in mitochondrial biogenesis and cellular metabolic functions in FTC-133 and RO82 W-1 cells by measuring lactate dehydrogenase and cytochrome *c* oxidase (COX) activities. We studied the action of ionomycin and BAPTA/AM, i.e. a calcium ionophore and a cytosolic calcium chelator, on whole genome expression and mitochondrial biogenesis in RO82 W-1 cells. COX activity and the dynamics of endoplasmic reticulum and mitochondrial networks were analyzed in regard to calcium modulating treatments.

In the FTC-133 and RO82 W-1 cells, the mitochondrial biogenesis induced by NO was mainly related to PRC expression as a retrograde mitochondrial signaling. Ionomycin and BAPTA/AM produced opposite effects on RO82 W-1 cells, with a reorganization of the mitochondrial network. This is the first demonstration that NO and calcium regulate mitochondrial biogenesis and cell cycle through the PRC pathway in thyroid cell lines.

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P32

NOTCH-1 RECEPTOR AS A PREDICTOR OF POOR PROGNOSIS IN PAPILLARY THYROID CANCER

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Objectives: Notch has been introduced as an oncogene or tumor suppressor according to the type of malignancy. The role of Notch in patients with papillary thyroid cancer (PTC) is uncertain because of lack of investigation. BRAF V600E mutation is commonly observed in thyroid cancer, and the role of BRAF V600E mutation in PTC has not yet been established. The aim of the study is to elucidate the clinicopathological characteristics in patients with PTC regarding to expression of Notch-1, Notch-3 receptor and BRAF mutation.

Methods: We evaluated clinicopathological characteristics according to Notch-1, Notch-3 receptor, and BRAF V600E mutation in 187 patients with PTC who underwent definitive surgery at Seoul St. Mary's Hospital. The expression of Notch-1 and Notch-3 receptor was evaluated using immunohistochemistry. A direct DNA sequencing was used for the analysis of BRAF V600E mutation.

Results: The expression of Notch-1, Notch-3 receptor, and BRAF V600E mutation was observed in 80.5%, 69.4%, and 84% of the patients, respectively. Notch-1 receptor expression was significantly associated with poor prognostic markers including large tumor size, nodal metastasis, capsular invasion, and extrathyroidal extension ($p< 0.05$). BRAF V600E mutation was significantly related with higher number of nodal metastasis ($p< 0.05$). However, no significant association was seen between other clinicopathological characteristics and the expression of Notch-3 receptor or BRAF mutation. In multivariate analysis for nodal metastasis, Notch-1 receptor expression showed a significant relationship with lymph node involvement ($p< 0.05$).

Conclusions: To our knowledge, this study may be the first investigation of the Notch-1 and Notch-3 receptor expression in patients with papillary thyroid cancer. Notch-1 receptor expression may be a predictor of lymph node metastasis and related to poor prognostic markers in patients with PTC. Further investigation of Notch-1 receptor expression may shed light on understanding of the pathogenesis of nodal metastasis in PTC.

P33

PAPILLARY THYROID CARCINOMA IS PART OF V804M RET GERMLINE MUTATION

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Background: Recently, the rearranged during transfection (RET) V804M proto-oncogene germline mutation, which is classified as low risk mutation regarding expression of familial medullary thyroid cancer (MTC) has been found to be additionally associated with papillary thyroid cancer (PTC). A kindred (24 familiy members, 5 generations) from Western Norway is analyzed particularly concerning the expression of PTC.

Patients: So far, twelve family members from the F3 (all older than 60 yr) and F4 generations were tested for RET mutations (no analyses from the F1 and F2 generation available). In eight cases the V804M mutation was found (5 of 7 tested F3 generation members and 3 out of 5 tested F4 generation members). All the five gene carriers from the F3 generation underwent surgery. All gene carriers were screened for pheochromocytoma (PC) and primary hyperparathyroidism (PHPT).

Results: The five gene carriers from the F3 generation presented in two cases (56-65 yr at surgery) with C-cell hyperplasia and multifocal nodal-negative MTC (< 10 mm) but also multifocal PTC (>10 mm), in one case with extrathyroidal extension and in one case with lymph node metastases. The other three gene carriers (61-65 yr at surgery) did not present with cancer neither C-cell nor follicular cell derived. In the F4 generation, so far, one (32 yr) revealed pathological pentagastrin test results whereas the other two carriers (33-37 yr) had normal test results. In all gene carries, PC and PHPT were excluded biochemically.

Conclusion: In this family with V804M RET germline mutation, MTC and PTC were found in the same frequency (40% in the generation older than 60 years). In both affected patients, the PTCs were clinically relevant. PTC seems to be part of late onset RET mutations and should be considered during decision-making regarding timing and extent of surgical therapy.

P34

MTOR INHIBITION HAMPERS CELL VIABILITY IN SELECTED HUMAN MEDULLARY THYROID CARCINOMA PRIMARY CULTURES

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It has been demonstrated that everolimus, an mTOR inhibitor, has potent anti-proliferative effect in a human Medullary Thyroid Carcinoma (MTC) cell line, TT, and in two human MTC primary cultures. We aimed at evaluating the possible antiproliferative effects of everolimus in a group of 20 human MTC in primary culture. To this purpose, 20 MTCs were dispersed in primary cultures, treated without or with 1 nM - 1 mM everolimus, 10 nM SOM230, and/or 50 nM IGF-I. Cell viability and apoptosis were evaluated after 48 h and Calcitonin (CT) secretion was assessed after a 8 h incubation. Somatostatin receptor expression was investigated by quantitative PCR. We found that in 14 cultures everolimus reduced cell viability (~40%), promoted apoptosis (+30%), inhibited p70S6K activity (-20%) and blocked IGF-I proliferative and anti-apoptotic effects. In selected tissues co-treatment with SOM230 had additive effects. It did not affect CT secretion, but blocked the stimulatory effects of IGF-I. In conclusion, everolimus reduced MTCs cell viability by inducing apoptosis, with a mechanism likely involving IGF-I signalling but not CT secretion, suggesting that it might represent a possible medical treatment for persistent/recurrent MTCs.

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PAPILLARY THYROID CARCINOMA INDUCED BY BRAF^{V600E} MUTATION IN MICE: GENE EXPRESSION PROFILING

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Introduction: Mutation in the $BRAF_{V600E}$ kinase, present in the significant proportion of papillary thyroid carcinomas (PTC), was considered to be more frequently associated with the older age at diagnosis and/or more aggressive phenotype. Recently this is of growing interest, as mutated BRAF kinase become a clinically druggable target. The aim of the study was to analyze $BRAF_{V600E}$-induced gene expression in the thyroid of transgenic mice by microarray profiling.

Methods: $BRAF_{V600E}$ construct under bovine thyroglobulin promoter (obtained by courtesy of Prof. J.E. Dumont) was injected into the pronucleus of one-cell mouse embryos and transgenic FVB/N mice were bred. After 6-12 months mice were sacrificed, and histopathological analysis of thyroid and other organs was carried out. The expression of the mRNA transgene in the thyroid was analyzed by the automatic sequencing. The preliminary microarray analysis was performed on 20 mouse PTC-involved and healthy thyroids (12 and 8, respectively) with the Affymetrix Mouse Gene ST 1.0 arrays.

Results and Conclusions: As a result of microinjection we obtained 6 founders in which the transgene was detected on the DNA level, but on the mRNA level expression was seen only in 2/6 cases. Three Tg- $BRAF_{V600E}$ animal lines were propagated for detailed analysis. In single cases the presence of lung metastasis was detected, confirming the metastatic potential of this particular *BRAF*-positive PTC. The preliminary microarray data revealed a significant differences in gene expression of mouse PTC compared to normal thyroid. When this signature was compared to human microarray data of BRAF-positive cancer, a subset of *BRAF*-related genes common for human and mouse PTCs was identified. This will be in-depth discussed in the context of their biological function.

Our data may indicate the major mechanisms of $BRAF_{V600E}$ -induced tumorigenesis and require further study.

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THE α1-ADRENERGIC RECEPTOR ANTAGONIST PRAZOSIN INDUCES APOPTOSIS IN HUMAN MEDULLARY THYROID CARCINOMA CELLS

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Objectives: Medullary thyroid carcinoma (MTC) is a rare tumor that is associated with a poor prognosis since MTC cells exhibit high resistance against chemotherapy and radiotherapy. Recent studies have shown that α1-adrenoceptor antagonists, which are primarily used in the treatment of hypertension, exhibit an unexpected non-adrenoceptor related pro-apoptotic effect on malignant cells including prostate carcinoma cells and leukemia cells. In order to screen for new therapeutic options for MTC, we examined the effects of the α1-adrenoceptor antagonist prazosin on growth and viability of MTC-SK- and TT cells, which are established *in vitro* model systems for MTC.

Methods: Proliferation and viability of MTC -cells were assessed using an automatic CASY®-1 Cell Counter and Analyzer (Innovatis) or the WST-1 cell proliferation assay (Roche). Ongoing cell death was characterized by flow cytometry using Annexin V/7-AAD (Pharmingen), microscopy and a luminescence assay for detection of activation of caspases 3 and 7 (Promega). Morphologic alterations of the cells were visualized by light microscopy and scanning electron microscopy.

Results: We observed that prazosin inhibits proliferation and reduces viability of both tested MTC cell lines. Cell death assays showed that prazosin induces apoptotic cell death in MTC-SK cells and TT- cells. Furthermore, we recognized prominent alterations in the morphology of MTC cells following prazosin treatment. Prazosin treated cells exhibited spicular polar structures reminiscent of lamellopodia. This observation suggests the involvement of distinct components of the cytoskeleton in the toxic effect of prazosin on MTC cells.

Conclusion: We demonstrated that the α1-adrenergic antagonist prazosin - a drug which has been used in clinical routine for more than 30 years - exhibits the potential to induce apoptosis in chemoresistant MTC cell lines MTC-SK and TT. Our study therefore provides a promising basis for further research regarding the use of α1-adrenergic antagonists in the treatment of medullary thyroid carcinoma.

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ROLE OF THE WNT/B-CATENIN IN HRAS- AND BRAF-TRANSFORMED THYROID CELLS

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Aberrant activation of the Wnt/b-catenin pathway is observed in a variety of human cancers. In thyroid, b-catenin (b-cat) is found mutated in poorly differentiated carcinomas and it is accumulated in cytoplasm and nucleus. In addition it has also been described that b-cat is involved in RET/PTC induced proliferation in thyroid cells but in this situation b-cat is not mutated, instead its stability is increased by phosphorylation.

The aim of this work is to study the role of the Wnt/b-cat pathway in HRAS- and BRAF-mediated transformation of thyroid cells.

For this purpose we used rat differentiated PCCl3 cells conditionally expressing HRAS or BRAF oncogenes.

Our results show that HRAS, but not BRAF, was able to translocate b-cat into the nucleus increasing 10-12 fold the activation of b-cat dependent transcriptional activity (Top/FopFlash reporters). In parallel there is a time dependent increase of GSK3b phosphorylation in the inhibitory Serine9 when mutated HRAS and BRAF were expressed.

We have demonstrated the involvement of bcat in TSH-induced proliferation in normal thyroid cells through induction of GSK3b phosphorylation. Since HRAS but not BRAF induce TSH-independent growth in PCCl3, we have explored whether b-cat is implicated in this phenomenon. Our preliminary results silencing b-cat by shRNA-lentiviral infections, suggest that this pathway may be responsible of the difference described between both oncogenes.

Currently we are also evaluating the activation of the Wnt/b-cat pathway in human tumoral thyroid cells carrying BRAF or HRAS mutations. We found several cell lines with nuclear b-cat, and we will analyze the role of b-cat in them.

Our results indicate a potential role of Wnt/b-cat pathway in the HRAS-mediated thyroid cell transformation.

P38

INDOLEAMINE 2,3-DIOXYGENASE (IDO) AND THYROID CARCINOMA: RET/PTC APPEARS AS A STRONG GENETIC DETERMINANT FOR IDO EXPRESSION

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Context: Indoleamine 2,3-dioxygenase (IDO) is a single chain oxidoreductase that catalyzes tryptophan degradation to kynurenine. In cancer, it appears to exert an immunosuppressive function as part of an acquired mechanism of immune escape. In view of this notion, IDO has started to be considered a novel target in cancer therapy.

Objectives: To evaluate IDO expression in papillary thyroid carcinoma (PTC) and to correlate its expression with genetic determinants of thyroid carcinogenesis.

Patients and Methods: IDO expression was evaluated by QPCR in 105 PTCs and by immunohistochemistry in a subgroup of 55. IDO expression was also analyzed in 5 human thyroid carcinoma-derived cell lines and in PCCL3 cells characterized either by the doxycycline-inducible or stable expression of BRAFV600E and ret/PTC3.

Results: IDO expression resulted significantly higher in PTC than in normal thyroid. In basal growing conditions, IDO was overexpressed in FTC133 and B-cpap cells, but after stimulation with γ-interferon, all analyzed cell lines (including also TPC-1, 8505c and C643) showed up-regulation of the enzyme. Correlation of IDO expression with genetic background in PTC demonstrated a close to statistical significant association between higher IDO mRNA expression and BRAFWT status, which was lost at immunohistochemistry. However, while BRAF-expressing PCCL3 cells did not show IDO overexpression, ret/PTC3-expressing ones demonstrated an increase of the enzyme mRNA and activity.

Conclusions: This study shows for the first time that papillary thyroid carcinoma overexpresses the immunomodulating protein IDO and that this event is correlated either to genetic determinants as ret/PTC or to the responsiveness of genetic programs to stimuli coming from the tumor microenvironment. Although the effects of IDO on the immune component of tumor microenvironment remain to be fully characterized in PTC, these data put forward the possible importance of testing novel targeted therapies against IDO for the treatment of papillary thyroid carcinoma.

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OGG1 AND XRCC1 EXPRESSION IN DIFFERENTIATED THYROID CARCINOMAS

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Objectives: 8-oxo-7,8-dihydroguanine (8-oxoG) is one of the most common DNA lesions occurring as a result of exposure to reactive oxygen species (ROS). In the thyroid ROS and free radicals participate in physiological and pathological processes. The primary enzyme responsible for the excision of 8-oxoG in humans is OGG1. Its activity is regulated by Base Excision Repair (BER) partners, e.g. XRCC1, which coordinates the whole repair process. Decreased repair of oxidative DNA damages is a risk factor for developing certain human malignances.

The aim of the study was to investigate impact of OGG1 and XRCC1 expression on DNA repair in differentiated thyroid carcinomas.

Methods: 8-oxoG level was measured by HPLC. OGG1 and XRCC1 expression was evaluated in papillary thyroid cancer (PTC), paired normal thyroid tissues (NT) and thyroid cancer cell lines by Q-Real-Time PCR and Western-blot methods.

Results: We detected higher level of 8-oxoG in PTC when compared to normal or non-malignant thyroid disease tissues. In PTC derived cell lines repair enzymes expression on both transcript and protein levels was lower than in non-transformed thyroid cells. In human tumor tissues however OGG1 expression was similar to that found in NT. We also did not notice significant difference of XRCC1 mRNA level between PTC and paired NT, although in some PTC cases higher protein expression in tumor tissues was found.

Conclusions: Although the expression of OGG1 and XRCC1 in thyroid tumors was not different from normal thyroid, the level of DNA oxidative damages in PTC was increased. Thus reduced excision of 8-oxoG in PTC is not caused by differences in the expression of repair genes. The activity of DNA processing enzymes depend on many factors like gene polymorphisms and posttranslational modifications. Further studies are required to fully investigate DNA repair mechanisms in thyroid tumor development.

PO5 Graves' Orbitopathy

P40

THE ROLE OF ^{99M}TC-DTPA SPECT IN STAGING AND FOLLOW UP OF DISEASE ACTIVITY BEFORE AND AFTER ORBITAL IRRADIATION IN GRAVES' ORBITOPATHY

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Objectives: The estimation of retrobulbar inflammatory activity (RIA) is crucial in Graves' orbitopathy (GO) both for treatment decisions and follow up. The current imaging methods characterizing disease activity are expensive (Octreoscan) or fail to provide data on the connective tissue (MR). We have shown that ^{99m}Tc-DTPA SPECT is a suitable tool to measure RIA in GO. The aim of the present study was to follow up patients before and after orbital irradiation to measure the effectiveness of treatment.

P**atients groups:** 32 patients (24 women, 8 men) suffering in GO treated with standard external irradiation were involved in this retrospective study (age 52,1±11,0 years). In another group (10 patients, 6 women 4 men) SPECTs were performed on both a 4 headed and a 2 headed SPECT unit to compare their images.

Methods: SPECTs were performed before and 12 weeks after irradiation. 400 MBq ^{99m}Tc-DTPA was administered intravenously. Imaging was performed on a Nucline Xring/4R unit. In addition to the visual assessment of the SPECT images, the orbital uptake of the radionuclide (activity uptake, AU) was calculated (ref. 4.7-12.2 MBq/cm^3). In the SPECT comparison group, the data acquisition was performed first with the 4 headed, and then with the 2 headed SPECT.

Results: After irradiation therapy, improvement was observed only at higher initial AU values (AU > 12.2 MBq/cm^3). We obtained comparable AU values with the 4 headed and 2 headed SPECTs. The AU with the 2 headed SPECT tended to be lower.

Conclusions: The higher the initial AU, the more effective is the irradiation in GO. The ^{99m}Tc-DTPA orbital SPECT is a suitable technique for the selection of GO patients who may benefit from irradiation therapy. The 2 and 4 headed SPECTs provide the same information, and both may be used in staging and follow up of patients.

P41

LOW TITER OF ANTI-TPO IS ASSOCIATED WITH AN INCREASED RISK OF GRAVES´ DISEASE AND OPHTHALMOPATHY

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Background: In Graves´ disease (GD) most patients have intraorbital morphological changes but only 1/3 of the patients will develop Graves´ ophthalmopathy (GO). Good markers for prediction of GO are lacking. In a previous study, low anti-TPO and increased titers of TRAb at diagnosis of Graves´ disease were overrepresented in patients with GO at diagnosis of GD.

Objective: To evaluate if low anti-TPO and/or increased TRAb predict the development of GO

Methods: In patients with newly diagnosed GD (TT2003), 2003-2005 (n=239), GO, smoking habits, anti-TPO (normal range < 35 kIE/L) and TRAb (normal range < 1 IE/L) were registered. In a biobank (GD2002) of GD patients (n=430) data on GO, menopause, anti-TPO and TRAb were continuously registered.

Results: In TT2003 30% of patients with GO at diagnosis of GD had anti-TPO < 10 kIE/L compared to 16% of patients without GO (p=0.05). This was not explained by increased prevalence of smokers with low anti-TPO. GO and TRAb showed a positive correlation when TRAb was >7 IE/L (p=0.04). In GD2002, 30 patients were identified without GO at diagnosis of GD who later (2-84 months) developed GO and 72% had anti-TPO < 35 kIE/L and/or TRAb > 7 IE/L.

The incidence of GD is highest in menopausal age, in GD 2002 we found a correlation between time after menopause and diagnosis of GD (p< 0.001). 44% of postmenopausal women with newly diagnosed GD had anti-TPO < 35 kIE/L compared with 24% of the premenopausal women (p=0.001). In addition we found that the proportion of GO patients was increased in postmenopausal women, 34% versus 17 % in premenopausal women (p< 0.004).

Conclusion: Low anti-TPO, and/or TRAb >7 IE/L at diagnosis of GD increase the risk to develop GO. In addition low anti-TPO in postemenopausal women increase the risk to develop GD and GO.

P42

PREDICTIVE FACTORS OF POOR RESPONSE AND OF SEVERITY OF GRAVES OPHTHALMOPATHY IN PATIENTS TREATED WITH ANTI-THYROID DRUGS (ATD) AND RADIOIODINE (131-I)

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Objectives: We determined factors affecting activity and severity of GO in patients treated with anti-thyroid drugs (ATD group) and with radioiodine (131-I group). We also determined predictive factors and frequency of poor response to glucocorticoid treatment in both groups.

Methods: There were 168 patients of mean age 52,2± 11,2 years in the ATD group and 46 patients of mean age 52,1±13,3 years in the 131-I group. Radioiodine treatment was offered to patients with ophthalmopathy index, IO < 3 points and CAS < 3 points. On admission 76% of 131-I patients were hypothyroid, with mean TSH concentration 23,9±24,5 µU/ml (median 15,4; max=91,7; min=1,7 µU/ml). SoluMedrol pulses (total dose 8,0g) followed by orbital irradiation (total dose 20 Gy). TSH, FT4, and TRAb levels, and CAS and IO indices were evaluated in all patients prior to, and after 1, 6, and 12 months of treatment.

Results: CAS was found to depend on IO (p≤ 0,05, chi^{2}test). 117/208 (56,2%) patients with CAS ≥ 4 presented with moderate severe or severe GO. Of factors (radioiodine therapy, age, sex, pretreatment TSH, FT4, and TRAb levels) likely to determine GO activity (CAS > 2 and IO > 2), using backward stepwise regression, only pretreatment TRAb level (RR=1,047, 95% CL,003-1,092, p≤ 0,05) and age (RR=1.028, 95% CL 0.999-1.059, p=0,06) were confirmed. Poor responders were 69/167 (41%) of ATD and 3/46 (28%) of 131-I patients who required further oral glucocorticoids following SoluMedrol pulses. Based on discriminant analysis, only pretreatment TSH and IO were predictive of poor response (p< 0.05), with IO ≥ 6 threshold.

Conclusions: Pretreatment TRAb is predictive of risk of severe GO (IO ≥ 5) only in 131-I patients. Pretreatment IO is a risk factor of being a poor responder to glucocorticoid therapy in ADT and 131-I patients.

P43

A SMALL DOSE OF RITUXIMAB MAY BE EFFECTIVE IN INDUCING LONG TERM INACTIVATION OF GRAVES' ORBITOPATHY

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Background: Preliminary studies have shown that two cycles of 1000 mg of RTX induce peripheral CD20+ cells depletion and clinical improvement

of active Graves'orbitopathy (GO). After having discontinued RTX infusion because of a marked infusion-related reaction, we have unexpectedly observed peripheral B cell depletion and a rapid therapeutic effect after only 100 mg of RTX.

Patients and Methods: Two women with primary myxedema and a woman with Graves'disease treated with I131, all euthyroid on LT4, have been treated with RTX for active GO. In two women infusion of RTX was stopped after 100 mg due to progressive edema of soft orbital tissue and decrease of vision. The third patient was electively treated with the low dose of drug. Peripheral cell subpopulation analysis by flow cytometry and ophthalmological evaluation were performed at baseline, after the infusion of 100 mg RTX and weekly thereafter.

Results: Total peripheral CD20+ and CD19+ cell depletion was found at 60 minutes after 100 mg of RTX, similarly to what is observed after a standard, full dose therapy. Clinical assessment on the day after therapy, and weekly afterwards, showed complete reversal of infusion-related side effects and progressive decrease of edema, inflammation and proptosis with inactivation of GO. Disease relapse was not observed in any of the patients at 40, 63 and 94 weeks of follow up, respectively.

D**iscussion:** We report, for the first time, that therapy with a low dose of RTX (100 mg) induces total peripheral B cell depletion and long term inactivation of GO. The rapidity of action suggests that RTX acts by activating complement and release of cytokines in the orbit with consequent rapidly ensuing edema. Should these findings be confirmed in a larger series of patients, low dose RTX might be employed in GO with fewer side effects and more cost effective.

P44

THE COURSE OF GRAVES OPHTHALMOPATHY IN PATIENTS TREATED WITH ANTI-THYROID DRUGS (ATD) OR FOLLOWING RADIOIODINE THERAPY (131-I)

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Objectives: Comparison between courses of GO in patients treated with antithyroid drugs (ATD) and after radioiodine therapy (131-I).

Methods: The ATD group consisted of 168 patients (mean age 52,2± 11,2 years) and the 131-I group of 46 patients (mean age 52,1±13,3 years). 131-I treatment was offered to patients with ophthalmopathy index IO < 3 and CAS< 3. On admission 76% of patients in the 131-I group were hypothyroid, with mean TSH concentration 23,9±24,5 µU/ml. SoluMedrol pulses (8,0g) were followed by orbital irradiation (20 Gy). Levels of TSH, FT4, and TRAb, and CAS and IO were evaluated in all patients prior to treatment, and 1, 6, and 12 months after.

Results: Age, sex, GO duration, IO, CAS and FT4 levels did not differ significantly in patients of either group. In the 131-I group, duration of hyperthyroidism was significantly extended (72.3 vs. 31.5 months, $p< 0.05$), and pre-treatment levels of TSH were significantly higher (6.7±16.3 vs 2.34±8.81 U/L, $p< 0.05$), as were TRAb levels in the course of observation ($p< 0.05$). In the ATD group the course of median IO (y) vs. time, in months (x), could be expressed by $y=4.0812*\exp(-0.0595*x)$, and the course of median TRAb level vs. time, by $y=2.6354-1.4099*\log_{10}(x)$. In the 131-I group the respective approximations were: for median IO: $y=4.6481*\exp(-0.0713*x)$, and for median TRAb level: $y=7.4554-3.4544*\log10(x)$. In both groups the median values of IO and TRAb levels decreased significantly in the course of observation, against respective pre-treatment values ($p\leq 0,05$).

Conclusions: Patients in ATD and 131-I groups did not differ with respect to activity and severity of GO despite systematic differences in TRAb levels. In the 131-I group TRAb levels always exceeded normal levels and were higher than those in the ATD group. For ATD patients TRAb levels returned to normal levels 1 month after treatment.

P45

ADMINISTRATION OF ORAL GLUCOCORTICOIDS (DEXAMETHASONE) IN THE TREATMENT OF ENDOCRINE OPHTHALMOPATHY

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Objective: To evaluate the efficacy and safety of oral dexamethasone in terms of adrenal function and clinical activity of endocrine ophthalmopathy (EO) in the treatment of patients with EO.

M**aterials and Methods:** Four years follow up of 99 patients (men 35, women 64) with EO: average age of the patients was 49± 9 yr, the average duration of EO was 6,8 yr, duration of thyroid disease was 8,4 ± 5 years. Weight: 70,1 ± 13,4 kg. Thyroid status: hyperthiroid - 46 subjects, hypothyroid - 37 subjects, euthyroid - 16 subjects.

The overall severity of EO was assessed using NOSPECS and CAS before the treatment and after. Before the treatment NOSPECS was 4 ± 2 and clinical activity score (CAS) 3 ± 3. The value of the retrobulbar tissue (RBT) by ultrasonography of the orbits (U.S. orbit) : OD OS = 18,2± 2,3/18,1± 2,4 mm. Treatment**:** oral Dexamethasone starting with 0,1 mg/kg on alternate days for 1,5 to 3 month. All patients received potassium preparations, omeprazole, diet with low intake of simple carbohydrates and fats.

Results: In all the patients significant reduction of EO's activity was observed - NOSPECS 3± 2 ($p=0,0005$). Weight ± 5 kg. There were no symptoms of adrenal deficiency - the normal level of cortisol restored during 7-14 days after completion of dexamethasone therapy. 47 patients were performed thyroidectomy during the treatment by indications.

Conclusions:

1. Oral dexamethasone on alternate days scheme is effective in treatment patients with endocrine ophthalmopathy.
2. Does not suppressed adrenal function and there is no withdrawal syndrome.

P46

SIDE EFFECTS TO GLUCOCORTICOID THERAPY IN PATIENTS WITH GRAVES´ ORBITOPATHY

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Background: Glucocorticoids are treatment of choice for active and moderate to severe Graves´ orbitopathy (GO).

Objective: The aim of this study was to evaluate side effects of different treatment protocols.

Methods: Study group consisted of 62 patients with moderate to severe GO treated with glucocorticoids. Group I (42 patients) was treated with 2 x0,5g iv methylprednisolone during 3 days, followed by oral prednisone 40mg/d tapered to 10mg/d in 4 weeks. The treatment lasted for 6 months and cumulative dose was 12g. Group II (20 patients) was treated with 0,5g/wk methylprednisolone then 0,25g/wk methylprednisolone (6 weeks each). Cumulative dose was 4,5g.

Results: Patients in group I had a high rate (35/42) of mild, minor steroid related adverse events including weight gain (76%), hirsutismus (63%), increase in serum lipids (20%), hypertension (20%) and urinary infections (17%), whereas 3 patients (7%) developed serious, major side effects including liver damage, tuberculosis and herpes zoster.In group II, mild side effects developed in 4/20 patients ($p< 0,05$ vs.group I) including increase in serum lipids in 3 patients (15%) and weight gain in 1 patients (5 %) whereas 1 patient had myocardial infarction (5%) following infusion (p=ns vs. group I).

Conclusion: Minor side effects appeared to be related to cumulative dose and treatment schedule, while serious side effects were dependent on preexisting disease.

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C-REACTIVE PROTEIN AND TSH RECEPTOR ANTIBODIES IN GRAVES' ORBITOPATHY

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Objective: The aim of the study was to evaluate the importance of C-reactive protein (CRP) and TSH receptor antibody (TRAb) levels as indicators of activity of Graves' orbitopathy (GO).

Material and Methods: We analyzed 48 patients with GO (36 females and 12 males, age range 32-71 years). ECLIA method was used to measure TRAb titer, and immuno-turbidimetric test for CRP levels. Based on clinical activity score (CAS), patients were divided into two groups: 20 patients with CAS ≤ 2 were classified as the group with inactive disease and the other 28 patients with CAS ≥ 3 as the group with active disease.

Results: The mean level of TRAb in the first group was 8.73 IU/l (range 0.6-34.2), and in the second group 21.86 IU/l (range 0.3-97.5). Mean CRP levels in the first and second group were 2.36 mg/l (range 0.4-8.2mg/l) and 3.17mg/l (range 0.3-9.4mg/l) respectively. We found no significant difference between CRP levels in the two groups (p = 0.187), and no correlation between CRP levels and the activity of GO (p = 0.281). We also found no significant differences in TRAb values between the two groups (p = 0.146), but we did prove that a correlation existed between the TRAb values and GO activity (p = 0.015).

Conclusions: 1) CRP values have no significance as predictors of GO activity. 2) TRAb levels should be regarded as a useful predictor.

P48

TWO-YEAR DYNAMIC MONITORING OF PATIENTS WITH ENDOCRINE' OPHTHALMOPATHY TREATED WITH ORAL GLUCOCORTICOIDS

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Objective: To evaluate the outcome of oral glucocorticoids administration in patients with moderate-to-severe active Endocrine' Ophthalmopathy (EO) regarding weight gain and total eye score within 2 years of follow up.

Material and Methods: Two years follow up of 23 patients (men 5, women 18) with moderate-to-severe active EO, were treated with oral glucocorticoids. Age 48.2 ± 9.3 yr. Weight: 80,3 ± 15,2 kg. Duration of EO was 9.2 ± 7.8 yr. Duration of thyroid disease 10.8 ± 10.8 years. The overall severity of EO was assessed using NOSPECS and CAS before the treatment and after.

Results: Before treatment NOSPECS was 4 ± 2 and clinical activity score (CAS) 3 ± 3. The value of the retrobulbar tissue (RBT) by ultrasonography of the orbits (U.S. orbit) : OD OS = 19,1 ± 3/18, 7 ± 3mm (11 patients had elements of fibrosis). Treatment: oral Dexamethasone starting with 0,1 mg/kg on alternate days for 1,5 to 3 month in combination with orbital radiotherapy or without (11 / 12), potassium preparations, omeprazole, diet with low intake of simple carbohydrates and fats. After treatment: NOSPECS 2± 2 (p- 0,0015); CAS 2 ± 2 (p>0,05). RBT: ODOS= 17,9± 2 (p=0,019)/17,3± 1,7 (p=0,019). Weight: 79 ± 13,8 kg (p>0,05). All patients had from 2 to 4 courses of oral dexamethasone.

Conclusion: Current evidence demonstrate the efficacy of oral dexamethasone on alternate days in decreasing total eye score (NOSPECS) and CAS, reducing swelling of RBT according to U.S. orbit. If strictly adheres to a diet, there is no weight gain. But to achieve remission several courses of oral dexamethasone are required.

P49

EFFECTIVE OF COMPLEX LYMPHATIC THERAPY OF ENDOCRINE OPHTHALMOPATHY, THREE MONTHS AFTER TREATMENT

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Purpose: To assess the effective of the complex lymphatic therapy of endocrine ophthalmopathy (EO).

Materials and Methods: A total of 220 men of the Uzbek population with EO. The patient was questioner, ultrasonography of the orbits and exophtalmometry. Dexamethasone and antiedematous drugs introduced periorbital, subcutaneously.

Results: In patients revealed complaints : watering-78, 1%, photophobia-43,8%, the feeling of sand -78.6%, retraction of the eyelids - 87,5%, edema of the eyelids - 12,5%, the symptoms Grefe -15,6%, Mebius - 10,9%. Proptosis of the eyeballs (PE) averaged at 17-25 mm. On ultrasonography of the orbits found: swelling of retro bulbar tissue (RT) in 90% of cases, changes in the extra ocular muscles (EOM) to -70%, and the presence of both symptoms in 86,7%. Changes not observed in 3,3%.Three months after treatment in 100% of cases regressed photophobia, and feelings of sand in the eyes, in 57,8% retraction of eyelids, in 34,4% watering. In 34,4% of PE decreased by 3 mm, while 41,3% of 1-2 mm. On ultrasonography of the orbits in dynamics was a decrease in RT edema in 48,5% and the thickening of the EOM in 55,5%, changes in both symptoms in 58,5% of cases.

Conclusions:

1. When ultrasound study revealed changes: swelling of RT in 90%, the transition to fibrosis in 21,7% of cases. Changes in the mixed nature (EOM and RT) were observed in 86,7%, only in the RT in 6,7%, in the EOM by 3,3% and 3,3% of the changes is not revealed.
2. Complex lymphatic therapy after three months leads to the disappearance of photophobia and the feeling of "sand" in the eyes of 100% of cases, regression retraction eyelids in 57,8% and watering in 34,3% of cases, to reduce the PE from 41,3% to 1-2 mm and 34,4% for 3 mm.

P50

QUALITY OF LIFE ASSESSMENT IN SERBIAN PATIENTS WITH GRAVES' ORBITOPATHY

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Background: Quality of life is markedly impaired in patients with Graves' orbitopathy (GO). A disease-specific quality-of-life questionnaire, GO-QOL, has been developed and confirmed as useful.

Aim: To determine quality of life in Serbian population of GO patients and to assess the benefit and limits of accepted GO-QOL questionnaire translated to Serbian.

Patients and Methods: We analyzed data of GO-QOL questionnaire obtained from 17 patients with active GO (3 males, 14 females; age range 41-62 years) before and after the treatment by intravenous corticosteroids (CS). All patients had a good response to CS.

Results: The whole group had statistically significant improvement of the score related to visual functioning after the treatment (42.1 ± 34.3 vs 60.7 ± 28.1, $p < 0.05$), but there was no significant difference between scores related to appearance (58.8 ± 28.5 vs 63.6 ± 26.4). In 8 patients with moderately severe GO there was significant improvement in both scores after CS (59.9 ± 36.5 vs. 79.5 ± 22, and 71.9 ± 19 vs. 79.7 ± 14.9, $p < 0.05$). In 9 patients with severe GO only the score for visual functioning was higher after CS (26.2 ± 24.3 vs. 44.0 ± 22, $p < 0.05$; appearance 47.2 ± 31.4 vs. 49.3 ± 26.6). Thirteen questionnaires contained one or two unanswered questions related to bicycling, driving, appearing on photos, or hobbies.

Conclusion: GO-QOL questionnaire may not be useful as an isolated parameter for steroid eye treatment evaluation, at least in smaller group of patients. We observed many unanswered questions in our population, so we feel the alternative questions will be useful, especially on using public transportation, mobile or doing at work.

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ASSESSMENT OF QUALITY OF LIFE IN RUSSIAN PATIENTS WITH GRAVES´ ORBITOPATHY

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Objective: To assess quality of life in Russian patients with Graves´ orbitopathy treated with intravenous glucocorticoids.

Methods: Thirty-seven patients with Graves' orbitopathy (mean age 49,5 year, sex ratio M:F=10:27) were included. All patients were treated with intravenous glucocorticoid (cumulative steroid dose was 5 g). Quality of life (QoL) was measured with Russian version of GO-QoL at three time points during the 6-month study period (before, in 3 and 6 months after treatment) as well as ophthalmological examination.

Results: During the follow-up there were no significant differences in subscale on visual functioning (p>0,05). Nevertheless, we obtained improvement in subscale on the psychosocial consequences of a changed appearance: p=0,005 and p=0,02 was in 3 and 6 months after treatment, respectively.

Conclusions: In spite of the treatment with intravenous glucocorticoid our patients did not report improvement of visual functioning as proptosis and diplopia are poorly responsive. We suppose that impact glucocorticoid on soft tissue changes leaded to improvement of GO-QOL appearance scale.

P52

DIAGNOSTIC GRAVES´ ORBITOPATHY IN PATIENTS WITH MYASTHENIA GRAVIS

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Purpose: To examine the particular signs of Graves´ orbitopathy (GO) in patients with myasthenia (M) with oculomotoris disorders (OMD).

Methods: In 42 patients with M, suspition of GO end OMD and 30 patients with GO without M determinated thyreoid, immunologe states, ranges of look in prozerin-test, leaded ophthalmoscopy, ultrasonography orbits, examinated by classification NOSPECS end scale CAS.

Results: GO have 26 patients with M, wich 61% had Hashimoto´s thyroiditis (hyperthyroidism - 16.7%, hypothyroidism - 5.5%), 8% - ganglion forms of goiter, 31% - without thyreopathy; the periorbital edema identified in 61.5%, enlargement of scleroconjunctival vessels - 46%, proptosis - 42.2%, a small edema of retroorbital cellular tissue (RCT) - 23% and moderate RCT - 69%. Severity and activity of GO in patients with M was less than in patients without M (p< 0.05) -stage 3 NOSPECS and 4 CAS. In the prozerin-test the ranges of look in upper quadrant has not changed in all patients with GO without M and 75% of patients with M and edema of RCT; the thickness of oculomotoris muscles no differented in patients with positive and negative prozerin-test (p>0,05). A negative link revealed between activity GO and volume of movement of eyeballs in patients with GO without M (rS-0.816, p = < 0.001), in contrast to patients with M end GO (rS=-0.295, p> 0.1).

F**indings:** Signs of GO patients were periorbital edema, enlargement of scleroconjunctival vessels, exophthalmos and edema RCT; minimum activity and severity of the GO identifies conditionality OMD sinaptic defect.

P53

FEATURES OF THERAPY OF COMPLICATION FORMS GRAVES´ ORBITOPATHY

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Purpose: Identify particular of therapy in patients with endocrine Graves´ orbitopathy (GO).

Materials and Methods: In 14 pathient with complication forms GO determinated thyreoid end immunologe states, ranges of look end ranges of vision, leaded ophthalmoscopy, computered thomography end ultrasonography orbits, computered retinal thomography; ophthalmostatus bu classification (NOSPECS) and the scale of activity (CAS).The treatment of ophthalmopaty leaded suppression dosas glucocorticoids (GC) combinated with X-ray therapy of orbits.

Result: Have found 12 patients with neuropathy optic nerve compression, 1- keratitis, 1- corneal ulcer; severity GO- V-VI, active - 4-8. The treatments leaded suppression dosas GC: in 1 patient with corneal ulcer - «pulse»-therapy 6.0g GR course, the rest - oral 1.25-1.0 g/kg by prednizolon, end radiation therapy orbits summary doses 17-20 Gray after the first 3 months of to beginning GC. Remission has achieved in 14 patients.

Conclusions: The peculiarity of therapy in patient with complication forms GO is necessary to application GK every day in suppression doses during the first 14-17 day treatment by control ranges of vision, ophthalmoscopy or computered retinal thomography with obligatory remittance suppression doses every other day combination with X-ray therapy of orbits after the first 3 months of to beginning GC, end also to delay X-ray therapy because danger to development early fibrousis of orbits.

PO6 Graves' Hyperthyroidism 1

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IN VIVO EFFECTS OF BLOCKING TYPE AND STIMULATING TYPE MONOCLONAL TSHR AUTOANTIBODIES

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The human monoclonal TSHR autoantibody (MAb) M22 has high binding affinity ($5x10^{10}$L/mol) for the TSH receptor (TSHR) and is a potent stimulator of cyclic AMP production in CHO cells expressing the TSHR. In contrast human MAb K1-70 (affinity for the TSHR $4x10^{10}$L/mol) is a potent inhibitor of M22 or TSH stimulation of cyclic AMP production in TSHR expressing CHO cells. We now describe the biological activities of M22 and K1-70 *in vivo*.

Serum levels of total T4, free T4 and MAbs were measured following intramuscular administration of M22 IgG (2-4µg/animal), K1-70 IgG (10-200µg/animal) or M22 + K1-70 into rats. Studies with M22 were carried out in T3 suppressed animals and thyroid pathology was assessed. Furthermore, specific binding of both MAbs to thyroid sections was demonstrated by immunohistochemistry.

Following administration of M22, rat serum concentrations of total T4 and free T4 increased in a dose dependent manner. Peak thyroid hormone levels coincided with the highest levels of M22 detected in the rat serum. Thyroid follicular cell hypertrophy correlated with the dose of M22 IgG. In contrast injections of K1-70 alone caused a dose dependent decrease of total T4 and free T4 in rats. When M22 was administered 3 hours after K1-70, 3 hours before K1-70 or together with K1-70, no increase in T4 levels was observed.

These studies show that M22 is a potent thyroid stimulator *in vivo* as demonstrated by a dose dependent increase in thyroid hormone secretion and thyroid follicular cell hypertrophy. In contrast, K1-70 is a potent inhibitor of thyroid hormone secretion *in vivo*. Furthermore K1-70 inhibits the thyroid stimulating activity of M22 *in vivo*. This potent *in vivo* activity of K1-70 emphasises its potential use in patients to block the effects of stimulating type TSHR autoantibodies.

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A CHIMERIC CELL LINE PERFORMS SIGNIFICANTLY BETTER THAN WILD-TYPE IN ANTI-TSHR BIOASSAYS

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Aims: We described a stably transfected cell line (CHO-MC4) expressing a chimeric TSH-receptor (TSHR) and a CRE-dependent luciferase for detecting thyroid-stimulating immunoglobulins (TSI bioassay, Thyretain™). To develop a complementary thyroid-blocking antibody (TBI) bioassay, we compared the performance of the chimeric to a wild type (wt) TSHR.

Methods: CHO cells expressing a wt or chimeric TSHR and a CRE-dependent luciferase were isolated. Cells were grown at 37°C for 15-18 hours and then inoculated with bTSH, TSI, TBI, and/or patient serum. Luciferase expression was measured after incubation for 3 hours. Blocking activity was defined as percent inhibition of luciferase expression relative to induction with bTSH alone.

Results: Both chimeric and wt cell lines showed induction of luciferase in response to bTSH in a dose-dependent manner, but displayed different levels of sensitivity and maximal induction. The wt TSHR-expressing cell line responded to concentrations of bTSH between 0.8 and 50 mIU/L, whereas the chimeric TSHR-expressing cell line had a wider dynamic range (1.6 to 200 mIU/L) and was induced to 8-fold higher levels. Both cell lines detected TSI in serum from patients with Graves' disease. When the cell lines were stimulated with either TSI or bTSH, luciferase expression was reduced in a dose-dependent manner by the addition of increasing concentrations of a blocking MAb, K1-70 (RSR, Cardiff, U.K.) or serum containing TBI. The chimeric cell line was more sensitive in that the inhibitory concentration 50% (IC50) of K1-70 was 3 to 5-fold lower on the chimeric cell line. Also, in contrast to the wt cell, the chimeric cell line displayed 3-4-fold higher inhibitory activity when tested with TBI-positive sera and uniformly displayed sigmoidal dose-response curves with serially diluted blocking sera.

Conclusion: Compared to the wt, the chimeric TSHR cell line performs better and is a unique vehicle to develop both stimulating and blocking bioassays.

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POST-RADIOIODINE MANAGEMENT OF PATIENTS WITH GRAVES' DISEASE

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Radioiodine is safe and effective treatment for Graves' disease. Iatrogenic hypothyroidism is common after treatment, and its onset is unpredictable. Even a short episode of hypothyroidism can result in significant morbidity and ideally should be avoided. In our centre a standard dose of radioiodine (400MBq) is used, but for historical reasons two different protocols are followed after radioiodine: Regimen A: regular clinical and biochemical monitoring with intent to commencing levothyroxine when serum thyroid hormones have normalized, and Regimen B: block and replace with Carbimazole and levothyroxine starting 2 weeks post-radioiodine and continuing for 6 months, then withdrawing Carbimazole, while continuing with levothyroxine long-term.

Objectives: To compare the two protocols for incidence of clinical hypothyroidism during a 12 month post-radioiodine follow-up period and effects on weight gain and development or progression of orbitopathy.

Methods: Patients with Graves' disease who were treated between January 2008-December 2009 were included. The medical records were reviewed and data were collected and analyzed.

Results: 122 patients were studied, 78 treated with Regimen A and 43 with Regimen B. Euthyroidism at 8 weeks, 6 months and 12 months post-radioiodine was achieved in 50%, 64% and 73% of patients with Regimen A and 65.1%, 71% and 65% in patients with regimen B respectively ($p< 0.05$). Clinical hypothyroidism during follow-up was commoner in Regimen A than B (52.6% vs 16.3% respectively, $p< 0.05$). Weight gain was reported more frequently in Regimen A than B (43.6% vs 20.9%, $p< 0.05$). The incidence of new Graves' orbitopathy developing after radioiodine was higher in Regimen A than B (11.1% vs 5.3%, $p< 0.05$).

Conclusions: A 6 month course of block and replace followed by levothyroxine after a standard 400MBq dose of radioiodine is associated with better clinical outcomes than a watchful approach and initiation of levothyroxine based on biochemical and clinical indicators.

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INCIDENCE OF HYPERTHYROIDISM IN SWEDEN, IN THE YEARS 2003 - 2005

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Introduction: The incidence of hyperthyroidism has been reported to be 23 - 93/100000 inhabitants/year. Studies of the local incidence of hyperthyroidism in Sweden has shown 26 - 43/100000/year. This study has evaluated the incidence for approximately 40% of the entire Swedish population of 9 million inhabitants. Sweden is considered iodine sufficient.

Methods: All patients including children, who were newly diagnosed with overt hyperthyroidism in the years 2003-2005, were prospectively registered in a multicenter study (cities; Malmö, Karlskrona, Göteborg, Örebro, Eskilstuna / Katrineholm, Stockholm and Uppsala). Inclusion criteria: clinical symptoms and/or signs of hyperthyroidism with plasma TSH concentration below < 0.2 mIE/l, increased plama levels of freeT3 and/or free T4. Patient with relapse of hyperthyroidism, thyroiditis, or exogenous thyrotoxicosis were not included. The diagnosis (Graves´ disease (GD), toxic multinodular goiter (TMNG) and solitary toxic adenoma (STA), smoking, initial treatment, occurrence of Thyroid Associated Ophthalmopathy (TAO) and demographic data were registered.

Results: 2916 patients were diagnosed with *de novo* hyperthyroidism, incidence of 27.6 / 100000 inhabitants/year. The incidence of subtypes were: GD 21.0/100000 toxic nodular goiter (TNG=STA and TMNG) occurred in 692 patients, corresponding to an annual incidence 6.5 per 100 000. The incidence was higher in women compared to men, (4.2:1). 75% of the patients were diagnosed as GD in whom, TAO occurred at diagnosis in every fifth patient. Geographical differences were observed, where the highest incidence was found in Malmö, 41.7 and the lowest incidence was found in Göteborg, 23.1/100000/year

Conclusion: The incidence of hyperthyroidism in Sweden is in the lower range compared to earlier international reports. Patients with hyperthyroidism had GD in 75% and 20% of them had TAO at diagnosis. The observed geographical differences require further studies.

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ADRENOCORTICAL RESERVE IN HYPERTHYROIDISM

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Background: Explicit data regarding the changes in adrenocortical reserve during hyperthyroidism does not exist.

Aim: To document the capability (response) of adrenal gland to secrete cortisol and DHEA-S during hyperthyroidism compared to euthyroidism, and to describe factors associated with these responses.

Methods: A standard-dose (0.25 mg i.v.) ACTH stimulation test was performed to the same patients before hyperthyroidism treatment, and when euthyroidism achieved after treatment. Baseline cortisol (Cor_{min0}), DHEA-S (DHEA-S_{min0}), cortisol binding globulin (CBG), ACTH, 60-min cortisol (Cor_{min60}), and DHEA-S (DHEA-S_{min60}), delta cortisol (Δ Cor), delta DHEA-S (Δ DHEA-S) responses were evaluated.

Results: Forty-one patients [22 females, 49.5±15.2 years old, 32 Graves disease, 9 toxic nodular goiter] had similar Cor_{min0}, DHEA-S_{min0}, DHEA-S_{min60} levels when they were hyperthyroid and euthyroid. However, $Cor_{min60,}$ both Δ Cor (12.5±4.4 vs 15.3±5.5 µg/dL, p=0.019) and Δ DHEA-S [100 (0-200) vs 200 (100-400) µg/dL, p=0.034] were lower in thyrotoxic state. Four (10%) of the patients had adrenal insuffiency during hyperthyroidism which resolved spontaneously with the treatment of hyperthyroidism. These patients had higher levels of free T4, T3, and fat free mass (FFM). Multiple regression analysis demonstrated an independent association of Cor_{min60} with FFM, Cor_{min0}, CBG; and of DHEA-S_{min60} with free T3, free T4, albumin, DHEA-S_{min0} and fat mass.

Conclusion: Relative adrenal insufficiency effects about 10% of the hyperthyroid patients. Moreover, both peak response of cortisol and DHEA-S to ACTH stimulation are blunted during thyrotoxicosis. As serum thyroid hormone levels increase, risk of hypocortisolemia increases. Increased fat free mass is independently associated with hypocortisolemia. On the other hand, baseline DHEA-S (positive), fat mass, and thyroid hormone levels (inverse) seem to independently correlate with DHEA-S_{min60}.

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THE DIFFERENCES IN LYMPHOCYTE AND THYROCYTE INTERACTIONS IN GRAVES' DISEASE AND HASHIMOTO THYROIDITIS

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Background: Graves' disease (GD) and Hashimoto thyroiditis (HT) are two common autoimmune thyroid diseases (AITD). The aim of the studies was to compare the interaction of T and B cell subsets in the thyroid tissue in patients with GD and HT.

Methods: We have studied paraffin thyroid specimens obtained from 30 children with GD, 30 children with HT and 30 children without a thyroid disease. The mononuclear T-cells were detected by CD3+, CD4+, CD8+ antibodies, and the B-cells by CD79 alpha+ antibodies and the antigen presenting cells with CD1a+ antibodies (DakoCytomation Denmark) and counted. The specimens from each patients were routinely estimated and investigated under the electron microscope.

Results: In GD and in HT, we observed a statistically significant, higher number of antigen presenting cells, T and B cells in comparison to the control group. In GD, a statistically significant increase in the CD4+cells (3,17%), in comparison to HT (0,93%), was found. In HT, CD8+ T cytotoxic-suppressor cells were predominant among T-cells (20,54%) in comparison to GD (6,86%). The percentage of plasmocytes was statistically significant higher in HT (31,65%) than in GD (22,89%)

The ultrastructural investigations showed diapedesis of T cells into thyroid follicles and formation of immunological synapses between thyrocytes and lymphocytes. In GD, the activity of B-cells producing antibodies involved in the processes of activation and proliferation of thyrocytes developed. In HT, a cytotoxic reaction again thyrocytes was induced.

Conclusions:

1. The autoimmune reaction in Graves 'disease consists in activation of T helper cells CD4+ and transformation of B cells to plasmocytes and production of thyroid antibodies which stimulate thyroids.
2. The autoimmune reaction in Hashimoto thyroiditis consists in activation of cytotoxic reactions between T-suppressor-cytotoxic cells CD8+ and thyrocytes.

P60

DILUTION STUDIES DEMONSTRATE GREATER ANALYTICAL SENSITIVITY OF CHIMERIC TSH-R BIOASSAY VS. TSH-R BINDING AUTOANTIBODIES

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Aims: We recently reported a novel chimeric TSH-R bioassay that measures thyroid stimulating-immunoglobulins (TSI). Here, we compared the analytical sensitivity of this FDA-cleared bioassay and assays that measure TSH-R binding inhibitory immunoglogulins (TBII) using sera from patients with Graves' disease (GD).

Methods: Serum samples from 18 thyrotoxic GD patients, positive for both TSI and TBII, were serially diluted into normal serum at final serum dilutions of 1:3, 1:9, 1:27 and 1:81 in triplicate. TSI levels, expressed as the percent specimen-to-reference-ratio, SRR%, were measured in a reaction containing 1 part serum to 10 part reaction buffer. Two TBII methods were used (Brahms RIA and Roche ECLIA Elecsys). Titres were expressed as the dilution of the serum that reduced the TSI or TBII level to below the cut-off of each assay (TSI SRR% < 140; Brahms < 1.0 IU/L and Roche < 1.75 IU/L).

Results: The analytical sensitivity of the TSI bioassay was significantly greater than the TBII methods. All 18 of the sera showed complete extinction of binding activity at dilution of 1:3 (Brahms) and 17 at dilution of 1:27 (Roche) in the TBII assays. In contrast, 85% of the serum samples retained TSI positivity at dilution of 1:3, 38% at 1:9, 20% at 1:27 and 10% at 1:81. Mean TSI and TBII titers were 1:8 and 1:5 respectively. Mean baseline TSI values of samples that had TSI titres of 1:3, 1:9, 1:27, 1:81 and above were SRR% 223, 308, 409, 485 and 507, respectively. GD patients with high TSI titres relapsed within weeks after thionamide withdrawal. Mean baseline TSI levels were SRR% 345 prior to thionamide therapy and decreased after 24 and 36 weeks of therapy to 270 and 236, respectively.

Conclusions: The TSI titer underscores the high analytical sensitivity of the chimeric TSH-R bioassay and shows clinical utility.

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DECREASE IN MAGNESIUM AFTER TOTAL THYROIDECTOMY FOR GRAVES´ DISEASE IS RELATED TO DEVELOPMENT OF PERMANENT HYPOCALCEMIA

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Background: Transient postoperative hypocalcemia is one of the most usual complications after thyroidectomy. Permanent hypocalcemia, however, is rare, but usually requires life long treatment and follow up. The risk for permanent hypocalcemia has been shown to be significantly higher in patients with Graves disease. In this study we evaluated short and long term changes in calcium, phosphate, magnesium and PTH in order to characterize subjects at risk for transient and permanent hypothyroidism.

Methods: 40 patients who underwent total thyroidectomy for Graves disease were included in this study. Vitamin D levels were measured prior to the operation. Calcium, Phosphate, Magnesium and PTH were measured before operation and 6 hours, 48 hours, 1 week, 1-6 and 12 months after operation.

Results: Postoperative hypocalcemia was seen in 21 of 40 patients (52.5%), undetectable PTH (< 0.6 pmol/l) in 11 of 37 patients (28.9%), low PTH (< 1.5 pmol/l) in 3 (8%) and PTH>1.5 pmol/l in 23 patients (62%). All patients with measurable PTH 6-48 hours after operation regained normal calcium. Of those with undetectable PTH after 6-48 hours, 4 patients developed permanent hypocalcemia.

We found no significant differences in serum levels of Vitamin D, magnesium or PTH before operation between patients who developed hypocalcemia and those who did not. We did, however, find a significant correlation between the decrease in magnesium from time 0 to 48 hours after operation and permanent hypocalcemia (p=0.012).

Conclusion: PTH and Mg levels 6-48 after operation may predict development of permanent hypocalcemia. Magnesium plays a role in stimulation of PTH secretion and modulates PTH receptor sensitivity and thus exerts pronounced effects on calcium homeostasis. Further studies are needed to investigate the role of magnesium in postoperative hypocalcemia.

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DOES THE SUPPRESSIVE TREATMENT OF L-THYROXINE IMPAIR HEART FUNCTION IN YOUNG PATIENTS WITH DIFFERENTIATED THYROID CANCER (DTC)?

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DTC patients need L-thyroxine treatment after thyroidectomy and subsequent 131-I therapy. Although insufficient L-tyroxine treatment has been reported to be related to the higher risk of recurrence, especially if TSH levels maintain over 2 mU/L, long term TSH suppression can results in cardiovascular side effects.

The aim of the study was the evaluation of influence of the long term suppressive L-thyroxine treatment on cardiovascular system of patients diagnosed with DTC in childhood.

The analysis was carried out in 111 nowadays adult patients diagnosed with DTC at the mean age of 15 years (7-18), after total thyroidectomy (92%) and radioiodine treatment (91%), treated with L-thyroxine for a mean time of 12 years (4-32). We analyzed TSH serum levels examined during the L-thyroxine treatment and excluded values measured during L-thyroxine withdrawal.

Methods: Patients were evaluated by physical examination, electrocardiography, echocardiography and lipid profile.

Results: Insufficient L-thyroxine dose (TSH>2mU/L in more than 20% of measurements) was found in 20,7% of patients. According to geometric mean of TSH levels during the whole follow-up patients were subdivided into three groups: with TSH < 0,1mU/l (56%); 0,1 - 0,4 mU/l (33%) and >0,4 mU/L (11%).

BMI analysis didn´t reveal association with TSH serum level.

Mean level of cholesterol in analyzed groups was respectively: 172,86; 177,0; 171,67 mg/dl; HDL - 55,81; 54,38; 56,67 mg/dl; LDL - 102,65; 112,54; 108,6 mg/dl; triglycerides - 69,91; 77,81; 63,0 mg/dl (no significant difference).

Mean left ventricular mass was within normal range in all patients: in group 1: 140,3g (woman) 174,5g (man), respectively in group 2: 148,9g and 183,5g, in group 3: 159,6g and 215g. In ECG only one case of tachycardia was found.

Conclusions: Despite long term L-thyroxine therapy, with suppressed or within lower normal range TSH level, there were no risk of cardiovascular system impairment in our young DTC patients.

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EFFECT OF AMIODARONE CONTINUATION OR WITHDRAWAL ON THE RESPONSE TO GLUCOCORTICOIDS IN PATIENTS WITH AMIODARONE DESTRUCTIVE THYROIDITIS

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Amiodarone-induced thyrotoxicosis (AIT) due to destructive thyroiditis (type II) is frequently treated with glucocorticoids (CS): recent surveys reported that 70% expert ETA, ATA or LATS thyrodologists consider amiodarone withdrawal beneficial, although not proven, in AIT patients.

Patients and Methods: Forty-two untreated type II AIT patients were included in a historical prospective study. All patients were treated with prednisone (starting dose, 0.5 mg/kg/day); amiodarone therapy was continued in eight (GROUP 1) and withdrawn in 34 patients (GROUP 2). The two patient groups were matched for age, sex, initial serum FT4 and thyroid volume. Follow-up lasted at least 12 months.

Results: Mean time (±SE) for first normalization of thyroid hormone after CS therapy was 53±60 days and 51±48 days in group 1 and group 2, respectively (p= 0.933). However, AIT recurred in 5 out of 8 patients (62,5%) of GROUP 1 and in 4 out of 34 patients (11.7%) of GROUP 2 (p= 0.002), requiring re-institution of CS therapy. Finally, restoration of stable euthyroidism was achieved after 117±68 days in GROUP 1 and 61±51days in GROUP 2 (p=0.02).

Conclusion: AIT2 patients achieve euthyroidism irrespective of amiodarone continuation or withdrawal. However, continuation of amiodarone increases the risk of thyrotoxicosis recurrence, delaying euthyroidism restoration and exposing heart to thyroid hormone excess for a longer period. Hence, decision on amiodarone withdrawal in AIT2 patients should consider the beneficial effect of amiodarone and the harmful one of thyrotoxicosis on the heart.

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ANALYSIS OF TSH RECEPTOR AUTOANTIBODY ACTIVITIES IN A SUBJECT WITH LONGSTANDING HASHIMOTO'S THYROIDITIS WHO DEVELOPED GRAVES' DISEASE WITH PRETIBIAL MYXOEDEMA

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Case Presentation: A 80 year old woman with Hashimoto's thyroiditis (HT) of 20 years' duration, was receiving 200 mcg/day of thyroxine. Her thyroxine had to be stopped because of over replacement. However, at presentation (A) several months after stopping thyroxine, her free T3 continued to be elevated and TSH undetectable. She had a smooth goitre (ultrasound indicated HT), pretibial myxoedema, but no orbitopathy (MRI normal). TPOAb was >1300IU/mL and TRAb >40IU/L. She eventually had radioiodine treatment and needed thyroxine thereafter.

Methods and Results: Serum taken at A and 1 year after (B) stimulated cyclic AMP production in CHO cells expressing the TSH receptor (TSHR) (1580% and 1530% respectively). Neither sample blocked TSH mediated cyclic AMP production.

The effects of TSHR mutations on the stimulating activity of samples A and B, the human monoclonal thyroid stimulating autoantibody M22 and TSH were then analysed. Stimulating activity of TSH was not affected by the mutations and the effect of a particular mutation on serum or M22 activity was expressed relative to TSH activity. TSHR mutations R80A, E107A and K129A had clear effects on M22 activity (15%, 30% and 54% relative to TSH respectively) while the effects on the activities of sample A (79%, 73% and 87% respectively) and sample B (65%, 57% and 72% respectively) were smaller. TSHR R109A mutation had similar effects on the activities of M22 and samples A & B. TSHR R255D caused loss of the stimulating activities of M22 (5%), sample A (10%) and sample B (4%).

Conclusions: These observations confirm that binding sites on the TSHR overlap, with variability of TSHR contact residues for different autoantibodies and such studies could provide a "fingerprinting" marker for individual patients. However TSHR R255 is critical for stimulating activity of all TSHR autoantibodies tested so far.

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SERUM LEVELS OF CIRCULATING SOLUBLE FAS LIGAND (SFASL) IN CHILDREN WITH AUTOIMMUNE HYPOTHYROIDISM AND AUTOIMMUNE HYPERTHYROIDISM

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Objectives: FasL participates in cell-mediated cytotoxicity by inducing apoptosis in susceptible cells via cell surface Fas receptors. Normal and neo-

plastic thyroid tissues are resistant to FasL-induced apoptosis. The Fas/FasL apoptosis pathway is up-regulated in chronic autoimmune thyroiditis (cAIT) where the thyroid destruction leads to hypothyroidism (hypoT) and may be present in Graves' disease (GD) manifested with hyperthyroidism (hyperT). The role of soluble FasL (sFasL), a proteolytic product of FasL, is less clear in induction of apoptosis in both, thyrocytes and lymphocytes.

Methods: We studied serum sFasL (ELISA) in 49 newly diagnosed children with cAIT and GD vs healthy euthyroid children: 11 with hypoT (10 girls and 1 boy aged 12,2±1,9 years, mean hormone levels: TSH 51,3 μIU/mL↑, fT4 0,45 ng/dL↓, fT3 2,14 pg/mL, TRAb negative, TPOAb 2902 IU/mL↑, TgAb 729 IU/ml)↑; 20 children with hyperT (16 girls and 4 boys, age 12,4±4,9 years, mean hormone: TSH 0,006 uIU/mL↓, fT4 4,19 ng/dL↑, fT3 18,75 pg/mL↑, TRAb 26,4 U/L↑, TPOAb 2358 IU/ml↑, TgAb 504 IU/ml↑); 18 healthy subjects (8 girls and 10 boys, age 10,5±4,8 years) as a control group.

Results: sFasL levels were significantly higher in children with hypoT (median 0,27 ng/ml IQR 0,18-0,32) vs control (median 0,07 ng/ml IQR 0,014-0,11) ($p< 0,001$). No difference was noticed in sFasL in hyperT (median 0,13 ng/ml IQR 0,08-0,20) vs control. There was a significant difference in sFasL levels between hypoT and hyperT group ($p< 0,05$).

Conclusions: Elevated sFasL levels in children with cAIT supports an active apoptosis of thyrocytes, resulting in hypothyroidism. Higher than control but not significant sFasL levels in GD confirms the co-apoptosis of thyrocytes parallel to the predominant stimulation with TRAb. Our data suggest that serum sFasL may serve as an indicator of apoptotic thyroid state. sFasl may also be a useful predictor of a clinical course in GD.

PO7 Thyroid Hormone and Metabolism 1

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EFFECTS OF TSH ON THERMOGENIC MARKERS IN BROWN ADIPOCYTES

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TSH through its receptor (TSHR), activates adenylate cyclase increasing cAMP and thyroid hormone synthesis. TSHR is also present in extrathyroidal tissues including white and brown adipose tissue (BAT). BAT thermogenesis increases under adrenergic stimuli (cold, diet) due to activation of the specific uncoupling protein, UCP1, process that requires T3. D2 deiodinase is adrenergically stimulated in parallel to UCP1 and produces T3 in BAT.

The expression of TSHR in BAT and the effect of TSH on thermogenesis through the stimulation of D2 and UCP1 have been demonstrated. TSHR is down-regulated under cold exposure. But the physiological role of TSH in adipose tissues (lipolytic, thermogenic) remains to be clarified.

Aim: To analyze the presence and regulation of TSHR in brown adipocytes and the effect of TSH on UCP1 and D2 and the signalling pathways involved in TSH action.

Methods: We used primary cultures of differentiated rat brown adipocytes. D2 activities were measured using 2nM T4. UCP1 and D2 expression were analyzed by RT-PCR, and p-ERK and p-AKT by Western blots.

Results: TSHR is upregulated by insulin and low doses of TSH, and down-regulated by NE, T3 and high doses of TSH.

TSH (10mU/ml) increased UCP1 mRNA by 190-fold and was synergistic with T3 (1000-fold).

TSH (100mU/ml) increased D2 expression by 13-fold and was synergistic with T3 (190-fold). TSH (0.1-100 mU/ml) increased D2 activity only in the presence of T3, while TSH decreased D2 activity in the presence of T3+NE (>60%). TSH inhibited p-ERK and increased p-AKT.

Conclusions: TSHR is upregulated by insulin and low doses of TSH and down-regulated by NE, T3 and high doses of TSH. TSH increases UCP1 and D2 mRNA and was synergic with T3. T3 is required for TSH stimulation of D2 activity, but TSH decreases the adrenergically stimulated D2 activity (NE+T3), possibly through p-ERK inhibition.

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P67

THYROID HORMONE EFFECT ON MITOCHONDRIAL FUNCTION IS DEPENDENT OF AGE IN LEAN FEMALES

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Thyroid hormones regulate mitochondrial function and subsequently oxygen consumption. It is also well known that concentrations of TSH and T3 are dependent of age.

In order to examine if mitochondrial function, dependent on thyroid hormone effect (genomic as well as non-genomic) is also age-related, mitochondrial function in lean female children (group A aged 9-13 years, n= 11, BMI < 80 age matched percentile) lean female adolescents (group B aged 15-20 years, n=9, BMI = 20-22 kg/m^2) and lean female adults (group C aged 35-52 years, n=19, BMI 21-24 kg/m^2) from the paediatric outpatient clinic, Naestved Hospital, Denmark. In addition to antromorphic data, basal oxygen consumption (VO2), serum values of TSH and T3 were registered.

Mitochondrial function was examined in mononuclear blood cells by flow cytometric measurement of mitochondrial membrane potential (MMP) (non-genomic thyroid hormone effect) and by PCR measurement of expression of mitochondrial-related genes (PGC-1α, PGC-1β, TFAM and NRF-2) (genomic thyroid hormone effect).

Table 1.

	Group A (Median, upper and lower quartiles)	Group B (Median, upper and lower quartiles)	Group C (Median, upper and lower quartiles)	Kruska-Wallis ANOVA
TSH mU/L	1.80 (1.70-2.40)	2.30 (2.20-2.70)	1.30 (0.89-2.20)	B vs C p<0.05
T3 pmol/L	6.50 (5.80-7.10)	6.40 (6.10-6.65)	4.90 (4.50-5.60)	A vs C p<0.05 B vs C p<0.05
VO2 O2/ min*m2	137 (134-157)	120 (113-121)	118 (112-128)	A vs B p<0.05 A vs C p<0.05
MMP a.u.	7875 (6375-9138)	4847 (3595-5340)	6151 (4554-7723)	A vs B p<0.05 B vs C p<0.05 A vs C p<0.05

Table 1 demonstrates that values of MMP and VO2 are depressed in lean female adolescents compared to lean female children contrasting the variations of TSH and T3 in these groups. Values of expression of mitochondrial-related genes (PGC-1α, PGC-1β, TFAM and NRF-2) showed no statistically significant difference between neither of the age groups and are not shown.

We conclude that non-genomic stimulation of mitochondrial function by thyroid hormone is impaired in lean female adolescents, in contrast to genomic stimulation. Factors linked to puberty might be responsible.

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EFFECTS OF THYROTOXICOSIS ON LEVELS OF GHRELIN, ADIPOCYTOKINES AND ENDOCRINE PANCREAS FUNCTION

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Background: Due to stimulated overall metabolism, a state of nutritional inadequacy often ensues, during thyrotoxicosis.

Aim: To investigate levels of some major components of the system that regulates energy stores, glucose, and fat metabolism, during thyrotoxicosis compared to euthyroid state.

Methods: Fasting serum ghrelin, leptin, adiponectin, insulin, glucagon, glucose, LDL-C, HDL-C, triglyceride, as well as body fat composition were analysed during thyrotoxicosis in 40 hyperthyroid patients (50.5±15.2 years old, 22 females, 31 with Graves disease, 9 with toxic nodular goiter). The same measurements were repeated an average 3 months later, when all patients achieved euthyroidism.

Results: Compared to euthyroid state, during thyrotoxicosis, patients had higher levels of circulating adiponectin (11.7 vs 9.8 µg/mL, p=0.020), lower ghrelin (8.1 vs 9.2 ng/mL, p=0.002); had comparable fasting blood glucose (94 vs 90 mg/dL, p=0.069), insulin (7.8 vs 9.1 µIU/mL, p=0.844), HOMA-IR (1.72 vs 1.85, p=0.453) and glucagon levels (540 vs 648 pg/mL, p=0.397). *Ghrelin* correlated with free T4 (r=-0.357, p=0.005), free T3 (r=-0.363, p=0.004), LDL-C (r=0.455, p< 0.001), and fat mass (r=0.308, p=0.025). *Leptin* correlated with HDL-C (r=0.397, p=0.002), fat mass (r=0.769, p< 0.001), fat-free mass (r=-0.361, p=0.008). *Adiponectin* associated with increased levels of free T4 (r=0.375, p=0.003), free T3 (r=0.267, p=0.039), fat free mass (r=0.354, p=0.009). *Glucagon* negatively correlated with age (r=-0.309, p=0.042), free T4 (r=-0.454, p=0.001), free T3 (r=-0.410, p=0.004), and positively correlated with HDL-C (r=0.356, p=0.014), leptin levels (r=0.343, p= 0.018), and fat mass (r=0.312, p=0.050).

Discussion: Serum levels of ghrelin (stimulates appetite) are decreased; leptin, insulin (stimulate satiety), glucagon levels are unchanged; and adiponectin levels are increased during thyrotoxicosis. Decreased adiposity may be associated with unimpaired/balanced endocrine pancreas function during thyrotoxicosis.

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GHRELIN AND OBESTATIN CHANGES IN HYPOTHYROIDISM AND HYPERTHYROIDISM AFTER TREATMENT

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Ghrelin and obestatin are two peptides deriving from the same precursor - prepro-ghrelin. Ghrelin proved to be an essential regulator of metabolism. The previous studies revealed, that its level increases in hypothyroidism and decreases in hyperthyroidism. The biological activity of obestatin is still discussed.

The aim of this study was to compare ghrelin and obestatin levels in hypothyroidism and hyperthyroidism before and after treatment. The study group consisted of 15 patients with severe hyperthyroidism (TSH 0,005 ± 0,001 uIU/ml, fT_4 43,3 ± 21,4 pmol/l, fT_3 18,1 ± 9,7 pmol/l) and 10 patients with severe Hashimoto hypothyroidism (TSH 92,8 ± 13,5 uIU/ml, fT_4 2,1 ± 1,3 pmol/l, fT_3 1,1 ± 0,6 pmol/l). Since BMI correlates negatively with ghrelin production, obese and underweight patients were excluded from the study.

Blood samples were collected at fast. Plasma ghrelin and obestatin concentrations were measured by RIA.

The study revealed, that ghrelin level in Hashimoto hypothyroidism significantly decreases after treatment (704,4 ± 455,8 pg/ml, *vs.* 222 ± 109,5 pg/ml, p < 0,01), despite of BMI reduction (25,8 ± 2,8 kg/m^2 *vs.* 25 ± 3 kg/m^2, p< 0,05). Obestatin level was also decreased (87 ± 44,3 pg/ml *vs.* 45,9 ± 16,6 pg/ml, p=0,08).

In hyperthyroidism ghrelin and obestatin levels did not present significant changes before and after treatment (227,9 ± 94,7 pg/ml *vs.* 263,2 ± 122,4 pgl and 80,7 ± 35,6 pg/ml *vs.* 86,2 ± 34,1 pg/ml, respectively). However, ghrelin concentration did not decrease despite of significant BMI rise (20,5 ± 2,7 kg/m^2 *vs.* 21,5 ± 2,3 kg/m^2, p< 0,05).

High ghrelin level in hypothyroidism and its reduction after treatment suggest a compensatory role of this peptide in metabolic disturbances. In state of thyroid hormone deficiency high ghrelin concentration increases metabolism rate. In hyperthyroidism relatively low ghrelin may decrease metabolism rate and reduce energy expenditure.

P70

IS NON-ENZYMIC PROTEIN GLYCATION OCCURRING IN DIABETES RELATED TO THE PRODUCTION OF ANTI-THYROGLOBULIN ANTIBODIES?*

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Diabetic patients frequently develop autoimmune thyroiditis and anti-thyroglobulin antibodies (ATGAbs). As diabetes is characterized by high levels of non-enzymic glycation of proteins, due to high glucose levels, we aimed to investigate whether enhanced protein-glycation is correlated to the production of ATGAbs and if so, whether thyroglobulin's (Tg) immunogenicity is enhanced due to its hyperglycation. In order to address these points, we studied a group of euthyroid pregnant women of which 55 had gestational diabetes, 40 had type 1 and 10 had type 2 diabetes, during the 12th - 28th pregnancy week. ATGAb titers were determined in all of them. For estimation of protein-glycation status in these patients we used the levels of glycated hemoglobin (HbA1c). Pregnant women with ATGAbs had higher mean HbA1c levels than those without ATGAbs (5.0±0,76 and 4,53±0,69, respectively, t=2,38, p< 0,02). Furthermore, 17 sera from these women [gestational diabetes (14), type 1 diabetes (2) and type 2 diabetes (1)], all containing ATGAb, were studied by ELISA for their reactivity against hyperglycated Tg (400 units of advanced glycation end products/mg of Tg) compared to the native one (normally glycated) (2 units of advanced glycation end products/mg of Tg). Hyperglycated Tg was artificially produced, using standard methodology applied for the non-enzymic glycation of proteins. Age-matched female Hashimoto's patients with high ATGAbs titers were used as controls. It was found that ATGAb reactivity of diabetic women sera was not enhanced against artificially hyper-glycated Tg in comparison to physiologically glycated Tg. In conclusion, it seems that enhanced protein-glycation occurring in diabetic pregnancy is correlated with the production of ATGAbs, but this does not appear to be due to enhancement of Tg's immunogenicity caused by its non-enzymic glycation.

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P71

ANALYSIS OF SERUM LEVELS OF NESFATIN IN PEDIATRIC PATIENTS WITH GRAVES' DISEASE AND HASHIMOTO'S THYROIDITIS

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Thyroid disease is leading to a change of weight - in hyperthyroidism body mass is reduced, but in hypothyroidism it is increased. It is emphasized that changes in hormones such as peptide levels are in close relationship with regulation of body mass. Nesfatin is a recently described anorexigenic peptide produced by the brain. Nesfatin also reduces body weight gain, suggesting a role as a new modulator of energy balance. Excess nesfatin in the brain leads to a loss of appetite, less frequent hunger, a ´sense of fullness´, and a drop in body fat and weight.

The aim of the study was to evaluate nesfatin levels in young patients with untreated Graves´ disease, subclinical Hashimoto´ thyroiditis and in healthy children. The study group formed 78 patients of the Outpatient Endocrinology Clinic. In all patients nesfatin level was analyzed by ELISA's method. In group with hyperthyroidism in Graves' disease we found lower levels of nesfatin compared to the healthy controls (19.37 vs 32.96 ng/ml; p< 0.02); during methimazole therapy nesfatin levels increased compared to the group with untreated hyperthyroidism, but were still lower in comparison to the healthy children (20.35 vs 32.96 ng/ml; NS). In addition, nesfatin levels were lower in

children with subclinical hypothyroidism in Hashimoto's thyroiditis compared to healthy controls (17.2 vs 32.96 ng/ml; p< 0.002). After treatment of l-thyroxine we found lower levels of nesfatin compared to a control group (14.5 vs 32.96 ng/ml; NS). We did not observe statistically significant relationships between nesfatin levels and concentration of thyroid hormones in examined patients. In conclusion, we suggested that disturbances in thyroid hormones in thyroid autoimmune diseases have not an essential effect on changes of peptide controlled appetite- nesfatin. However, nesfatin levels were lower in children with untreated autoimmune thyroid diseases, but mechanism is still unknown.

P72

SERUM ADIPONECTIN, RESISTIN, C-REACTIVE PROTEIN, AND LIPOPROTEIN (A) LEVELS IN AUTOIMMUNE THYROIDITIS

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Background: In addition to the well-established cardiovascular risk factors, altered levels of some emerging risk factors such as C-reactive protein (CRP), homocysteine, Lipoprotein (a) [Lp (a)], and there associations with adiponectin and resistin, may play important roles in the development of atherosclerosis in patients with AIT (autoimmune thyroiditis) and hypothyroidism.

Aims: To examine the interrelationships between thyroid function, lipid profile, inflammation, resistin and adiponectina in AIT, with and without hypothyroidism.

S**ubjects and Methods:** We recorded thyroid function tests, BMI, the levels of total cholesterol, HDL, LDL-cholesterol, triglycerides, apolipoprotein B (ApoB), ApoA1, Lp[a], homocysteine, CRP, adiponectin and resistin in 35 patients with AIT and hypothyroidism, and in 30 patients with AIT without hypothyroidism. Statistical analysis was performed with unpaired t-Student and Spearman's correlations tests. Results are expressed in mean ±.SD. A two-tailed p value < 0.05 was considered significant.

Results: Both groups did not differ significantly in age and sex. We found that patients with AIT and hypothyroidism had significantly higher levels of CRP (0.56±0.55 vs 0.30±0.24mg/dl;p< 0.01), adiponectin (21.0±13.3 vs 19.3±9.0µg/ml;p=0.02), and resistin (20.7±22.6 vs 13.5±13.7 ng/ml;p< 0.03). In the whole group we found significant correlations between resistin and adiponectin (r=0.493;p< 0.001), and CRP (r=0.317;p=0.01). In both groups adiponectin and resistin were not correlated with BMI. In the group of patients with AIT without hypothyroidism there was a significant correlation between TSH and adiponectin (r=-0.623;p< 0.001). In the group of patients with AIT and hypothyroidism there was a significant correlation between adiponectin and Lp(a) (r=0.417;p=0.03). Resistin levels were not correlated with TSH, free T3 and free T4 in both groups.

Conclusions: In our study, adiponectin and resistin levels are increased in patients with AIT and hypothyroidism, independently from adiposity. The interrelationships between resistin and CRP, and between TSH, adiponectin and Lp(a) may explain the increased cardiovascular risk associated with AIT.

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INSULIN RESISTANCE, LIPID PROFILE, C-REACTIVE PROTEIN, AND HOMOCYSTEINE IN PATIENTS WITH GRAVES' DISEASE, AND AUTOIMMUNE THYROIDITIS

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Objective: To examine whether Graves' disease (GD) and autoimmune thyroiditis (AIT) are associated with insulin resistance (IR) and other cardiovascular (CV) risk factors.

S**ubjects and Methods:** We recorded thyroid function tests, BMI, IR markers comprising the HOMA-IR, HOMA-B, QUICKI, HISI, WBISI, IGI and the levels of total cholesterol(TC), HDL, LDL-cholesterol, triglycerides(TG), apolipoprotein B(ApoB), ApoA1, lipoprotein(a)(Lp[a]), homocysteine, CRP(C-reactive protein), folic acid and vitamin B12 levels, in 126 patients with GD and in 354 patients with AIT, 93.5% woman, with a mean age of 46±15.5 years. The patients in both groups were properly treated in order to normalize TSH, FT3 and FT4 levels. A 75-g OGTT was performed and measurements of plasma glucose, insulin, and C-peptide were obtained at 0 minutes(`), 30`, 60`, 90´and 120`. Statistical analysis was performed with the Mann-Whitney and Spearman's correlations tests. A two-tailed p≤0.05 was considered significant.

Results: We found that patients with AIT had significantly higher levels of BMI (27.2±5.2vs26.0±4.6 kg/m^2, p=0.03), C-peptide 60' (10.54±4.25vs9.34±3.27 ng/ml, p=0.007), TC (200±39vs192±45 mg/dl, p=0.02), LDL (124±31vs116±33 mg/dl, p=0.005), TG (116±70vs104±75 mg/dl, p=0.03), ApoB (97±23vs86±24 ml/dl, p≤0.001), VitB12 (467±308vs372±174 pg/ml, p=0.002) and Anti-Tg (141.7±179vs121.2±160.3 UI/mL, p=0.01) than patients with GD. Within the AIT group we found significant correlations between FT3 and HDL (r=0.11;p=0.02) and ApoB (r=0.12;p=0.02), between FT4 and homocysteine (r=-0.14;p=0.04) and between TSH and HOMA-IR (r=0.14;p=0.01), QUICKI (r=-0.12;p=0.05), HISI (r=-0.14;p=0.01) and WBISI (r=-0.14;p=0.01). In the GD group we observed significant correlations between FT4 and CRP (r=0.19; p=0.04) and between TSH and ApoB (r=0.23; p=0.01), VitB12 (r=0.19; p=0.04), WBISI (r=0.33;p=0.01) and IGI (r=-0.30;p=0.003).

Conclusion: In our study, patients with AIT had significantly higher levels in BMI, C-peptide, TC, ApoB and LDL than patients with GD. The interrelationships between thyroid function and IR, lipid profile, CRP and homocysteine suggest an increased cardiovascular risk in patients with autoimmune thyroid diseases.

PO8 Hypothyroidism 1

P74

ACUTE ALTERATIONS IN THYROID FUNCTION OF MALE HYPER MARATHON RUNNERS: A NEW CATEGORY OF "EUTHYROID SICK SYNDROME"

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Introduction: Acute and chronic stressful events alter the thyroid function in order to maintain human homeostasis. Hyper-marathon running (HMR) is such a stressful event. Data concerning these consequences are still conflict-

Table 1 (for Abstract P74).

	TSH μU/ml	FT4 ng/dl	T4 μg/ml	FT3 pmol/l	T3 ng/ml	rT3 ng/ml	T3/rT3	TBG mg/l
Controls	1.6±1.0#	1.2±0.1#	7.4±0.9#	5.1±0.4#	1.2±0.1#			20.1±2.6
Athletes before	2.1±1.0*†	1.1±0.1*†	6.0±0.9*†	4.4±0.4*	0.9±0.1*	0.2±0.0*†	4.2±1.4†*	18.8±5.8
Athletes after	2.6±1.5	1.3±0.1	7.6±0.9	4.9±0.1	1.1±0.1	0.6±0.1	2.0±0.7	23.4±6.7
Athletes 12h after	1.6±0.7	1.2±0.1	6.5±0.7	4.1±0.5	0.9±0.1	0.4±0.1	2.2±0.5	21.1±5.3

# $p < 0.05$ athletes pre vs controls
* $p < 0.05$ athletes pre vs athletes after
† $p < 0.05$ athletes pre vs athletes 12 hours after

ing. Euthyroid sick syndrome is an euthyroid state seen in patients with critical illness.

Objectives: To determine the acute influence of long term strenuous exercise on thyroid function in male HMR.

Methods: Twenty (28) male runners (mean age 48.8±9.6y) who participated in the hyper marathon Nemea-Olympia, Greece (distance 180 km, mean duration 26h) and 22 healthy controls (34.6±7.6 ετών) were recruited. Blood samples were taken 4 hours before the start, immediately and 12 hours after the completion of the race. Hormonal determinations were performed with electrochemiluminescence and RIA (rT3, TBG)

Results: See Table 1.

Conclusions: The acute alterations of thyroid function in HMR have all the criteria of euthyroid sick syndrome and appear to be similar to those seen in critically ill patients.

P75

LOWER FREQUENCIES OF CD4+CD25^{HIGH} AND CD4+FOXP3, BUT NOT CD4+CD25+CD127^{LOW} FOXP3^{+} T CELL LEVELS IN CHILDREN WITH HASHIMOTO'S THYROIDITIS

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Background: The essence of Hashimoto's thyroiditis is loss of tolerance of own tissues caused by malfunction of the T lymphocytes, which effect the production of antibodies reacting with particular cell structures and tissues. Regulatory T cells (Tregs) take part in regulation of immune response and play a leading role in developing immune tolerance through active suppression.

O**bjective and hypotheses:** The forkhead box protein P3 (FoxP3), which is a characteristic and functional marker of Treg cells coding skurphin, negative gene transcription factor blocks expression inflammatory cytokines involved in activation of lymphocytes Th1.

The aim of the study was to estimate the percentage of CD4+CD25^{high},CD4+FoxP3^{+} and CD4+CD25+CD127^{low}FoxP3^{+} T cells in patients with Hashimoto's thyroiditis (HT) (n=20, mean age 15.8 years) before and after 6-12 months of L-thyroxine therapy and in healthy controls (n=40, mean age 15.3 years).

Methods: Polychromatic flow cytometry using a FACSCalibur (BD Biosciences) cytometer was applied to delineate T regulatory cell populations.

Results: In untreated patients with HT we observed a significant decrease of CD4+FoxP3 ($p< 0.01$) and CD4+CD25^{high} ($p< 0.04$) T lymphocytes in comparison to the healthy controls. After 6-12 months of L-thyroxine therapy these phenotype of Tregs were normalized. The analysis of CD4+CD25+CD127^{low}FoxP3^{+} T cells in the peripheral blood did not reveal statistically significant differences in compared to the controls. In new recognized HT patients negative correlation between percentage of CD4+CD25^{high} T cells and serum level of anti-TPO ($r=-0.56$, $p< 0.03$) antibodies was detected.

Conclusions: We conclude that the reduction number of Tregs with CD4+CD25^{high} and CD4+FoxP3 phenotype suggested their role in initiation of development of autoimmune processes in HT.

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CLINICAL SIGNIFICANCE OF TSH CIRCADIAN VARIABILITY IN EUTHYROID INDIVIDUALS AND PATIENTS WITH HYPOTHYROIDISM

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Objective: To investigate clinical significance of TSH circadian variability in patients with euthyroidism and hypothyroidism.

D**esign:** 27 euthyroid individuals, 20 patients with subclinical hypothyroidism and 22 patients, taking L-T4 therapy for overt hypothyroidism, were enrolled in the study. Measurements of serum TSH were performed twice a day: between 8.00-9.00 AM and 14.00-16.00 PM.

Results: Median TSH concentrations in euthyroid patients in the morning was 2,28 mIU/L and in the afternoon - 1.6 mIU/L ($p < 0,05$). The amplitude of TSH circadian variability reached 58% (Me-21,5%). Nevertheless fluctuations of TSH values occurred within the current reference ranges (0,4 - 4,0 mIU/L). According to the proposed TSH reference interval (0,4 - 2,5 mIU/L) 12 participants (44,4%) in the morning and 4 participants (14,8%) in the afternoon have been classified as having a hypothyroidism. About 95% of patients with subclinical hypothyroidism have their afternoon TSH level much lower compare to the morning one. Morning median TSH value was 5.83 mIU/L and in the afternoon - 3.79 mIU/L. The range of TSH circadian variability reached 73%. According to the current TSH reference interval hypothyroidism was not diagnosed in about 50% of patients in the afternoon. The afternoon TSH levels in all patients taking L-T4 were lower than in the morning. Median TSH level in the morning was 3.27 mIU/l and in the afternoon decreased to 2.18 mIU/l. The range of TSH circadian variability reached 64.7%.

Conclusion: The time of blood sampling has important role in the interpretation of TSH level. TSH circadian variability should be taken into account in discussions about narrowing of TSH reference range and target TSH range in patients on L-T4 replacement therapy.

P77

DIFFERENCES IN AUTOIMMUNE THYROID DISEASE PRESENTATION BETWEEN FAMILIAL AND NON-FAMILIAL CASES*

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Objectives: There is indirect evidence that familial and non-familial cases of autoimmune thyroid disease (AITD) differ regarding the nature of thyroid auto-antibody positivity. It is possible that anti-Tg are affected by environmental factors to a greater extent than anti-TPO. This study aimed to record differences in the presentation between familial and non-familial cases of AITD.

Methods: 154 patients with newly diagnosed AITD were studied. Subjects reporting ≥1 first degree relatives with AITD constituted the family +ve group (N=97), and the remaining 57 constituted the family-ve group.

Results: 38.5% of family+ve group had positive anti-Tg antibodies, compared to 63.4% of family-ve ($p=0.01$, Pearson's χ^2). Anti-TPO antibodies were found in 50.1% of family+ve and in 65.9% of family-ve ($p=0.122$). Mean anti-Tg levels were higher in family-ve compared family+ve group (294.5±686 vs. 193.8±511 UI/ml, $p< 0.05$, Mann-Whitney); anti-TPO levels did not differ (354.19±679 vs. 362.54±416). 33.3% of cases in the family+ve group were

male, compared to 14.3% in the family-ve (p< 0.01, Fisher's exact). AITD diagnosis was established earlier in the family+ve (35.77±19 years) compared to the family-ve group (47.72±15 years) (p< 0.001, Mann-Whitney). 37.9% of familial cases had concomitant subclinical hypothyroidism at AITD diagnosis compared to 51.2% of family-ve, p< 0.05).

Conclusions: Positive anti-Tg antibodies are more frequently found in non-familial cases of AITD and their mean levels are significantly higher. These differences don't seem to apply in the case of anti-TPO antibodies. This differentiation, may possibly represent an increased effect of environmental factors in the development of anti-Tg antibodies; genetic and environmental factors are probably contributing equally in the case of anti-TPO antibodies. In familial cases, AITD is diagnosed at an earlier age (probably due to increased patient awareness).

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P78

SHORT-TERM COMBINED TREATMENT WITH L-THYROXINE PLUS L-TRIIODOTHYRONINE (LT4 PLUS LT3) DROPS IN PATIENTS WITH PERSISTENT HYPOTHYROIDISM AND MALABSORPTION DURING REPLACEMENT THERAPY WITH L-T4

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The objective of our study was to evaluate the potential benefit of short-term combined treatment with LT4plusLT3 in patients with persistent hypothyroidism and malabsorption during replacement therapy with LT4. We report 10 cases of patients with hypothyroidism secondary to total thyroidectomy in which high doses of LT4 (2,7-3.5 mcg/kg/die) were not adequate to normalize thyroid function. TSH was persistently high with low serum levels of thyroid hormones. All of the patients presented symptoms of hypothyroidism and did not have history of drugs interfering with gastric function or history of previous gastric surgery, psychiatric or pituitary disorders, cirrhosis, chronic renal insufficiency and/or alcohol abuse. Serological tests, such as anti-endomysium, anti-tissue transglutaminase and parietal cell antibodies, and lactose hydrogen breath tests, were performed in all of the patients. Gastric endoscopy was also necessary in some of the patients. An Helicobacter pylori infection was found in 4 of the patients. One patient presented a gastroesophageal reflux associated with congestive gastropathy, whereas lactose intolerance was found to be responsible for the malabsorption in 2 patients. In 3 of the patients the cause of malabsorption was not identified. Combined therapy with LT4-LT3 was started in all of the patients to improve the severity of hypothyroidism. This combined treatment was able to normalize serum TSH, improving the symptoms of hypothyroidism in all of the cases in about 2 weeks. TSH values progressively normalized and LT3 administration was withdrawn. Specific treatment for the causes responsible for malabsorption was contemporarily performed, and we were able to shift the treatment to LT4 tablets. Our results support the potential benefit of combined treatment with LT4-LT3 in patients with persistent hypothyroidism due to malabsorption. This treatment improves symptoms rapidly and reduces the negative effects of thyroid hormone deficiency at tissue level, while waiting for the effects of specific treatment for malabsorption

P79

INTERLEUKIN 1 BETA (IL-1 BETA) GENE POLYMORPHISMS (SNP-511 AND SNP+3953) IN HASHIMOTO´S THYROIDITIS AMONG THE POLISH POPULATION

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Objective: The role of IL-1 beta in the pathogenesis of Hashimoto´s thyroiditis (HT) is well confirmed, but the association of IL-1 beta gene polymorphisms with susceptibility and/or course of this disease is still unclear.

Aim: This study presents the association between IL-1 beta gene polymorphisms (SNP-511 and SNP+3953) and susceptibility to the development of Hashimoto´s thyroiditis among the Caucasian-Polish population.

Patients and Methods: The group studied comprised of 115 unrelated patients withHT. All patients were euthyroid on thyroid replacement therapy, and all patients had extremely high serum anti-TPO levels. The control group consisted of 103 healthy blood donors without raised anti-TPO antibodies in whom a personal and a family history of thyroid and autoimmune as well as inflammatory diseases was excluded. No goiter or thyroid dysfunction was found.

Two polymorphisms of the IL-1 beta gene (C-511T and C+3953T) were studied by PCR-RFLP analysis. To confirm the accuracy of the method employed, randomly selected patients were analyzed bi direct sequencing.

Results: Significant statistical differences between the frequency of C allele and T allele for both SNPs in the studied group and in the controls were found (p=0.008). The frequencies of the genotype of C-511C compared to C-511T and T-511T as well as C+3953C compared to C+3953T and T+3953T were statistically significant (p=0.0190; OR=2.210 and p=0.0129, OR=2.338, respectively).

Conclusion: An association was found between the SNPs of IL-1 beta gene and susceptibility to the development of Hashimoto´s thyroiditis in the group studied.

P80

IMPAIRED L-THYROXINE (L-T4) ABSORPTION AFTER INGESTION OF LARGE AMOUNTS OF PAPAYA FRUIT

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We observed biochemical evidence of hypothyroidism (TSH: 25 mU/l) in 37 yrs old man, stably euthyroid (TSH 1.2-1.9 mU/l in the last 5 years) on L-T4 (1.6 µg/Kg/day) after total thyroidectomy for goiter. He assumed L-T4 under fasting condition and denied use of other drugs or reduced compliance. No malabsorption symptoms were reported. Hypothyroidism was documented 7 days after 2 week holidays in a Caribbean country, where the patient reported regular assumption of the same L-T4 preparation, no symptoms of gastroenteric disease or significant dietary changes, with the exception of large intake of papaya (5-6 fruits/day). After 45 days without ingestion of papaya, serum TSH normalized (1.4 mU/l) without any change in L-T4 dose. We therefore asked the patient to eat papaya fruits as during his holidays, without changing L-T4 therapy. Serum TSH, FT4, FT3 and TBG were measured before and after 7 - 14 days of papaya fruit intake. Marked TSH elevation and FT4 reduction, minor FT3 decrease and no change in TBG were observed (Table). Forty days after interruption of papaya fruit intake, TSH and FT4 returned into the normal range (1.0 mU/l and 16.2 pmol/l, respectively).

Days	TSH (mU/l)	FT4 (pmol/l)	FT3 (pg/ml)	TBG (μ/ml)
Day 0 (before papaya)	0.8	16.6	2.9	16.0
Day 7 of papaya intake	1.1	15.9	2.1	17.0
Day 14 of papaya intake	15.0	7.7	2.1	17.0

Papaya has never been reported to interfere with absorption of L-T4. Although the evidence obtained in this patient is compelling, further studies on larger groups of hypothyroid patients are needed to confirm whether papaya fruit should be included in the list of food to be avoided by patients on L-T4 therapy.

P81

PREVALENCE OF THYROID DISEASE IN A POPULATION-BASED SURVEY IN TURKEY: TURDEP-II

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Objectives: The aim is to determine serum TSH, free-T4 (f-T4) and antithyroperoxidase (TPOAb) antibodies from a population-based sample of 26,499 people (63% female, response rate 89%) aged 20 yr and older representing the geographic, age and sex distribution of the Turkish population and provide a database for the prevalence of thyroid disease in Turkey.

Methods: Data derived from the recently completed 'The Second Turkish Diabetes, Hypertension, Obesity and Endocrine Disease Epidemiology Survey (TURDEP-II). Mean concentrations of TSH, f-T4 and TPOAb were determined for the 25,124 people who did not report any thyroid disease, or thyroid medications (disease-free population). We also selected a reference population of 22,190 people from the disease-free population by further excluding those cases with current pregnancy, taking medications such as androgens or estrogens, who had high levels of TPOAb, or subclinical hypothyroidism or subclinical hyperthyroidism.

Results: Clinical hyperthyroidism was found in 0.4% (0.6% female and 0.2% male, 0.4% urban and 0.5% rural) and hypothyroidism in 1.1% (1.4% female and 0.5% male, 1.1% urban and 1% rural) of the Turkish population. Subclinical hyperthyroidism was found in 0.5% (0.6% female and 0.4% male), and subclinical hypothyroidism was found in 3.4% (4.2% female and 2.2% male) of the population. The most prevalent thyroid disease among Turkish population was autoimmune thyroiditis and it was found in 10% of the population (12.2% female and 6.1% male, 10.3% urban and 9.8% rural). For the disease-free population, mean serum TSH and FT4 were 2.10 (median 1.55; 25-75 percentiles, 1.02-2.31 mIU/L) and 15.60 (median 15.42; 25-75 percentile 13.90-17.04 pmol/L) respectively.

Conclusion: A large proportion of the Turkish population appeared unaware of having laboratory evidence of thyroid disease, which favors of screening for early detection particularly in the female population.

P82

HEMATOLOGIC ABNORMALITIES IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM: CHARACTER AND RELATIONSHIP TO LEVOTHYROXINE TREATMENT

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Objectives: Subclinical hypothyroidism (SH) can be associated with iron deficiency and hematology abnormalities but no consensus has been reached about their significance and response to levothyroxine treatment. The aim of this study was to assess character and evolution of hematologic disorders in SH patients with regard to levothyroxine therapy.

Methods: Two phase study; in the first phase, we studied hemoglobin, ferritin, serum iron levels, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) etc in 96 women aged 20-50. 36 of them were euthyroid (controls), 60 had new, untreated primary SH (TSH 7,0±3,41 U/L). In the second phase, 49 SH patients were followed for a period of 1 year and reinvestigated. Among them, 14 had no levothyroxine treatment (group 1) and 35 received replacement therapy (group 2).

Results: Compared to controls, SH patients presented lower hemoglobin (p=0.005), MCV (p=0.022), MCH (p=0.001), ferritin levels (p=0.021) and higher anemia prevalence (28.3% vs 11.1%, p=0.039), both microcytic (p=0.035) and normocytic (p=0.12). By follow up, group 1 demonstrated decrease in ferritin (p=0.011) whereas anemia prevalence became greater (p=0.016). On the contrary, group 2 developed slight increase in ferritin (p=0.23) and decrease in microcytic anemia prevalence (p=0.001); ferritin increase negatively correlated with body mass index (p=0.003), age (p=0.09), starting MCV (p=0.037), MCH (p=0.049) and ferritin (R=-0.50, p=0.0004).

Conclusions: SH is associated with iron deficiency, microcytosis and anemia which can progress if not treated. The efficacy of levothyroxine regarding hematologic abnormalities can be negatively affected by obesity and age whilst is greater in patients with more severe preexisting iron deficiency and microcytosis.

P83

SCREENING FOR UNDIAGNOSED HYPOTHYROIDISM IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN ARMENIA

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Objectives: Hypothyroidism is often under-diagnosed due to the lack of symtoms and increases the risk of lipid disturbances and neuropathic complications of diabetes mellitus (DM). Chronic autoimmune thyroiditis is frequently associated with type 1DM in children. Approximately 30% of children with type 1DM have thyroid autoantibodies, and approximately 10-20% have elevated serum TSH levels worldwide. Current study is a pilot epidemiological screening study to investigate prevalence of hypothyroidism in type 1 DM children and adolescents in Armenia.

M**aterials and Methods:** There are 326 type 1 DM patients under 18 years of age registered in Armenia in 2010. From 2009 to 2011, 224 type 1DM patients, age under 18 years old, with unknown thyroid status were enrolled in the study for clinical evaluation of hypothyroidism, for assessment of HbA1c, TSH, freeT4, Anti-TPO levels and for thyroid ultrasonography. Hypothyroid patients were defined by TSH >4,0mU/l, including subclinical hypothyroidism.

Results: Out of 224 investigated children 47 (20,9%) were found to have hypothyroidism, including subclinical hypothyroidism, and 27 (12,0%) had high Anti-TPO levels with or without TSH elevation. Elevated HbA1c was observed in 9,3% of hypothyroid patients versus 9,4% in euthyroid patients (p>0,05). 28,6% of investigated patients with associated hypothyroidism had ultrasonographic appearance of hypoplasia or atrophy of thyroid gland. Majority (71,2%) of these patients were in pubertal and post pubertal age (10-18years), and only 28,8% were under 9 years of age.

Conclusion: Prevalence of undiagnosed hypothyroidism in diabetic children and adolescents in Armenia is 20,9%. Physicians should anticipate the possibility of hypothyroidism in patients with type 1DM by examination of the thyroid gland and serum TSH levels at the onset of DM and yearly thereafter. While hypothyroidism was significantly associated with type 1DM, poor diabetes control did not seem to predispose to hypothyroidism and was not associated with severety of the disease.

P84

IS FREQUENCY OF ETIOLOGIES AND INCIDENCE OF CONGENITAL HYPOTHYROIDISM CHANGING?

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Background: The world-wide incidence of Congenital Hypothyroidism (CH) is 1:3,500 - 4,000 live births. Thyroid dysgenesis is considered the most common etiology of CH.

Objective: To determine the incidence and etiology of CH in children born between 1997 and 2007 in the northeast region of São Paulo State-Brazil and detected by Neonatal Screening Program (NSP).

Methods: All infants with blood spot TSH value ≥10 mIU/L (AutoDELFIA) were evaluated for diagnostic confirmation by serum TSH measurement. If serum TSH ≥10mIU/L, 99mTc thyroid scintigraphy was performed and the treatment with thyroxine was started. After 3 years of age, children with topic thyroid were reevaluated with 131I thyroid scintigraphy and TRH test after withdraw thyroxine for 4-6 weeks.

Results: Between 1997 and 2007, 247,168 newborns were screened by NSP. 139 presented neonatal TSH ≥10mIU/L and confirmatory TSH ≥5mIU/L. After reevaluation, 64 (46%) had the diagnosis of definitive CH confirmed (29 (45.3%) with thyroid dysgenesis and 35 (54.7%) with dyshormonogenesis); 52 (37.4%) normalized thyroid function (transient hypothyroidism); 1 patient was diagnosed with Thyroid Hormone Resistance; 6 newborns died and 9 were lost to follow-up. Seven patients remained with basal serum TSH between 5-10mIU/L and had normal response to TRH test (hyperthyrotropinemia). The annual incidence of CH per 10,000 live births was: 1997=4.2; 1998=1.8; 1999=1.7; 2000=1.8; 2001=1.9; 2002=1.9; 2003=2.1; 2004=4.0; 2005=3.6; 2006=2.1; 2007=2.4 (overall incidence = 1:3,862).

Conclusions: Using a neonatal TSH cut-off of ≥10mIU/L, the overall incidence rate of CH in the northeast region of São Paulo State-Brazil in the period 1997-2007 did not increase. Instead of dysgenesis, dyshormonogenesis was the most frequent etiology of CH using a neonatal TSH cut-off of ≥10mIU/L. This observation is similar of recent studies conducted in Japan and Italy.

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SUBCLINICAL HYPOTHYROIDISM AND THE RISK OF CORONARY HEART DISEASE

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Introduction: Subclinical thyroid disease is defined by an abnormally high (subclinical hypothyroidism-SH) or low (subclinical hyperthyroidism) serum thyrotropin (TSH) with peripheral thyroid hormone concentrations whit in the laboratory reference ranges. SH is common especially in elderly women. SH does result in small increase in low density lipoprotein cholesterol and a decrease in high density lipoprotein, changes that enhance the risk for developement of atherosclerosis and coronary artery disease. These changes are reversible when euthyroidism is restored.

Objective: To assess the risks of coronary heart disease (CHD) for adults with subclinical hypothyroidism.

Methods: We examined 30 patients with SH and 20 healthy controls. SH was defined as a TSH level of 4.5 to 19.9 mIU/L with normal thyroxine concentrations. In all the participants we determined body mass index (BMI), blood pressure, TSH, FT4, antibodies to thyroid peroxidase, antibodies to thyroglobulin, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglicerides, total cholesterol/HDL cholesterol ratio and LDL/HDL cholesterol ratio.

Results: Mean BMI in patients with SH was significantly higher ($p < 0.05$), as well as diastolic blood pressure ($p < 0.01$) compared with the controls. Average levels of total cholesterol (5.70±0.62 vs 5.06±0.19 mmol/l, $p < 0.01$) and triglycerides (3,2±0.56 vs 1.89±0.24 mmol/l, $p < 0.05$) were also significantly higher in the group with SH. Individual analysis revealed that the percentage of patients with SH having borderline elevated total cholesterol (63.33%), hypertrigliceridemia (47.33%) and elevated total cholesterol/HDL cholesterol ratio (34.67%) were significantly higher than the percentage in the controls.

Conclusion: SH was associated with higher BMI, diastolic hypertension, higher total cholesterol and triglicerides levels and higher total cholesterol/HDL cholesterols ratio. This might increase the risk of accelerated arteriosclerosis in patients with SH, particularly in those with a TSH concentration of 10 mIU/L or greater.

P86

RISK FACTORS FOR THE DEVELOPMENT OF HYPOTHYROIDISM AFTER RADIOIODINE THERAPY OF FUNCTIONAL THYROID AUTONOMY

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Objective: Determination of the risk factors for hypothyroidism after radioiodine therapy (RIT) of functional thyroid autonomy (FA).

Methods: 100 patients with various clinical variants of FA subjected to RIT were included in the study. Demographic and clinical profile of patients was as follows: females - 63, males - 37, median age 65.5. years old (54; 72.5 years old, 1st and 3rd quartiles); 33 patients had a family history of thyroid diseases; 50 patients (50%) were taking Carbimazole (45 patients) or Methimazole (5 patients) as antithyroid drugs (ATD) in a dose of 10 mg (5; 10, 1st and 3rd quartiles) commonly withdrawn 2 days before RIT. 9 elderly and multimorbid patients continued ATD therapy after RIT. The therapeutic activity of ^{131}I was calculated using Marinelli' formula; the target dose for unifocal and bifocal autonomy was 400 Gy, and 150 Gy for the thyroid for multifocal and disseminated autonomy. A 24-hour radioiodine test was done 2-3 days prior to RIT to estimate thyroid uptake. The activity of ^{131}I ranged from 4.08 to 58.89 mCi.

Results: 4 months (4; 5, 1st and 3rd quartiles) after RIT, euthyroidism was registered in 67% of patients, hypothyroidism in 28% patients, relapse of hyperthyroidism in 5%. Patients' gender, age, body mass index, severity of hyperthyroidism, ATD before and after RIT, initial thyroid volume, applied activity of ^{131}I/initial thyroid volume, TSH, fT3 and fT4 levels, ^{131}I-uptake and family history were considered as possible predictors of hypothyroidism in a multivariate analysis. As a result, the only independent factors appeared to be male gender (p=0.03), increasing radiation dose for the thyroid (p=0.01) and ATD before RIT (p=0.06).

Conclusion: Male gender, increasing radiation dose for the thyroid and antithyroid medication should be considered for both planning RIT of FA, and for monitoring the thyroid status within 4-6 months after treatment.

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CHARACTERISTICS OF CELLULAR PART OF IMMUNE RESPONSE IN POSTMENOPAUSAL WOMEN WITH AUTOIMMUNE THYREOIDITIS

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Menopausal period is characterized by the age involution of the thymus, which leads to a reduction in the activity of cellular immunity, namely its violation underlie the pathogenesis of autoimmune thyroiditis (AIT).

Aim: Concretize the particularities of cellular part of the immune response in postmenopausal women with AIT.

Materials and Methods: Investigated immunophenotype of lymphocytes (CD3+, CD4+, CD8+, CD16+, CD21+) and the activity of pro-and anti-inflammatory cytokines (IL-1β, IL-4) in women with AIT in their menopausal (51,7±0,57 years, n=25) and reproductive (31,8±0,59 years, n=25) periods. The control group consisted of women without thyroid pathology in the same ages.

Results: Women with AIT´s state of cellular immunity was characterized by decreasing CD8+, more marked in postmenopause than in reproduction (26,3±0,87 vs. 27,6±1,27). In addition, postmenopause was characterized by significantly lower levels of CD3+ (66,5±1,7 vs. 72,2±1,65%, P< 0,02) and CD4+ (39,7±1,9 vs. 44,6±1,4%, P< 0,05); Levels CD21+ were 10,7% lower (12,5±0,7 vs. 14,1±0,53%), but NK-cells levels were 10% higher (18,6±0,75 vs. 16,9±0,85%). As a result, postmenopausal women had lower immunoregulatory indecises: CD4/CD8 (1,6±0,11 vs. 1,7±0,13), CD4/CD16 (1,9±1,7 vs. 2,7±0,15), and especially CD8/CD16 (13±0,05 vs. 1,6±0,12, P< 0,02).The levels of IL-1β and IL-4 in postmenopause did not differ significantly from the control groups. At the same time in reproduction they were significantly higher with AIT than in control (P< 0,01 and P< 0,05, respectively) and than in postmenopausal women with AIT´s (P< 0,02 and P< 0,05).

Conclusions: Thus, in postmenopausal women with AIT develop a more pronounced immunodeficiency of cytotoxic-suppressive type than in reproduction. They also experience the increased activity of natural killer cells that causes the disruption of the relationship between the individual clusters of lymphocytes. Cytokine activation of Th-1 and Th-2 lymphocyte pools is also less pronounced in postmenopausal women with AIT.

PO9 Cytology

P88

SHOULD WE ASSESS ALL THYROID NODULES BY FINE NEEDLE ASPIRATION BIOPSY FOR THE DIAGNOSIS OF THYROID CANCER? AND IS BRAF MUTATION ANALYSIS HELPFUL?

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Currently published guidelines indicate that fine needle aspiration biopsy (FNAB) should be performed only in thyroid nodules with clinical and/or ultrasonographic (US) characteristics suspected for malignancy. We and others already demonstrated that BRAF mutation analysis significantly increases cytology accuracy for the diagnosis of papillary thyroid carcinoma (PTC). We here investigate whether performing FNAB also in thyroid nodules without clinical and/or US characteristics of malignancy might be useful to increase the diagnostic accuracy for thyroid cancer and whether BRAF analysis may further enhance this parameter. We examined 1856 patients (1436 males and 420 females; age 52 ± 0,32) undergoing thyroid US at the Section of Endocrinology of the University of Ferrara, due to thyroid nodules. A total of 2421 nodules (diameter ≥ 4 mm) were detected and divided in "suspected" (S= 829) and "non suspected" (NS=1529) according to the current guidelines. The 2421 FNAB samples were examined by cytology and BRAF mutation analysis. Cytology was consistent with malignancy in 13.9% of S nodules and in 6.5% of NS nodules, mostly PTC at final histology. By adding BRAF mutation analysis, diagnostic sensitivity significantly increased in both groups by ~15%. In particular, sensitivity was greater for S nodules with indeterminate cytology, 20% of which displayed BRAF mutation. Therefore our data demonstrate that even nodules not displaying clinical and/or US characteristics of malignancy should undergo FNAB and that BRAF mutation analysis increases diagnostic sensitivity for PTC also in this group.

P89

THE USE OF SET OF GENETIC MARKERS HELP TO DISCRIMINATE BENIGN AND MALIGNANT THYROID NODULES WITH A FINE NEEDLE ASPIRATION PATTERN OF FOLLICULAR PROLIFERATION IN AN AREA OF BORDERLINE IODINE DEFICIENCY

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To evaluate a set of 6 marker genes (TG, LGALS3, ADM3,TFF3, HGD1 and PLAB), and to investigate their diagnostic potential to distinguish thyroid nodules with microfollicular pattern of growth. Ultrasound-guided fine-needle aspiration citology was performed for patients with thyroid nodules. One hundred and fifty-three thyroid samples obtained from 151 consecutive patients. FNA samples were collected and total RNA extraction was performed. To determine differences in mRNA expression of the 6 genes in the series of 56 benign thyroid nodules and 43 malignant thyroid nodules the median of each gene expression was evaluated. To perform a prediction of malignancy of the 54 microfollicular thyroid nodules, we adopted PART algorithm. All cDNA samples were also analyzed for V600E BRAF mutation. The expression of all genes was demonstrated in all 153 specimens. A significant decrease in TFF3 and HGD1 expression was observed in malignant thyroid nodules with respect to benign thyroid nodules, while an increase in PLAB expression was demonstrated in malignant thyroid nodule. Our results of the decision model of the three genes expression profile obtained at fine needle aspiration of the 54 aspirates of nodules with follicular pattern of growth was valid for 37 of 54 cases (68.5%), with a total of 8 False Positive (14.8 %) and 9 Negative predictions (16.6 %), with a Sensitivity of 43.7%, and a Specificity of 78.9%. The mutated form V600E of BRAF gene in the heterozygous state was demonstrated by direct sequencing in 19/43 (44%) malignant thyroid nodules, in 0/56 benign thyroid nodules and in only 1/54 (1.8 %) microfollicular thyroid nodules. The gene expression profiles of three genes (TFF3, HGD1 and PLAB) allowed a good prediction for the differentiation of benign thyroid lesions and thyroid cancer starting from cells of fine needle aspiration of thyroid nodules with a follicular pattern of growth.

P90

CLASS III β-TUBULIN EXPRESSION IN PAPILLARY THYROID CARCINOMA: AN IMMUNOHISTOCHEMICAL ASSESSMENT

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Objectives: Tubulin, the major component of microtubules, is a multifunctional protein involved in many essential cellular roles, including cell movement, intracellular transport and mitosis.

Class III β-tubulin (TUBB3) is expressed in neural tissue and in neuroendocrine cell and also in several human malignancies, including ovary, breast, prostate, and non small cell lung carcinomas. Overexpression of TUBB3 in these tumours is associated with an unfavourable outcome and resistance to taxane-based therapies. In thyroid tissue, TUBB3 immunostaining remains relatively uncharacterised.

The aim of the current study was to test TUBB3 protein expression in various thyroid neoplasms in an attempt to clarify the relationship between TUBB3 expression and tumor type.

Methods: The study included 20 papillary thyroid carcinoma (PTC), 7 follicular adenoma and 5 nodular hyperplasia. The normal thyroid tissue was also evaluated. Immunohistochemical analysis was performed using a monoclonal antibody (Covance, Princeton, NJ).

Results: In the normal thyroid, TUBB3 immunoreactivity was detected both in the nerve fibres and C-cells, but not in the follicular epithelium. Moreover, no positivity was observed in nodular goiter and follicular ade-

noma. In PTC samples, the reactivity was heterogeneous and demonstrated strong cytoplasmic staining in widely infiltrating PTC associated with fibrous stroma, particularly at the invasive front of tumour, or in moderately differentiated PTC with loss of cellular polarity/cohesiveness.

In contrast, the encapsulated variant PTC or PTC with well developed papilla or follicles were constantly negative.

Conclusions: We report for the first time TUBB3 expression in thyroid tissue.

In analogy with various carcinomas of other sites, TUBB3 expression appears to be increased in PTC with "aggressive" histological features, thus suggesting a possible role of this cytoskeleton protein in the invasive activity and metastatic potential of cancer cells.

Further investigations are needed to determine whether our findings may have clinical implications.

P91

THE ROLE OF IMMUNOHISTOCHEMISTRY FOR THYROID PEROXIDASE, GALECTIN-3, CYTOKERATIN-19 AND HBME1 IN THE DIFFERENTIAL DIAGNOSIS OF THYROID TUMORS

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The distinction between diverse types of follicular thyroid neoplasms remains a difficult task in the histological diagnosis and is critical for the post surgical management and follow-up of patients. Various antibody panels have been recommended for the diagnosis of thyroid cancer, with no overall consensus about their usefulness.

We evaluated immunohistochemical expression of proposed molecular markers: thyroid peroxidase (TPO), galectin-3 (gal-3), Hector Battifora mesothelial antigen-I (HBME-1) and cytokeratin-19 (CK19), and their combination in a total of 242 archival thyroid tissue sections. The 242 samples comprised of 28 conventional follicular adenomas (FTA), 14 Hürthle cell adenomas, 18 follicular carcinomas (FTC), 35 Hürthle cell carcinomas (HTC) and 147 papillary carcinomas (PTC). Using multiple statistical tests, all obtained data were analyzed in detail for diagnostic purposes.

Expression of each individual marker was most helpful for the diagnosis of PTC and its follicular variant. The diagnostic accuracy of these markers is rather limited with regard to follicular thyroid tumors belonging to other classes. Namely, none of them has proved sensitive and specific enough to discriminate HTA from HTC, while gal-3 and HBME-1 could be used as single discriminators that indicate FTC but, HBME-1 is significantly better choice.

All analyzed markers TPO, gal-3, HBME-1 and CK19 proved to be useful tools to identify differentiate thyroid carcinomas with diagnostic accuracy of 82.2%, 80.2%, 78.6% and 68.5% respectively. The diagnostic accuracy was improved by using combinations of some proposed markers. Only two antigens, TPO and HBME-1, have distinct predictive value for different diagnostic alternatives i.e. their sequential combination improve diagnostic accuracy between overall benign and malignant thyroid tumors to 89.1% and also between FTA and fv-PTC to 92.6%.

Conclusion: Individual antibodies or a panel of only two antibodies combined with histopathological analysis could be useful in the differential diagnosis between benign and malignant well-differentiated thyroid tumors.

P92

DIAGNOSTIC ACCURACY OF FINE NEEDLE ASPIRATION BIOPSY CYTOLOGY AND ULTRASONOGRAPHY IN PATIENTS WITH THYROID NODULES DIAGNOSED AS BENIGN OR INDETERMINATE BEFORE THYROIDECTOMY

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Introduction: Fine-needle aspiration biopsy cytology (FNABC) and ultrasonography (US) play an important role in differentiating benign thyroid nodules from malignant nodules, however, accurate preoperative diagnosis of follicular thyroid carcinoma is difficult even when both of these diagnostic modalities are used. We retrospectively investigated diagnostic accuracy of FNABC and US in patients with thyroid nodules diagnosed as benign or indeterminate before thyroidectomy.

Patients and Methods: Between 2007 and 2008, 3333 patients underwent thyroidectomy at our institution, and the 995 of them who had thyroid nodule that had been diagnosed as benign or indeterminate preoperatively were the subjects in this study. The FNABC findings were classified as benign or indeterminate and the US findings as adenomatous goiter (AG) or follicular tumor (FT). The final postoperative diagnosis was made histologically, and concomitant incidental micropapillary carcinomas were not included in the final diagnosis.

Results: The postoperative histological diagnosis was AG in 630, follicular adenoma in 234, follicular carcinoma in 109 (widely invasive follicular carcinoma in 19), and other thyroid disease in 24. The final diagnosis was thyroid cancer in 77 (9.3%) of the 830 patients with preoperative diagnosis of AG and 51 patients of the 168 patients with diagnosis of FT by US, and the sensitivity and specificity of US were 86.6% and 40.2%, respectively. The final diagnosis was thyroid cancer in 42 (8.3%) of the 505 patients with a preoperative diagnosis as benign and in 75 (32.2%) of the 233 patients with preoperative diagnosis as indeterminate by FNABC, and the sensitivity and specificity of FNABC were 86.3% and 55.2%, respectively.

Conclusion: FNABC has been the mainstay for the diagnosis of thyroid nodule. However, the results of this study showed that US can also be a useful tool for the diagnosis of thyroid nodule.

P93

NEW CLASSIFICATION OF THE THYROID FNAB RESULTS - THE IMPACT ON FREQUENCY OF PARTICULAR DIAGNOSES FROM FOLLICULAR LESIONS IN POSTENDEMIC AREA

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Objectives: Fine-needle aspiration biopsy (FNAB) is limited by poor distinguishing between follicular lesions, among which hyperplastic nodules and follicular adenomas dominate in postendemic areas. Aspirates from follicular lesions usually show monotonous population of thyroid follicular cells (tfc) arranged in three-dimensional groups including microfollicles and decreased or absent colloid. The aim of the study was to assess the influence of the application of new classification of the thyroid cytological outcomes in postendemic area in respect to lesions from which monomorphic tfc (comprising oxyphillic cells) were aspirated.

Methods: Analysis included cytological outcomes, where monomorphic tfc dominated in aspirates, formulated in 2 periods: year 2009 and between May 2010 and February 2011. In the later period new classification of thyroid FNAB outcomes was used that was based on National Cancer Institute (NCI) classification, concordant with European Thyroid Association recommendations. The difference from NCI classification was in the exclusion of cases with low cellularity from „follicular lesion of undetermined significance" subgroup.

Results: It was found that in both examined periods incidence of aspirates with monomorphic tfc was similar: 4.5% and 4.4% respectively. The introduction of new FNAB classification caused significant ($p< 0.0001$) decrease in number of outcomes without diagnostic conclusion.

Cytological results 2009	No/%	Cytological results V 2010 – II 2011	No/%
Monomorphic tfc without conclusion	168/72.1%	Monomorphic tfc without conclusion - usually low cellularity smears	66/30.4%
Benign follicular nodule	10/4.3%	Benign follicular nodule	4/1.8%
Follicular neoplasm probably benign	6/2.6%	Follicular lesion of undetermined significance	106/48.9%
Follicular neoplasm	21/9.0%	Suspicious for a follicular neoplasm	21/9.7%
Follicular neoplasm Hürthle cell type probably benign	0/0.0%	Follicular lesion of undetermined significance Hürthle cell type	3/1.4%
Follicular neoplasm Hürthle cell type	28/12.0%	Suspicious for a follicular neoplasm Hürthle cell type	17/7.8%
Number of follicular lesions	233/100.0%	Number of follicular lesions	217/100.0%

Conclusions: In postendemic areas introduction of the subcategory of „follicular lesion of undetermined significance" significantly decreases the percentage of FNAB outcomes without diagnostic conclusion.

P94

IN FINE NEEDLE CYTOLOGY SPECIMENS CLASSIFIED THY 4, NUCLEAR INCLUSIONS HAVE A HIGH PREDICTIVE VALUE FOR THYROID CANCER

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Introduction: Fine needle cytology aspirates (FNA) classified THY4 include a heterogeneous group of lesions suspicious for malignancy (Papillary Thyroid Cancer, PTC), which in the literature is reported to be confirmed after surgery in 20-80% of cases.

Patients and Methods: We retrospectively analyzed 74 thyroid nodules, all classified THY4 at FNA and with available subsequent histological diagnosis. THY4 class assignation was based on the presence of nuclear inclusions (ICI), atypical signs of cells' morphology and/or hypercellular trabeculae in the absence of papillae. Two subgroups were identified: group 1 (37 nodules) showing either ICI alone (group1A, n=21) or ICI associated to trabeculae and cellular atypia (group 1B, n=16); group 2 (37 nodules) showing trabeculae and atypia but without ICI.

Results:

Histological diagnosis	Group 1A	Group 1B	Group 2
PTC	19(90.4%)	16(100.0%)	18(48.6%)
HTA	1(4.8%)		
Benign	1(4.8%)		19(51.4%)

PTC was detected at histology in 53/74 patients classified THY4 (71.6%) while 20/74 (27.0%) were benign nodules and 1/74 (1.4%) had a diagnosis of Hyalinizing Trabecular Adenoma (HTA), a borderline for malignancy lesion, characterised by the presence of ICI in the absence of papillae. Malignancy occurred in 35/37 (94.6%) in group 1 and in 18/37 (48.6%) in group 2.

Conclusions: Our data suggest that the presence of ICI, associated or not with other suspicious aspects (trabeculae, atypia), in THY4 class is the most specific finding indicating a high risk of PTC. ICI presence has a Positive Predictive Value (PPV) for PTC of 97.2% with a sensitivity of 66.0% and a specificity of 95.0%. In presence of only ICI, a similar PPV (95.0%) and specificity (95.0%) have been obtained, with a decreased sensitivity (51.3%). When THY4 FNA doesn't show ICI, the PPV is only 48.6%. Therefore, in THY4 lesions surgery is mandatory because of the high risk for PTC but the PPV ranges from 48.6% (ICI negative) to 97.2% (ICI positive).

P95

GENOME-WIDE MICRORNA ANALYSIS PERFORMED ON SINGLE IN VIVO FINE-NEEDLE ASPIRATES FROM SOLID COLD THYROID NODULES: A PROSPECTIVE TRANSLATIONAL STUDY

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Objective: Preoperative classification of cold thyroid nodules is uncertain and molecular profiling may improve selection and reduce superfluous surgery. We aim to generate a diagnostic classification model based on microRNA (miRNA) expressions from single *in vivo* fine-needle aspirates (FNA) in a prospective translational study.

Methods: FNA-specimens were collected in an outpatient clinic from patients with a solid cold thyroid nodule, undergoing US guided examination including FNA for cytopathological examinations. If patients agreed to participate in the study, an additional FNA was obtained, washed out in an RNA preserving media (1), and shipped to an array core unit for RNA extraction and miRNA microarray analysis. 100ng of total RNA was labeled and hybridized to the Exiqon v.11.0 microRNA Array, containing probes for 841 human miRNAs. Data from scanned images was pre-processed by the LIMMA package of the Bioconductor project and normalized using quantile normalization method.

Results: 184 patients were included in the study. Based on RNA yield and purity, we selected 70 samples on which miRNA microarray analysis was performed.

At present time miRNA expression profiles from each FNA are being correlated to the histopathological diagnose and classification algorithms are tested.

Conclusion: Remaining results are in progress and we look forward to present our final conclusions at the ETA Congress in September 2011.

(1) A simple procedure for routine RNA extraction and miRNA array analyses from a single thyroid in vivo fine needle aspirate. Rossing M et al. Scand J Clin Lab Invest. 2010;70:529-34.

P96

CONTRIBUTION OF ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION CYTOLOGY (UGFNA) TO AMBULATORY SURGICAL MANAGEMENT OF THYROID NODULES – RETROSPECTIVE ANALYSIS OF 132 CONSECUTIVE CASES

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Aims: Contribution of UGFNA in the cohort of patients submitted to partial thyroidectomy at Ambulatory Surgery Unit (2005-2010) and the impact of UGFNA in surgical option for thyroid nodules.

Methods: We studied 132 consecutive patients (17 men) with solitary (75%) or multinodular goitre (25%), submitted to partial thyroidectomy in the outpatient setting. The cohort was characterized for clinical presentation, hormone assay, ultrasonography, UGFN diagnosis, histological diagnosis,post-operative complications and thyroidectomy completeness. Relative UGFNAC

contribution was considered: essential, additional, non-contributory, misleading.

Results: The cohort was characterized: 49.2 ± 14.5 yrs o., mean nodule size 3.9 ± 1.2 cm, compressive symptoms 17% and nodule enlargement 33%. Microcalcifications 6.8%. UGFNAC diagnosis was: benign 71.3% (70 benign colloid goitre, 24 benign cystic goitre), follicular lesions 22.7% (30), suspicious 0.7% (1) and nondiagnostic 5.3% (7). Histological diagnosis was: nodular hyperplasia 54.5% (72), follicular adenoma 25% (33 cases including 3 Hurthle-cell adenoma), follicular carcinoma 9 % (12 cases including 3 Hurthle-cell carcinoma), papillary carcinoma 10.7% (7 PTC, 3 follicular variant and 4 microfoci) and lymphoma MALT 0.75% (1 case). None malignant nodules after UGFNA diagnosis were found (previously excluded for this cohort and send to conventional surgery).

Prevalence of post-operative complications was 6% (2 transitory dysphonia, 2 local hematoma, 1 seroma and 1 recurrent nerve palsy). Thyroidectomy completeness was performed in 24 patients (18.2%). False negative were 9.8% (13 cases: 3 microfoci PTC, 9 PTC and 1 follicular carcinoma). Follicular tumours were: follicular adenoma 50% (15), nodular hyperplasia 16.7% (5), microfoci PTC 3.4% (1) and follicular carcinoma 30% (9).

Conclusions: Contribution of UGFNA in ambulatory surgery of thyroid nodules was: essential 61.4%patients (benign lesions), additional 23.5% patients (follicular tumours), non-contributory 5.3% (specimens inadequate) and misleading 9.8% (false negative). UGFNA has significant impact in surgical option for thyroid nodules. Thyroid ambulatory surgery is safe, accessible and low cost.

P97

DIFFICULTIES IN DIAGNOSIS OF FOLLICULAR TUMORS IN FINE NEEDLE ASPIRATION BIOPSY OF THE THYROID GLAND

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Introduction: Fine Needle Aspiration Biopsy of the thyroid gland is a basic, widely accepted test in the preoperative diagnosis of thyroid nodules. Group IV, the most heterogeneous one in Bethesda cytology classification, is a group of follicular tumors, in which the risk of malignancy is 5-15%. Due to impossibility of differentiation of cancer from follicular adenoma, the majority of these patients are qualified for surgical treatment.

The aim of this study was to analyze histologic results of patients operated due to the presence of follicular tumor and to assess the diagnostic value of FNAB of the thyroid.

Material and Methods: Medical records of 223 patients who underwent operational procedure due to follicular neoplasm in the period of 10 years were analyzed retrospectively. F:M ratio was 9:1, mean age- 51 years. FNAB of the thyroid was assessed by different cytologists, histologic samples were interpreted by the constant group of pathologists.

Results: Among 223 patients who underwent surgical treatment due to thyroid follicular tumors in the postoperative histologic examination the following results were obtained: multinodular goitre-102 (45.7%), follicular adenoma-75 (33.6%), inflammatory goitre 16 (7.17%), thyroid cancer 30 (13.45%). In the group of thyroid cancer results were as folows: papillary carcinoma-18, follicular carcinoma-9, Huertl cells cancer-2, medullary cancer-1.

Conclusions:

1 There is a high ratio of overdiagnosis of follicular tumors in the FNAB that reaches up to 40%.
2) FNAB of the thyroid should be evaluated by at least 2 cytologists to avoid overdiagnosis.
3) Because of its significant influence on the choice of treatment method there is a need to distinguish in the FNAB results the unspecified changes from the follicular tumors.

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FREQUENCY AND INTENSITY OF PAIN OCCURRING DURING AND AFTER FINE NEEDLE ASPIRATION BIOPSY OF THYROID NODULES

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Background: Fine needle aspiration biopsy (FNAB) is a key invasive diagnostic procedure for thyroid nodules.

Objective: To evaluate the frequency and intensity of pain occurring during and after FNAB, despite the use of Eutectic Mixture of Local Anesthetics (EMLA) and to evaluate whether anxiety could explain part of this pain

Method: Single centre prospective study in the setting of a one-stop outpatient clinic for the diagnosis of thyroid nodules. Pain was evaluated using a 10-mm visual analogue scale (VAS) right after the FNAB procedure (VAS1) and 30 minutes after (VAS2). Anxiety symptoms, present on the day of FNAB were assessed after the application of EMLA, using the Spielberger State-Trait Anxiety Inventory form (STAI, form Y-A), a 20-item self-administered questionnaire.

Results: 114 consecutive patients (89 F, 25 M, mean age: 52 yrs) undergoing FNAB of 1 to 3 nodules of 8 to 66 mm were included. A VAS of 1 or greater was present in 51 patients (45%). Among them, the mean VAS1 was 3 (range: 1-6.5) and the mean VAS 2 was 1.6 (range 0-6). A VAS of 3 or above was present in 29 (25%) patients right after the procedure and in 17 (15%) patients 30 minutes after the procedure. An STAI score above 40 was found in 52/58 patients. Pain was correlated with the number of nodules biopsied. No correlation was found between sex, age, nodule size, interval of time between the application of EMLA and the FNAB, the existence of a previous procedure or the STAI score.

Conclusions: FNAB remains a painful procedure in one fourth of the patients, justifying the use of pain killers to prevent pain. Because of the correlation between pain and the number of FNAB, it is not reasonable to aspirate more than 2 nodules during a single procedure.

P99

THYROID ULTRASOUND AND ULTRASOUND GUIDED FNA WITH THYROGLOBULIN DETERMINATION IN THE FOLLOW-UP OF THROID CANCER PATIENTS

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In our institution we routinely perform ultrasound in the follow-up of thyroid cancer patients.

We present the data of the thyroid cancer patients referred for ultrasound from June 2008 to January 2011. During this period 102 patients have undergone a cervical exploration, 66 of which had biochemical data of persisting disease.

In 54 (81%) of the patients with elevated thyroglobulin, the lesion was detected with ultrasound, the size of the lesion varied from 0,4 -2cm. After performing FNA the sample was sent to the pathologist and the wash out fluid was diluted in 1ml of saline and. sent to the laboratory for determination of thyroglobulin levels.

The pathologist confirmed the presence of cancer cells in 41 patients whereas thyroglobulin determination in the fluid wash out was positive in 53 (only one patient had negative thyroglobulin and positive cytology). The thyroglobulin levels in the fluid wash out varied from 27.18 to >92460 ng/ml.

Conclusions: Ultrasound can render better results than other imaging modalities in the follow up of thyroid cancer patients with less costs and no side effects. In our series the determination of thyroglobulin in the fluid wash out allowed us to detect an additional 22% of patients with negative cytological results.

P100

FINE NEEDLE ASPIRATION BIOPSY IN THYROID NODULAR DISEASE – 10 YEARS OF EXPERIENCE IN A MILITARY UNIVERSITY HOSPITAL

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Introduction: Fine needle aspiration biopsy (FNAB) plays an essential role in the evaluation of thyroid nodular disease (TND). It reduces the rate of unnecessary thyroid surgery for patients with benign nodules, and allows the choice of the appropriate surgery. In our department, 2124 FNAB were performed in 10 years. 60% of them are now ultrasound guided (UGFNAB).

Objective: To access the accuracy of FNAB in our hospital.

Methods: Retrospective study of 204 patient's medical files who underwent FNAB and who were submitted to surgery, between 1999 and 2010. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAB (without UG and UG) were examined based on cytohistologic correlation. All statistical evaluation was made using an SPSS software. A p-value < 5% was considered statically significant. Classification of cytological results were adapted from Bethesda system.

Results: Cytological results were benign in 78% of the cases. From the remaining, 8,6% were malignant and 13,4% were follicular neoplasms. Histological results were benign in 86,7% and malignant in 13,3%, being 9,1% papillary carcinomas. After the evaluation of cytohistologic correlation, there were 79,4% of true-negatives, 15,7% of true-positives, 3,4% of false-negatives and 1,5% of false-positives. All the false-negatives (7) correlates with large nodules (6) or with non dominant nodule in histology (not analized by FNAB). The sensitivity was 95,9%, the specificity was 91,4%, the negative predictive value was 82,1% and the positive predictive value was 98,2%. The comparison of FNAB without UG or UGFNAB demonstrates a false predictive value of 64,7% vs 100% and a positive predictive value of 100% vs 88,9% There were no unsatisfactory samples.

Discussion: The results show a good accuracy of FNA in our hospital, with a high sensibility and specificity. Our results are similar to the published data.

P101

HASHIMOTO'S THYROIDITIS AT US: IMAGING-CYTOLOGIC CORRELATION

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Purpose: To evaluate the echotextures of parenchyma or dominant nodule in Hashimoto's thyroiditis (HT) and correlate with their cytologic findings

Materials and Methods: Between June 2009 and March 2010, 22 patients with suspicious HT at US had underwent fine needle aspiration (FNA) using high-resolution US machine at our institute. The FNA was done for thyroid parenchyma or a dominant nodule in 22 patients with suspicious HT. We evaluated the echotexture (strong hypoechoic, hypoechoic, isoechoic or hyperechoic) of thyroid parenchyma or a dominant nodule at US and correlated with their histopathologic findings as follows: lymphocytic, lymphoid or mixed (of lymphocytic and lymphoid type); absence or presence of fibrosis; absence or presence of non-HT.

Results: All 22 patients were made diagnosis of Hashimoto's thyroiditis (HT) after histopathologic examination. Of 27 parenchyma, at US-histopathologic correlation, strong hypoechoic area corresponded to mixed (n=1) or lymphocytic type with fibrosis (n=1), all hypoechoic area to mixed type (n=5) and isoechoic area to mixed (n=3) or lymphocytic type (n=17). In 22 dominant nodules, 17 nodules (77%) were proved to be nodular hyperplasia. Nodular hyperplasia without fibrosis showed isoechoic (n=3) or hyperechoic (n=6) pattern. Nodular hyperplasia with fibrosis showed strong hypoechoic (n=2), hypoechoic (n=2) or isoechoic pattern (n=2). Nodular hyperplasia with lymphocytic infiltration showed hypoechoic pattern (n=2). Of the remaining five nodules (23%), one strong hypoechoic nodule was proven to be a mixed type of HT with fibrosis, three hypoechoic nodules included follicular neoplasm, lymphocytic type of HT with fibrosis or lymphoid type of HT, and a hyperechoic nodule was lymphocytic type of HT.

Conclusion: We think that it will be helpful of making an accurate diagnosis of HT and decision of the candidate for aspiration when the parenchymal pattern will be heterogeneous at thyroid US in a patient with HT.

PO10 Pregnancy

P102

ALTERATIONS IN MILK AND URINARY IODINE VALUES IN EARLY PREGNANCY IN THE ABSENCE OF A SALT IODISATION PROGRAMME

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In the absence of salt iodisation programmes dietary iodine intake has in the main been attributed to dairy milk consumption. In N. European countries milk iodine shows seasonal variation, being higher in winter. This study examines changes over the 20 year period (1988-2007) in both dairy milk iodine and urinary iodine (UI) in 1st trimester (T1) pregnant women. Monthly values for milk iodine showed a similar seasonal variation for 1988 and 2007 being higher during winter months. However there was a significant increase in milk iodine from an annual median value of 122 ug/L in 1988 to 213 ug/L in 2007 which may be attributable to improved dietary supplementation in cattle feed. The increase in milk iodine was not reflected in median UI in T1 pregnant women, which despite showing seasonal variation, summer median 70μg/L; winter 90 μg/L, had a lower annualised median value of 79μg/L in 2007 in comparison to that of 135μg/L in 1988 ($p < 0.01$). These values were also reflected by the percentage of individual values suggestive of iodine deficiency (< 50μg/L) which increased from 20.0 % in 1988 to 29.4 % in 2007. The findings emphasise that despite its common acceptance, increasing dairy milk iodine content alone is not sufficient to correct iodine deficiency at least in T1 pregnant women. The diminished UI in such an at risk group at a time of optimal fetal brain development is a matter of concern particularly where iodised salt availability is limited and dietary habits, such as milk intake, are changing. The findings therefore suggest an urgent need for a more directed form of iodine supplementation in both females of child bearing age and pregnant women.

P103

PROSPECTIVE STUDY OF CLINICAL EVALUATION AND OUTCOME OF PREGNANT WOMEN FOR THYROID DYSFUNCTION

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Background: Thyroid disease during pregnancy has been associated with multiple adverse outcomes. Whether all women should be screened for thyroid disease during pregnancy is controversial.

Objective: The aim of this study was to verify the ability of case-finding or universal screening in detecting thyroid dysfunction during pregnancy.

Methods: 191 pregnant women had clinical evaluation and a serum sample collected for TSH, FT4, Total T4 and antibodies in the first trimester of the pregnancy. The serum samples were analyzed at the end of the pregnancy,

except for the high risk pregnant women identified based on clinical evaluation. All of them had follow-up until delivery.

Results: 40 women were classified as high risk for thyroid dysfunction. Of these, 6 had abnormal results [5 for subclinical hypothyroidism (HypoSC) and 1 for overt hyperthyroidism (Hyper)]. Of the remainder, whose hormonal measurements were performed at the end of pregnancy, other eight pregnant women with thyroid dysfunction were detected [6 with HypoSC and 2 with subclinical hyperthyroidism (HyperSC)]. Over all, HypoSC was detected in 11 women (5.7%). During follow-up pregnancies resulted in 16 abortions, 3 in HypoSC women, 1 in women with Hyper and in 12 women with normal TSH. Eclampsia occured in 3 women and placental abruption in other 2 women, all of these with normal thyroid function. The occurrence of abortion was 8.4% (16/191), 25% of them in pregnant women with thyroid dysfunction. Detection of thyroid dysfunction by clinical data showed a sensitivity of 42.8%, specificity 80.7% and positive predictive value of 15%.

Conclusions: Our data suggest that case-finding was not effective for detection of hypothyroidism in pregnancy and support the introduction of a universal screening for hypothyroidism.

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P104

PREVALANCE OF GESTATIONAL DIABETES MELLITUS IN PATIENTS WITH GESTATIONAL TRANSIENT THYROTOXICOSIS

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Objective: In this study, we aimed to determine prevalence of gestational diabetes mellitus (GDM) in patients with gestational transient thyrotoxicosis (GTT) and investigate the relation between GTT and anthropometric measurements and biochemical parameters

Methods: Fifty two pregnants with GTT (18-42 years old) and 100 healthy pregnants (19-37 years old) were included in the study. Weight, height and body mass index (BMI) were meaured and fasting plasma glucose (FPG), uric acid, LDL-cholestereol, HDL-choloesterol, triglyceride (TG), hemoglobin A1c (HbA1c), thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase antibody (Anti-TPO), anti-thyroglobulin antibody (Anti-Tg), TSH receptor antibody (Trab) were studied in all subjects. Conventional thyroid ultrasonography was performed. After basal and first hour glucose were evaluated with 50 gram oral glucose tolerance test (OGTT) at the 24-28th gestational weeks, all subjects were also evaluated with 100 gram OGTT in the following week.

Results: Mean age of 52 GTT pregnants was 28.46±5.45 and BMI was 21.66±2.92 kg/m^2. Mean age and BMI of 100 healthy pregnants were 26.17±3.75 and 21.12±1.48kg/m^2, respectively. Age, BMI, FPG, TG and uric acid were similar in GTT and healthy pregnants ($p>0.05$). We found significantly higher HbA1c, LDL-cholesterol and HDL-cholesterol in GTT pregnants ($p< 0.001$, $p< 0.001$ and $p=0.034$, respectively). 50 gram OGTT was positive in 14 (26.9%) GTT pregnants and in 10 (10%) healthy pregnants ($p=0.01$). TSH was significantly lower in pregnants with positive 50 gram OGTT compared to pregnants without glucose intolerance ($p=0.001$). Also, pregnants with both positive 50 gram and 100 gram OGTT (n=9) had lower TSH compared to pregnants without glucose intolerance, but the difference was not statistically significant ($p>0.05$).

Conclusion: GTT is a transient abnormality that can be seen in the early periods of pregnancy. However, like other hyperthyroidism states, it seems to have effect on carbohydrate metabolism later in pregnancy.

P105

PERMANENT BUT NOT TRANSIENT SECONDARY HYPOTHYROIDISM IN A NEWBORN OF MOTHER WITH A PAST HISTORY OF GRAVES' DISEASE: TRANSITION FROM HYPER- TO HYPOTHYROIDISM

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Objectives: Graves' disease (GD) in a pregnant woman is a health hazard for the fetus and the newborn. The placenta is permeable for thyroid hormones (TH), antithyroid antibodies, antithyroid drugs and β-blockers. High TRAb levels can be persisted in an active phase of GD, but also after surgery and particularly long-time after radioiodine treatment. TRAb level at the 3rd trimester has a predictive value for the newborn's disease.

Methods: The mother of a male newborn (Hbd 35, birth weight 1930g, Apgar 7) had a history of hyperthyroidism, was treated twice with surgery, 3 and 2 yrs before delivery and received 75 µg of L-thyroxine before and 100 µg during pregnancy.

Results: On 7th day of postnatal life exophthalmos, tachycardia and umbilical haernia were noticed. TH levels [fT4 7.24 ng/ml (N 0.71-1.85) and fT3 13.5 pg/ml (N 1.45-3.48) and TSH [0.01 µIU/ml (N 0.470-4.640), TRAb 33.8 U/l (N< 1.5)] confirmed autoimmune hyperthyroidism of maternal origin (maternal TRAb: 96.9 U/l). Therapy with antithyroid drug and β-blocker was started with rapid normalization of TH levels. fT4 dropped to low normal level (0.71 ng/ml) but TSH level was still decreased therefore 18.75 µg of L-thyroxine was given and subsequently 37.5 µg. TRAb level normalized at 6th week of life however until now (at 14 months of life) there is still decreased TSH level (< 0.006 uIU/ml), also suppressed after TRH test. fT4 was normal during treatment (1.21-1.44 ng/dl).

Conclusions: This the first evidence of such a long-term persistent secondary hypothyroidism in a child of mother with a history of a severe GD. TH-dependent mechanism via TRH/TSH suppression during fetal and early postnatal life seems to be dominant however no recovery of the axis is observed. The role of TRAb (stimulatory or inhibitory) and its direct effect on thyrotrophs should be considered.

P106

THE EFFECT OF SUPEROVULATION STIMULATION ON THYROID FUNCTION IN CARRIERS OF THYROID PEROXIDASE ANTIBODIES

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The aim of this work was to study changes in the levels of TSH and free factions of T4 and T3 against the background of superovulation stimulation in patients who had undergone infertility treatment using in vitro fertilization. 160 patients with tubal-peritoneal infertility and no thyroid pathology, were included in the investigation. 36% (n=58) of the patients, who constituted the study group, were tested for anti-TPO antibodies carrier state. Tests for TSH, f. T4 and f. T3 levels were performed in the cycle preceding the superovulation stimulation, in the day of ovulation trigger introduction, and 14 days after the embryos transfer. Positive correlation between the TSH level before starting the protocol (1) and after the embryo transfer (3) was detected in both groups. The group of antibodes-positive patients demonstrated r=0.42; p=0.005, while the control group showed r=0.79; p=0.05. Moreover, TSH level increase was significantly higher in the anti-TPO carrier group, than in the control group (p=0.02). The variability of f. T3 level demonstrated no clinical and statistical significance (p=0.15 for the study group, and p=0.33 for the control group). The patients with high antiserum titre were marked by significantly smaller number of oocytes obtained as a result of transvaginal puncture (p=0.035). However the in vitro fertilization and -embryos transfer program outcome did not differ significantly (p=0.1).

Keywords: TSH, f. T4, f. T3, superovulation stimulation, positive anti-TPO carrier state

P107

THYROID FUNCTION IN PREGNANT THYROID PEROXIDASE ANTIBODY-POSITIVE WOMEN LIVING IN AN AREA WITH MILD IODINE DEFICIENCY

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Objectives: The aim of the study was to examine thyroid function in pregnant TPO-Antibody (TPO-Ab) - positive women living in an area with mild iodine deficiency.

Methods: In moderately iodine-deficient, pregnant, TPO-Ab-positive women the role of iodine supplementation was studied in randomized trial. Screening for TPO-Ab was performed in early pregnancy in a population of healthy pregnant Ukrainian women with no previous diagnosed thyroid disease (prevalence 17.3%). All participants received a daily vitamin and mineral tablet with 200 mcg iodine or no iodine. A total of 44 TPO-Ab positive women were followed with biochemical evaluation of thyroid function and antibody level. Compliance was evaluated by 24-h urinary iodine measurements.

Results: The basic predictors of hypothyroxinemia in women with the increased TPO-Ab level have relatively a high level of TSH and relatively low level of fÒ4 at the beginning of pregnancy. In accordance with the used mathematical model it is not determined by the TPO-Ab level and thyroid volume. At the TSH level at the beginning of pregnancy >2 mU/ml probability of development of hypothyroxinemia is about 50%. Iodine supplementation by the physiology doses (200 mcg) during pregnancy to TPO-Ab-positive women living in an area with mild iodine deficiency did not increase of risk of thyroid dysfunction. The study confirmed that screening for TPO-Ab in early pregnancy can predict women at high risk for development. Increase of TPO-Ab level without other signs of thyroid autoimmune pathology does not accompanied by the substantial increase of risk of development of gestational hypothyroxinemia.

Conclusions: Increase of thyroid volume and relatively high for the early terms of pregnancy TSH level (> 2 mU/ml) are the risk factors of gestational hypothyroxinemia in TPO-Ab positive women during pregnancy.

P108

THE PECULIARITIES OF THYROID DYSFUNCTION AND ANTI-THYROID PEROXIDASE ANTIBODIES DURING PREGNANCY AND AFTER DELIVERY

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Objectives: The thyroid dysfunction is common problem during pregnancy and after delivery. Pregnancy-induced autoimmune thyroiditis is most frequent among thyroid problems and can influence on thyroid function of breast-feeding women and newborns. Aim of our investigation was to study the impact of initiated therapy on the frequency of autoimmune thyroiditis during pregnancy and after delivery.

Material and Methods: The data of 3 groups have been analyzed. Group 1 - patients with initiation of thyroid function control on 8-12 weeks (n=98); group 2 - patients with initiation of thyroid function control on 18-22 weeks (n=58); and group 3 - patients with initiation of thyroid function control on 26-32 weeks (n=56). Serum levels of TSH, FT4, anti-thyroid peroxidase (anti-TPO) antibodies were determined during pregnancy and after 1 month after delivery. Adequate therapy was defined by L-thyroxine (25-100mcg).

Results: Initially, elevated levels of Anti-TPO were found in 19.39% of group 1. On 26-32 weeks the amount was decreased to 9.18% (OR=2.37,95%CI=1.01-5.58) and after delivery - 8.16% (OR=2.71,95%CI= 1.12-6.52). Initially, elevated levels of Anti-TPO were observed in 31.03% of group 2. On last stage of pregnancy the amount was decreased to 8.62% (OR=2.37,95%CI=1.01-5.58) and after delivery - 8.16% (OR=2.71,95%CI=1.12-6.52). Compared to group 1 on 20-22 weeks OR was 4.45 (95%CI=1.84-10.76), on the last stages the difference between these groups didn´t observed. Initially, elevated levels of Anti-TPO were found in 26.78% of group 3. The difference between group 1 and 3 on this stage was significant (OR=3.61,95%CI=1.46-8.95), between group 2 and 3 on this stage was also significant (OR=3.88,95%CI=1.30-11.55); After delivery the frequency was still high (25%), OR in comparison with group 1 was 3.75 (95%CI=1.46-9.63), and with group 2 - 3.53 (95%CI=1.18-10.60).

Conclusion: The initiation of adequate therapy in time significantly decreases the progression of autoimmune thyroiditis during pregnancy and after delivery.

P109

ASSESSMENT OF THYROID FUNCTION AND IODINE SUPPLY OF THE GROUP OF HEALTHY PREGNANT WOMEN FROM CENTRAL POLAND

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Even mild thyroid dysfunction in pregnant woman due to mild iodine deficiency can negatively affect fetal development and pregnancy course.

Aim: Prospective observation of thyroid function and iodine intake in healthy pregnant women supplemented with 150 µg of iodine daily.

Methods: Assessment of thyroid function: concentration of TSH, free thyroid hormones, morning urinary iodine in consecutive trimesters of pregnancy Study group: 67 healthy pregnant women (age 24 -38 y, mean 29). Single pregnancies, resulting in birth of healthy neonates.

Results: Mean and median of TSH were within values recommended for pregnancy and were 1,47; 2,01 and 1,82; median 1,47;1,92 and 1,58 µIU/ml respectively in the following trimesters of pregnancy. Free T4 was within non-pregnancy reference values and decreased in the III trimester, mean concentrations were 1,23; 0,99; 0,98 and median 1,18;0,97;0,93 ng/dl in subsequent trimesters. Urinary iodine concentrations (UIC) were unexpectedly low at the beginning of pregnancy: mean 104µg/l, median 85 µg/l. In 2/3 of the subjects UIC was lower than 150ug/l. In spite of supplementation with at least 150 µg iodine per day, mean and median UIC were respectively 141; 125 µg/l in the second and 126; 112µg/dl in the third trimester.

Conclusions: Observations are preliminary. The results presented are a part of the research plan aiming at determining the reference value of thyroid hormones for consecutive trimesters of pregnancy.

1. TSH and free T4 values did not exceed population reference values, dynamics during pregnancy were as expected.
2. Low urinary iodine concentration at the beginning of pregnancy and during supplementation reveals that recommended prophylaxis does not ensure sufficient iodine supply in the group of pregnant women.

Key words: pregnancy, iodine, thyroid

P110

A CASE OF PROPYLTHIOURACIL-INDUCED HEPATITIS DURING PREGNANCY, REQUIRING CESSATION OF PROPYLTHIOURACIL AND SUBSEQUENT SUCCESSFUL TREATMENT WITH CARBIMAZOLE

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A 32 year old lady with no clinical evidence of pre-existing liver disease was diagnosed with Graves' Disease at week 7 of pregnancy. TSH was undetectable with markedly elevated T_4 levels and positive thyroid receptor antibodies. She was started on a reducing regime of propylthiouracil (PTU).

At 20 weeks pregnancy she highlighted that the British Thyroid Foundation recommended that PTU should only be used in the first trimester, due to concerns of PTU-induced hepatitis. She was advised that current practice in Bath and Bristol was for PTU to be used throughout pregnancy, because of increased risks of congenital abnormalities with carbimazole.

Three days later, she became jaundiced and contacted the endocrine department, she was seen that day by the endocrine registrar. Her initial bloods revealed: Bilirubin 91, ALT 1796 ALP 200 INR 1.2 PT 12.4 Alb 33. A presumptive diagnosis of PTU-induced hepatitis was made.

PTU was immediately discontinued and best supportive care instigated. Serum markers for autoimmune and viral hepatitis were negative, ferritin and caeruplasmin were normal. An US upper abdomen revealed normal liver appearance and normal portal blood flow. Although her ALT immediately began to fall, her bilirubin continued to rise peaking at 378.

Two weeks after PTU cessation she became thyrotoxic again and was started on a reducing regime of carbimazole 20mg. Her thyroid function stabilized and LFT continued to improve with carbimazole stopped at week 32. Growth scans throughout pregnancy remained normal and she is currently euthyroid and 38 weeks pregnant.

This report highlights that good outcomes can still be achieved in PTU-induced hepatitis in pregnancy, provided there is immediate cessation of PTU, early supportive care and subsequent treatment with carbimazole. Patients on PTU should be warned of the potential risk of hepatic failure and advised to seek medical advice immediately if they develop jaundice.

P111

DYNAMICS OF CHANGES IN THE ATPO LEVEL IN PREGNANT WOMEN IN EACH TRIMESTER OF PREGNANCY WITH NORMAL AND INCREASED LEVEL OF ATPO

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Introduction: Pregnancy is known as a period of physiological immunosuppression. Results of decreased humoral immune response is decreased level of antibodies since 1st trimester of pregnancy with the lowest concentration in 3rd trimester. Increased level of anti-thyroid peroxidase antibodies (antiTPO) is connected with increased risk of miscarriage and premature delivery. Some researches showed the benefits of levothyroxine administration in pregnant women with increased antiTPO level.

Aim: Assessment of changes in the concentration of anti-thyroid peroxidase antibodies in case of healthy euthyroid pregnant women with normal level and increased level of antiTPO.

Methods: 130 women with normal level of antiTPO (< 50 U/ml) in 1st trimester and with negative history pregnant of the thyroid gland diseases was examined in each trimester (first group). The second group were 30 women with increased level of antiTPO in 1st trimester of pregnancy with normal level of TSH and thyroid hormons. Assay of the antiTPO in blood serum by the electrochemiluminescence method (ECL). For the statistic evaluation of results Mann-Whitney non-parametric test was used.

Results: There were no significant differences between antiTPO concentration in particular trimester in case of women from the first group (p>0,05). In second group obtained results indicate on significant differences between aTPO concentration in 3rd trimester in comparison to the 1st (p= 0,03).

Discussion: Obtained results revealed tendency to decrease the level of antiTPO with development of pregnancy. Significant differences in second group between the aTPO concentration in 3rd trimester compare to 1st trimester of pregnancy were revealed. Immunosuppression in period of pregnancy have considerable influence on the antiTPO concentration, mainly in 3rd trimester. On basis of such facts it's seems to be unnecessary to start levothyroxine treatment in case of women with positive antiTPO and normal level of TSH and thyroid hormones in first trimester of pregnancy.

P112

PREVENTATION OF IODINE DEFICIENCY IN PREGNANT AND LACTATING WOMEN: EPIDEMIOLOGICAL STUDIES

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The aim of study was to research the state of iodine prophylactic in pregnant women in Russian Federation and offer the optimal levels of daily iodine intake during pregnancy and lactation.

414 pregnant and breast-feeding women and 256 newborns from 3 various regions of Russian Federation were observed in this survey. Women have been divided into 2 groups: 1st - taking of 200 mg of KI per day, 2nd group - 250 mg KI per day during pregnancy and lactation.

The following surveys were performed: TSH; fT4; AT-TPO; urinary iodine concentration (UIC); indicators of hemoglobin, erythrocytes, hematocrit, iron, ferritin; ultrasound examination of a thyroid.

Initially, the median of UIC in all regions is below threshold level - 150 mg/l. in Nizhny Novgorod it is 140,8 mg/l; Smolensk - 62,7 mg/l and Moscow Region - 127,5 mg/l that confirms iodine insufficient in pregnant women.

Optimal iodine nutrition during pregnancy and lactation is reached by the only regular iodine prophylactic, and the requirement of iodine should be at least 250 mg/day.

With presence of the iron deficiency anemia which was revealed in 22,3% of pregnant women, efficiency of iodine prophylactic is decreasing and optimum preventive doses of iodine for this category of pregnant women is at least 250 mg/day.

Key words: Iodine deficiency, iodine prophylaxis, iodine deficiency disorders, pregnant and lactating women, iron, anemia.

P113

CHANGES IN THE VOLUME OF THYROID GLAND IN PARTICULAR TRIMESTER OF PREGNANCY -OWN OBSERVATION

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Introduction: During pregnancy thyroid gland is under influence of factors specific for this condition. Enlargement of thyroid gland volume in case of pregnant women who received proper iodine supplementation is decreased after delivery. It is caused by an increased vascularisation of the gland and high concentration of the growth factors during pregnancy including Insulin-like Growth Factor 1 and epidermal growth factor.

Aim: Assessment of changes in thyroid gland's volume during pregnancy.

Methods: 130 pregnant women in each trimester of pregnancy with negative history of the thyroid gland diseases was examined. USG examinations for all pregnant women were conducted in USG Laboratory in Jagiellonian University, Medical College, Department of Endocrinology by using GE Voluson Pro. The thyroid gland's volume was evaluated by the pattern of the ellipsoid in revolution, separate for each lobes: length x wide x thickness x 0,475 (ml). For the statistic evaluation of results Mann-Whitney non-parametric test was used.

Results: On the base of the obtained results statistical significance enlargement of thyroid gland in 2nd trimester in comparison to the 1st (p< 0,0005), in 3rd trimester in comparison to the 1st (p< 0,0001) and in 3rd in comparison to the 2nd (p< 0,01) was revealed.

Conclusion: Obtained results revealed enlargement of thyroid gland averaged out at 14,7% in 3rd trimester in comparison to the 1st, 7,9% in the 3rd trimester in comparison to the 2nd and 7,87% in the 2nd trimester in comparison to the 1st.

Significant differences between the volumes of the thyroid gland in each trimester of pregnancy were revealed. During diagnosis and treatment changes of the thyroid gland in the period of pregnancy should be taken under consideration.

Key words: Pregnancy, volume of the thyroid gland

P114

SEVERE HYPEREMESIS GRAVIDARUM ASSOCIATED TO PANCREATITIS AND CHOLECYSTITIS

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We report the case of a 32 year old, G3P1, Guinean woman who presented at 5 weeks of amenorrhea (WA) of a twin pregnancy with major vomiting, weight loss and mild signs of hyperthyroidism. She had a history of transient hyperthyroidism during a previous pregnancy and no family history of similar problem. She was very thin (15% weight loss), without goiter or eye symptom. Despite rehydration and antivomiting drugs, clinical symptoms worsened and PTU was introduced (50 mg/day at 6WA+1 day,100 mg/day at 7WA+5days, decreased to 50 mg/day at 10WA).

The evolution was complicated with the occurrence of pancreatitis and liver anomalies that first improved, before a secondary relapse in a context of acute cholecystitis. Imaging showed initially sludge in the gallbladder, with Balthazar A pancreatitis on MRI. One week later, acute cholecystitis occurred with Balthazar C pancreatitis. The table shows the biological evolution of bHCG, thyroid and hepato-pancreatic tests. Anti R TSH and anti TPO antibodies were negative.

The extremely high levels of bHCG (possibly an isoform with high affinity for TSH receptor) due to twin pregnancy are likely responsible for the thyroid stimulation. Though liver abnormalities are classical in hyperemesis gravidarum, to our knowledge, only one case associated with secondary pancreatitis has been published, with spontaneously favourable evolution. The mechanisms of hepato-pancreatic disturbance will be discussed.

Term	5WA+1d	6WA+1d	7WA+5d	9WA	9WA+6d	10WA+5d
Treatment	–	–	PTU 50	PTU 100	PTU 100	PTU 50
TSH	0.028	<0.015	<0.015	<0.015	<0.015	<0.015
fT4	21.5	61.2	54.3	55	30.6	43.5
βHCG	173446	319450	787200	481317	307700	366700
Lipase	28	141	234	423	123	129
C bilirubin	0	3	8	7	4	51
SGPT	12	59	83	162	96	305

P115

HEALTH OF NEWBORNS FROM MOTHERS WITH HASHITOXICOSIS

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Purpose: Studying of the influence on newborns health of the degree of Hashitoxikosis compensation of mother during a pregnancy.

Materials and Methods: 32 newborns are surveyed: 1st group - 16newborns from mothers with non-compensated Hashitoxikosis, 2nd group - 16 newborns from mothers with compensated Hashitoxikosis. The health estimation was spent on a scale of Apgar, anthropometry, neurologic and endocrinology status. For 3-4 days after a birth (born in time) and on 8-10 days (at prematurely born) defined levels TTG, T3, and T4 in blood serum by radioimmune method sets Immunotech, Czechia.

Results: At comparison of the basic indicators of a state of health of newborn of the 1st and 2nd groups is established that in 1st group in 4 times there are more than cases of neonatal transitory thyreotoxicosis (8/50%; Ð < 0,05), in 7 times more number of prematurely born children (7/43,8 %; Ð < 0,05), in 2 times more often a delay of pre-natal development and small weight at of a birth (4/25 %; Ð < 0,05), in 1,5 times - prenatal defeats of a brain (12/75 %; 0,05). In the 1st group in an asphyxia condition were born 8 newborn (75 %) against 1 (6,3 %), Ð < 0,05..

Conclusions: At newborns from mothers with non-compensated in the early period of pregnancy Hashitoksikosis prenatal defeats of a brain develop in 70 % of cases, 50 % - neonatal transitory hyperthyreosis, 25 % - a delay of pre-natal development and small weight at a birth, 43,8 % of children are born prematurely, 75 % in an asphyxia condition.

PO11 Thyroid Cancer (clinical) 4

P116

THYROID CANCER: A SURVEY OF THE PATIENT JOURNEY IN THE UK

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Thyroid cancer is associated with an excellent prognosis, but the patient journey from first symptoms to investigation, diagnosis and treatment is a stressful process.

Objectives: To elucidate how information is given to the patient, by whom, which professionals are most important to the patient, and which parts of the journey cause most anxiety.

Methods: Web-based questionnaire posted between August 2010 and February 2011. Patients were encouraged to take part through the website of the patient-led organisation Butterfly Thyroid Cancer Trust and mailshots from the same organisation.

Results: 79 questionnaires were returned. At the time of discovering a thyroid lump, 40% of respondents used the internet prior to seeing their family doctor. 31.8% of internet users felt less assured about their condition than before. Receiving copies of correspondence between health professionals was helpful and reassuring to 52% of responders, while in 9% found it caused anxiety. 41.7% of responders stated that the news of a cancer diagnosis was unexpected. 71% of responders wished more information from the clinical team throughout the pre-diagnosis period. The most stressful period in the cancer journey was a few days after receiving the news of having cancer and a few days after thyroidectomy.

Conclusions: This survey indicates the need for good quality information for patients even before the diagnosis of thyroid cancer is made. Use of internet was associated with negative effects, possibly due to contradictory and a mix of good and poor quality sites accessed. This survey also identified important timelines associated with maximum patient anxiety. Support of patients with cancer seems to be needed throughout their journey but particularly immediately after their diagnosis and shortly after thyroidectomy. The need for more information throughout the patient journey has been highlighted, which may better prepare people for a diagnosis and improve understanding.

P117

VIDEO ASSISTED THYROIDECTOMY IN THE TREATMENT OF THYROID CARCINOMA USING HARMONIC SCALPEL

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The application of video assisted techniques in thyroid surgery broadens in recent years.

Aim: To present our results in the treatment of thyroid carcinoma using video-assisted approach with harmonic scalpel.

Patients and Methods: For three years period (2008-2010) 125 patients with thyroid nodules have been operated on using harmonic scalpel and video assisted approach in our institution. In 24 of these patients (21 females and 3 males, age from 21 to 49 years) thyroid carcinoma was found**.** Patients have been selected on the basis of criteria accepted in our clinic and discussed in previous papers. Thyroid resections were performed by harmonic scalpel (Ethicon Endo-Surgery). The operative time, intra- and postoperative complications, length of postoperative hospital stay and presence of residual thyroid tissue have been evaluated.

Results: In 21 patients papillary thyroid carcinoma and in 3 patients follicular type of papillary thyroid carcinoma was found, from 0.5 to 2 cm in size. Lymph node micro-metastases in the central cervical compartment were detected in 3 patients. Video-assisted thyroidectomy through a central collar incision, 1.5 to 2.5 cm in length has been used in all cases.The use of harmonic scalpel reduces the need for hemostatic instruments. Only one ligature to adapt the margins of the superficial tissues at the end of the procedure was enough in all patients. All procedures were finished without need for drain-

ing. Complications were not observed. All patients leaved the hospital within the 24 postoperative hours. Postoperative thyroid scans were negative in all patients.

Conclusions: The video-assisted thyroidectomy using harmonic scalpel is a very effective, safe and adequate minimally invasive technique in selected patients with thyroid carcinoma.

P118

HYPERTHYROIDISM AND CONCURRENT CARCINOMA OF THE THYROID GLAND

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Objectives: The purpose of our study was to find the features of thyroid cancer with hyperthyroidism.

Methods: We studied 23 patients with thyrotoxicosis and carcinoma of the thyroid gland who have been undergone surgery treatment for hyperthyroidism in our department from 2006 till 2011.

Results: The rate of thyroid cancer with concomitant hyperthyroidism was 4,4%. A neoplasm occurred in 7 cases of Graves´ disease - 30.5% (3 of 7 cases were relapse Graves' desease), in 13 cases of toxic multinodular goiter - 56.5% and in 3 cases of hyperfunction adenomas - 13%. Our sample included only females. The mean age of the patients was 43.6±2.8 years. The duration of hyperthyroid clinical symptoms ranged from 8 months to 17 years (mean 3.8±1.2 years). Thyroid ultrasonography with fine-needle aspiration cytology was performed in 14 cases - patients with one or more nodules in thyroid gland. Only 1 of these patients had evidence of papillary carcinoma. The mean diameter of tumors was 9.2±1.9 mm (range, 2-26 mm). The tumor size in 20 patients (87%) was 10 mm or smaller. Total thyroidectomy (16 patients), subtotal thyroidectomy (5 patients) and hemithyroidectomy (2 patients) were performed. The histopathological type of the thyroid cancer associated with hyperthyroidism in all cases was papillar carcinoma. Multicentric growth of papillary carcinoma has been found in two cases of diffuse goiter. The follow-up period ranged from 4 months to 5 years 2 months: each patient.

Conclusions: Most of thyroid cancer with concurrent hyperthyroidism were 10 mm or smaller. The rate of thyroid cancer with concomitant hyperthyroidism is more frequent in toxic nodular goiters than in diffuse goiters. Consequently, all thyroid nodules require careful diagnostic for exclusion of malignancy, even with presence of hyperthyroidism.

P119

SECOND PRIMARY MALIGNANCIES IN THYROID CANCER PATIENTS

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Introduction: The increasing incidence and improved prognosis of thyroid cancer led to the development of second primary malignancies (SPM).

Objectives: To determinate the incidence of SPM in patients with thyroid cancer.

Methods: Retrospective study of 415 thyroid cancer patients (320 females and 95 males) in follow-up on a thyroid outpatient clinic of a general hospital, between 1980 and 2010.Sex, histological type of thyroid cancer, treatment, age at diagnosis of both thyroid cancer and SPM, and mean time of follow-up were recorded.Cancer incidence was compared with that of the general population matched for age, gender and period.

Results: Among thyroid cancer patients, 77% were female and 23% male, mean age at diagnosis was 45 years, 3% were treated with external radiotherapy and 48% received ^{131}I, the mean follow-up period after thyroid cancer diagnosis was 14 years, and most thyroid tumors were papillary (74%) or follicular (13%) carcinomas.During the observation study, 35 second cancers had been observed, the mean interval of time between thyroid cancer diagnosis and SPM was 9 years, at a mean age of 59 years. Of those, 29 occurred among women and 6 among men.Compared with general population incidence rates, there was an increased risk of SPM after a primary thyroid cancer [standardized incidence ratio (SIR)=1,27; 95% CI: 1,20-1,40].Breast cancer contributed 23% of all SPM after female thyroid cancer, with a significantly increased risk (SIR=1,3; 95% CI: 1,10-1,50).No significant associations to specific histological groups of thyroid cancer were found.No significant association was found between exposure to external radiotherapy and ^{131}I for the risk of SPM.

Conclusions: In the present study about 8,4% of thyroid cancer patients developed a SPM during the follow-up, and the occurrence of second cancers was significantly increased compared with the general population.There was also an increase in breast cancer after thyroid cancer.

P120

FACTORS RELATED WITH METASTASIS OF RIGHT RETROESOPHAGEAL LYMPH NODES IN PAPILLARY THYROID CANCER

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Objectives: Right retroesophageal lymph nodes(LN) should be involved in central lymph node dissection(CLND) in patients with papillary thyroid cancer(PTC). But, there is a possibility of injuring to the nerve during the procedure. The purpose of this study was to assess the incidence and factors related to right retroesophageal LN metastasis.

Methods: From January 2008 to March 2010, 129 patients were underwent total thyroidectomy with CLND including right retroesophageal LN for PTC. There were 101 women and 28 men whose mean age was 41.6±12.9 years. We retrospectively reviewed these patients. The following criteria were used to study the predictive value of Right retroesophageal LN metastasis : age, sex, tumor size, multiplicity, preoperative LN enlargement, number of central LN metastasis, number of central LN removed, extrathyroidal extension, lateral LN metastasis, capsular invasion and T stage.

Results: 26 of 129 patients exhibited nodal metastasis in right retroesophageal LN(20.1%). Metastasis of right retroesophageal LN was associated with large tumor size more than 1 cm ($p< 0.01$), multiplicity ($p=0.03$), preoperative LN enlargement($P< 0.01$), metastasis of non-retroesophageal lateral LN($p< 0.01$) and large number of central LN metastasis($P< 0.01$) in univariate analysis. With use of multivariate analysis, tumor size(>1cm) and metastasis of non-retroesophageal lateral LN were independent correlates of right retroesophageal LN metastasis.

Conclusions: Right retroesophageal LN may be removed during operation for PTC particularly in patients with tumor larger than 1.00cm and lateral LN metastasis.

P121

PAPILLARY THYROID MICROCARCINOMAS ARE DIFFERENT FROM LATENT THYROID CARCINOMAS AT AUTOPSY

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Background: There has been still no evidence of similarity between papillary thyroid microcarcinomas and latent thyroid carcinomas at autopsy. The aim of this study was to compare the clinicopathologic features of papillary thyroid microcarcinomas to those of latent thyroid carcinoma detected at autopsy.

Methods: Searching the PubMed for published articles regarding latent thyroid carcinoma at autopsy was performed. Suitability was assessed by using pre-defined inclusion and exclusion criteria. A meta-analysis was performed to find out the differences between the clinicopathologic features of papillary thyroid microcarcinomas published at our institution (Group I) and those of latent thyroid carcinomas at autopsy studies (Group II).

Results: There were 1,355 cases in Group I and 1,022 cases in Group II. Age at diagnosis was 47.3 years in Group I and 64.5 years in Group II. Sex distribution differed between two groups; male/female ratio was 1/10.9 in Group I and 1/1 in Group II. In Group I, the majority (67.6%) of them was larger than 0.5 cm in size, whereas in Group II, most of the series reported that latent thyroid carcinoma showed small foci (< 1-3 mm). Multifocality was 24.7% in Group I and 30.5% in Group II. Cervical lymph node metastasis was 33.4% in Group I and 10.0% in Group II.

Conclusions: Based on the currently available data, it appears that clinically evident papillary thyroid microcarcinomas are different from latent thy-

roid carcinomas found at autopsy studies. Thus, these two entities should be considered differently.

P122

SIZE OF CERVICAL LYMPH NODE METASTASES SUCCESSFULLY TREATED BY RADIOIODINE IN PATIENTS WITH DIFFERENTIATED THYROID CANCER

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Aim: SPECT/CT identifies radioiodine-positive lymph node metastases in roughly one fourth of patients with thyroid carcinoma at first radioablation (1). The purpose of this study was to further characterize lymph node metastases (LNMs) successfully treated by radioiodine.

Methods: From 07/05 until 06/10, at our department, in 38 of 165 patients (24 female, 14 male) 45 radioiodine-positive LNMs were identified by SPECT/CT at time of radioablation after thyroidectomy for differentiated thyroid carcinoma (papillary 33/ follicular 4/ insular 1; staging: 20 pT1, 5 pT2, 13 pT3; 12 pN1, 26 pNx or 0). Three LNMs were surgically removed before further analysis, this procedure had been performed due to the presence of additional iodine-negative LNMs in these patients. Follow-up was available for 36 LNMs and included, in particular, diagnostic I-131 scans performed 4-6 months later.

Results: 32/36 LNMs were no longer seen on radioiodine scans performed 4 - 6 months after radioablation. The size of LNMs not eliminated (2.9 ± 4.42 ml, range 0.1 - 9.49) was significantly greater than that of LNMs eliminated by radioiodine (0.4 ± 0.5 ml, range 0.04 - 2.65; $p < 0.05$). 30/32 LNMs smaller than 1 ml were eliminated by radioiodine, whereas this was the case of only 2/4 nodes exceeding this threshold.

Conclusions: Radioiodine given at radioablation removes the vast majority of iodine-positive LNMs persisting after thyroidectomy in differentiated thyroid cancer. Therefore surgical removement of LNMs < 1 ml should be discussed only for patients with additional iodine-negative LNMs or if pathological radioiodine accumulation persists in the follow-up. (1) Mustafa et al. EJNM 2009

P123

THE PATTERN AND PREDICTIVE FACTORS OF LYMPHATIC METASTASIS IN PAPILLARY THYROID CANCER : PROSPECTIVE STUDY

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Objective: A prospective study to evaluate the lymphatic metastasis in papillary thyroid carcinoma and its predictive factors to explore the surgical managing modality for papillary thyroid carcinoma (PTC).

Methods: Prospectively evaluation of 176 patients (41 male and 135 female) with PTC from January 2007 to December 2010. All patients received bilateral central neck dissection, and patients with lateral lymph node (LN) metastasis undertook modified radical neck dissection (MRND). The patterns of central and lateral LN metastasis were analyzed, its correlation with clinicopathologic factors were also evaluated.

Results: Central LN metastasis was observed in 59 patients (33.5%) ipsilateral, and 13 patients (7.4%) contralateral. Ipsilateral metastasis according to the T stage was T1, 44/140 (31.4%), T2, 5/15 (33.3%), T3, 7/16 (43.8%), T4, 3/5 (60.0%). Contralateral metastasis was T1, 8/140 (5.7%), T2, 3/15 (20.0%), T3, 1/16 (6.3%), T4, 1/5 (20.0%). Ipsilateral lateral LN metastasis was 0% in level I, 40.0% in level II, 46% in level III, 42% in level IV, 10.0% in level V, and contralateral side was 4.2% in level I, 33.3% in level II, 29.2% in level III, 25.0% in level IV, 12.5% in level V.For the predictive factor of LN metastasis, only sex was significantly related to central LN metastasis ($p=0.025$), and ipsilateral central LN metastasis was related to contralateral central LN metastasis ($p=0.001$). For the lateral LN metastasis, sex ($p=0.033$) and central LN metastasis ($p=0.003$) were statistically significant predictive factors.

Conclusions: Ipsilateral central LN metastasis was observed even in early T-stage, and this was a predictive factor of contralateral central LN metastasis. Lateral LNs were involved usually confined to level II, III and IV. Male sex was a significant predictive factor for central and lateral LN metastasis, and central LN metastasis was also a predictive factor of lateral LN metastasis.

P124

VIRAL DISEASES AND RISK OF DIFFERENTIATED THYROID CANCER

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Background: The carcinogenic action of some viruses: HPV, HBV, HIV, EBV, HTLV-1 was proved in the case of many cancers. In histologic specimens of benign and malignant thyroid tumours viruses like Coxackie, EBV, HCV, HIV were detected.

T**he aim of the study** was to assess the influence of having history of viral diseases on the risk of DTC.

Material and Methods: The "case-controll" study was performed in 232 patients with DTC: 31 men (mean age 55,3±14years) and in 201 women (mean age 50,7±13,1years) and 342 healthy subjects: 58 men (mean age 60,2±12years) and 285 women (mean age 53,4±14,3years). Based on the same questionnaire there was an interview conducted concerning information of selected viral diseases: chicken pox, herpes, measles, mumps and hepatitis. To assess the relative risk of DTC and impact of these factors the logistic regression adjusted to age was used. Statistical significance was at $p< 0,05$.

Results: The viral diseases were more common in DTC patients than in controls: in men 87,1% v.s. 75,9% and in women 93% v.s. 88,1% respectively. Passing one of viral diseases increases the risk of DTC by 88% in the whole group, in men even two times (with regard to PTC in women over 3 times and in men 2,45- times). Measles increased the risk of DTC in men over three times while of PTC eight times. On the other hand measles in women increased the risk of DTC only by 41%. Herpes increased the risk of FTC in men eight times.

Conclusions: Viral diseases could be the risk factors of DTC.Measles may increase the risk of PTC whereas herpes FTC, especially in men.

P125

OFF-LABEL TREATMENT OF SUNITINIB IN ADVANCED THYROID CANCER PATIENTS: A CASE SERIES

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Objectives: Thyroid cancer can originate from activating mutations or rearrangements in the RET gene and is characterized by a marked angiogenic activity. Sunitinib, a novel tyrosine kinase inhibitor binding to the vascular endothelial growth factor receptors and other mutant kinases associated with thyroid cancer, showed promising results in preliminary clinical experiences. Aim of this report was to evaluate the clinical response and safety profile of sunitinib in off-label treatment of advanced thyroid cancer patients.

Methods: Five adult patients with a diagnosis of RAI-refractory advanced thyroid cancer (papillary, follicular and Hurthle cell) were treated with sunitinib and followed by both FDG-PET-CT every six months and thyroglobulin level evaluation, and monitored for adverse events.

Results: Patients (two women and three men) with DTC were treated for at least 9 months (mean 14.5 months). All the patients started sunitinib at 50 mg daily dose (4/2 weeks schedule). We documented partial response in one patient with substantial regression of lymph node, lung and liver metastases, progression disease (bone metastasis) in one patient and stable disease along with marked improvement of clinical symptoms in the other three patients. Sunitinib therapy was free of significant adverse events up to the first 3-4 months in all the patients when fatigue, mainly at the end of treatment cycle, hypothyroidism (TSH elevation), hypertension (worsening of blood pressure

control by current treatment), diarrhea, mucosal aphthae, headache, hematologic toxicity (macrocytosis) and amenorrhea were experienced. No grade IV toxicity was observed during treatment. In two patients we observed low fT3 levels that needed an increase dosage of LT4 or LT4/T3 combined therapy.

Conclusion: In patients with refractory thyroid tumors who have evidence of progressive disease, sunitinib is able to induce responses or disease stabilization in the great majority. Side effects represent the main obstacle to long term therapy.

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EXCELLENT LONG-TERM OUTCOME FOLLOWING 1.1 GBQ RADIOIODINE REMNANT ABLATION FOR DIFFERENTIATED THYROID CANCER

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Objectives: To evaluate the long-term outcome of patients with differentiated thyroid cancer (DTC) following 1.1GBq radioiodine ablation.

Methods: Sixty three patients with DTC were treated with 1.1GBq Iodine-131 ablation after thyroidectomy (total, sub-total or completion) between 1977-1984. Exclusion criteria included incomplete excision, metastatic disease at presentation or ablation, external beam radiotherapy (EBRT) or prior Iodine-131. Successful ablation was defined as both absence of uptake on diagnostic scan (185MBq Iodine-131) 3-6 months following ablation and serum thyroglobulin < 1 (immunoradiometric assay) on TSH stimulation.

Results: Fifty four patients (11 male, 43 female), mean age 45 years (range 17-75) were available for analysis. Median follow-up for the whole cohort was 323.5 months (range 40-397). 29/54 (54%) underwent successful ablation (group 1) and 25/54 (46%) required further Iodine-131 within 9 months of ablation (group 2). In group 1, 5 patients required 5.5GBq Iodine-131 at a median of 26.5 months (range 11.5-124) post ablation, 3 patients also received EBRT for local recurrence. In group 2, all patients received further Iodine-131; the median number of further treatments and total cumulative dose of Iodine-131 administered were 1 (range 1-9) and 5.5GBq (range 3.7-49.5GBq) respectively, 3 patients additionally received EBRT.

30-year survival for groups 1 and 2 is 75% and 82% respectively (p=0.96). No patients in the cohort are known to have died as a result of thyroid cancer at the time of last follow-up. Eight patients (15%) developed a second malignancy during follow up.

Conclusions: Long-term outcome following 1.1GBq Iodine-131 ablation for DTC is excellent in terms of disease control. Although 46% of patients were unsuccessfully ablated, this may reflect historically less extensive surgical resection and an early time-point of assessment of success (3 months in the majority) as 56% required only 1 further treatment.

P127

DOES EARLY DECREASE OF CEA OR CALCITONIN MEASUREMENTS AFTER CYTOTOXIC CHEMOTHERAPY CONSTITUTE A SURROGATE MARKER OF SURVIVAL IN MEDULLARY THYROID CARCINOMA PATIENTS?

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Introduction: Recently the prognostic value of plasma calcitonin (CT) and carcino-embryonic antigen (CEA) doubling time has been validated in medullary thyroid carcinoma (MTC) patients. However, no data support yet the use of these markers as surrogate markers of survival after initiating any type of treatment. The aim of this study was to evaluate the correlation between early variation of these markers after the start of cytotoxic chemotherapy and the overall survival (OS).

Patients and Methods: Monocentric retrospective study including 37 patients (27 men, 10 women) followed in a tertiary referral center between 2000 and 2008 for a metastatic MTC and treated with cytotoxic chemotherapy. Follow up included plasma calcitonin determination, CEA measurement and radiological RECIST evaluation collected every three months. Correlation between CT and CEA decrease of more than 50% at 3 months and OS was estimated using Kaplan-Meier curves and log-rank test (p=0.05).

Results: Thirty seven patients were included with a median follow-up of 68 months. An objective response, stabilization or progression was observed in 6, 17 and 13 cases respectively. Median OS after the start of cytotoxic chemotherapy was about 36 months. Median OS among patients with and without a significant CT decrease (> 50%) at 3 months was 35.6 and 36.9 months respectively (HR=1.03, [0.4; 3.0], p=0.95). Median OS among patients with a significant CEA decrease (> 50%) at 3 months was 51.3 months whereas it was only 35.6 months when CEA decreased by less than 50% (HR=0.42, [0.10; 1.8], p=0.24).

Conclusion: Early decrease of CEA but not CT measurements appears as a good surrogate candidate of overall survival after cytotoxic chemotherapy in MTC patients.

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ANALYSIS OF ULTRASOUND ELASTOGRAPHY, POWER DOPPLER, AND B-MODE ULTRASOUND FEATURES IN DIFFERENTIAL DIAGNOSIS OF MALIGNANT LYMPH NODES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

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Background: There are yet a few studies to evaluate the power of USE on detecting malignant lymph node (LN) in patients with differentiated thyroid carcinoma (DTC).

Objective: To assess the diagnostic power of USE in detecting malignant LNs and to compare this technique with B-mode (BM) and power Doppler US (PD) features.

Method: 34 cervical LNs having suspicious malignant features (short/long ratio>0,5, hilus loss, prominent hypoechogenicity, cystic component, hyperechoic spotting, irregular margin, peripheral blood flow) from 27 patients with DTC were examined using BM, PD, and USE. USE scores were classified from 1 to 3 according to the presence of elasticity in (1: soft, 2: intermediate, 3: hard). The strain ratios (SR) of all LNs were calculated according to adjacent muscle tissue. Fine needle aspiration cytology (FNAC) and LN thyroglobulin washout (LN-Tg) were performed to all LNs. LNs having benign FNAC and low LN-Tg levels (< 12 ng/ml) were accepted as benign.

Results: The sensitivity, specificity, positive and negative predictive values (PPV and NPV) of the features of different ultrasonographic procedures were summarized in table 1. Malignant LNs had significantly higher levels of

Table 1 (for Abstract P128)

USE scores	Total	Benign	Malignant	% Sensitivity	% Specificity	% PPV	% NPV
1.....	10.....	10.....	0.....	57	70	33	–91
2.....	12.....	9.....	3.....				
3.....	12.....	8.....	4.....				
Peripheral and/or central blood flow	12	3	9	86	89	67	96
Short-long ratio >0.5....	4.....	3.....	1.....	14.....	89.....	25.....	80.....
Hypoechogenicity.....	17.....	13.....	4.....	57.....	52.....	24.....	82.....
Hilus.loss.....	20.....	13.....	7.....	100.....	52.....	35.....	100.....
Cystic component.....	1.....	0.....	1.....	14.....	100.....	100.....	81.....
Hyperechoic spotting.....	8.....	4.....	4.....	57.....	85.....	50.....	89.....
Irregular Margin.....	4.....	2.....	2.....	29.....	93.....	50.....	83.....

mean SR in comparison to benign LNs (4.34 ±6.55 vs. 2.77± 2.63, p=< 0,036) (Table 1).

Conclusion: USE was found to have a similar power compared to BM technique. Power Doppler was found to have a superior power compared to USE techniques. Although USE was not an alternative to BM, FNAC, LN-Tg, it was found to be a good predictive procedure to determine the malignancy in LNs.

P129

CLINICAL MANAGEMENT OF THYROID DYSFUNCTION IN AN ADULT ONCOLOGY POPULATION

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Background: Thyroid dysfunction may be more common in oncology patients than the general population given the effects of cancer treatments (tyrosine kinase inhibitors, alpha interferon, radiotherapy and steroids) on thyroid function. Furthermore, symptoms of thyroid disease may be confused with those of cancer. No clear guidelines exist for monitoring or management of thyroid dysfunction in cancer patients.

Objective: This is a retrospective study assessing the thyroid management of cancer patients attending a large regional Cancer Centre.

Methods: Thyroid function tests (TFTs) requested from oncology wards and clinics between January 2007 and December 2009 were recorded, excluding thyroid cancer and paediatric cases. Patients with abnormal TFTs were identified, noting the type and severity of dysthyroidism. Electronic records were accessed to determine outcomes for cases with abnormal TFTs.

Results: The records of 572 patients were reviewed. The prevalence of thyroid dysfunction was 16.4%. Of the 94 patients identified with abnormal TFTs, subclinical disease was most common (34% subclinical hypothyroidism, 28% subclinical hyperthyroidism, 23% hypothyroidism, 15% hyperthyroidism). 93.3% of patients with subclinical hypothyroidism did not have follow-up TFTs 4-6 weeks later to determine whether the thyroid disturbance was persistent. 35% of cases with a serum TSH >10 mu/l were not given levothyroxine treatment.

Conclusions: The prevalence of thyroid dysfunction in an oncology population is high and may justify routine screening. A structured approach is required for thyroid disease management in an oncology population.

P130

CLINICOPATHOLOGIC FEATURES OF FAMILIAL NONMEDULLARY THYROID CANCER AT A SINGLE INSTITUTION

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Background: Familial nonmedullary thyroid cancer (FNMTC) is estimated to about 5% of thyroid cancer. It is controversial whether the clinical features of FNMTC are more aggressive and have a worse prognosis than sporadic nonmedullary thyroid cancer. There are a few studies of familial nonmedullary thyroid cancer in Korea. The goals of this study were to determine the prevalence and to evaluate the clinicopathologic features of familial nonmedullary thyroid cancer at a single institution.

Methods: From March 2007 to December 2010, a retrospective review of 913 patients with differentiated thyroid cancer that underwent primary thyroidectomy. The clinicopathologic results were reviewed between familial and sporadic thyroid cancer.

Results: The 58 patients (6.4%) representing 50 families have family history of thyroid cancer. There was no significant difference in sex, age (48.6211.90 vs. 46.00, NS), mass size (1.0.2 vs. 1.12, NS), extrathyroid extension (70.7% vs. 57.7%, NS), lymph node metastasis (48.3% vs. 45.9%, NS) in the FNMTC and sporadic thyroid carcinoma, respectively. FNMTC have more multiplicity than sporadic carcinoma (43.1% vs. 30.1%, p = 0.04). In FNMTC, the patient relationship of 2 relatives is 77.6%, 3 or more relatives is 32.4%, and 1st generation is 56.9%, 2nd generation is 43.1%

Conclusion: The treatment of modality should be total thyroidectomy, because the clinical feature of FNMTC has more multiplicity than sporadic thyroid cancer. However, the prognosis was not estimated because the follow up period was too short. So, the ultrasound should be recommended for screening of asymptomatic family members of patients with FNMTC.

P131

THE RISK OF THYROID CANCER RELATED TO THE VESUVIUS IN THE REGION OF CAMPANIA, ITALY

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Our study was based on the epidemiological observation of an increased risk of differentiated thyroid cancer (DTC) in some volcanic areas in the world. In particular, in Italy, the highest incidence of thyroid cancer was reported in Catania, Sicily, an area around Etna.

On this basis, we retrospectively analyzed the results of 500 new cases of DTC admitted to the University of Federico II from 2000 to 2010. An increased number of cases with DTC was detected in subjects living in the volcanic area of Vesuvius, a dormant volcano. This has brought our attention to analyze the water from the aqueduct of these areas. The evaluation was easy to carry out because the areas around the Vesuvius are reached by the same aqueduct; this made it possible to compare the water of these areas to other areas of the Campania region that are connected by another aqueduct. Furthermore, we analyzed specimens of drinking water from different areas of the Vesuvius, all from the same aqueduct. The results showed a higher risk of DTC in the Vesuvius area than in other non-volcanic areas of the same region, suggesting a relationship between volcano or environmental factors of this area. The analysis of the water samples from volcanic-areas showed a higher concentration of fluorine when compared to non volcanic areas. Vanadium concentration was not particularly as high as the study from Catania.

Our results showed a higher risk of papillary thyroid cancer with an early onset of this disease in the park of the Vesuvius, although this risk was not as high as in Catania around Etna; moreover, we did not find an excessive con-

centration of vanadium. In our opinion, this difference may be explained by the different characteristics between these two volcanoes.

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TUMOR SIZE DISCREPANCY BETWEEN ULTRASONOGRAPHIC AND PATHOLOGIC SPECIMEN MEASUREMENT IN PAPILLARY THYROID CARCINOMAS

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Background: The treatment outcome of thyroid cancer patients is usually analyzed based on the postoperative pathologic measurement of tumor size. Tumor size discrepancy exists between ultrasonographic measurement and pathologic specimens, but there are no studies about this discrepancy. The aim of this study was to evaluate the size discrepancy between ultrasonographic and pathologic specimen measurement of papillary thyroid carcinoma.

Materials and Methods: Between November and December 2010, 224 patients underwent thyroid cancer surgery for papillary thyroid carcinomas were enrolled. Tumor sizes by preoperative ultrasonographic measurement compared with size of postoperative pathologic specimen. Size discrepancy was found in all of 224 patients and mean tumor size discrepancy was 2.2mm. Patients were divided in two groups: patients with small size discrepancy (less than 2mm) (Group I, n=121) and patients with large size discrepancy (more than 2mm) (Group II, n=103).

Results: Sex distribution, multiplicity, and coexisting lymphocytic thyroiditis were similar between two groups. Old age (≥45 years) (40.5% versus 58.2%), tumor margin with infiltrative growing pattern (79.3% versus 88.3%), capsule invasion (43.0% versus 57.3%), and existing scattered psammomatous calcification around PTC (24.0% versus 34.0%) were more prevalent in Group II than Group I with statistical significance.

Conclusion: Tumor size discrepancy between ultrasonographic and pathologic specimen measurements exists in most patients, particularly in patients with old age (≥45 years), infiltrative tumor margin growing pattern, capsule invasion, and existing scattered psammomatous calcification. When studying on treatment outcome of thyroid carcinoma patients, it appears more logical to use a preoperative ultrasonographic measurement of tumor size rather than that of pathologic specimen measurement.

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THE SIGNIFICANCE OF DETERMINATION OF THYROGLOBULIN (TG) AND CALCITONIN IN DIAGNOSIS OF THYROID CANCER METASTASES

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Aim: To evaluate the possibility of the determination of thyroglobulin and calcitonin in neck regional lymphatic nodules for the early diagnosis of thyroid cancer metastases.

Methods and Material: We have examined 84 patients - 73 of them with papillary and 11 with medullary carcinoma. Earlier all the patients underwent thyroidectomy with central lymphodisection. The patients were examined for FT4, TSH, Tg and antibodies to Tg, calcitonin, and ultrasound examination of thyroid was carried out. In the course of ultrasound examination all patients showed neck limphadenopathy. We have carried out FNAB of lymphatic nodules followed by cytological examination. Apart from FNAB aspirate was taken in a test tube for the determination of Tg and calcitonin.

Results: Metastases of papillary carcinoma in lymphatic nodules have been verified cytologicaly in 20 patients of 73 and of medullary carcinoma - in 8 patient of 11. All the 28 patients showed tumor markers in aspirate from lymphatic nodules - Tg (200-3000 ng/ml) and calcitonin (more than 200 pg/ml) in considerable amount. All the patients underwent surgery. In all cases tumor metastases in lymphatic nodules histologicaly were confirmed. In 8 patients Tg in aspirates from lymphatic nodules was also found in considerable quantities. At the same time thyroid cancer metastases were not confirmed cytologically. All the 8 patients underwent surgery. During postoperative histological examination lymphatic metastases were confirmed.

Thus, the determination of thyroid tumor markers in aspirates from neck lymphatic nodules is a promising method of early diagnosis of thyroid regional neck cancer metastases.

Conclusions:

1. The discovery of Tg and calcitonin in aspirates of lymphatic nodules allows to diagnose thyroid cancer metastases at early stages.
2. The determination of Tg and calcitonin in regional neck lymphatic nodules must be included in the standard of postoperative observation of patients with thyroid differentiated and medullary carcinoma.

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THE IMPACT OF DIETARY IODINE RESTRICTION ON THE EFFICACY OF LOW DOSE RAI REMNANT ABLATION IN PATIENTS WITH PAPILLARY THYROID CANCER IN IODINE-SUFFICIENT AREA

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Objectives: Most guidelines for the management of papillary thyroid cancer (PTC) recommend that patients preparing for radioactive iodine therapy (RAIT) should be on a low iodine diet, particularly in iodine-sufficient area. It, however, still remains controversial whether low iodine diet preparation might affect the success rate of thyroid remnant ablation. We evaluated the association between urine iodine excretion (UIE) and the rate of successful ablation.

Methods: Two hundred ninety-nine patients with PTC who received low dose RAIT and whole body scan (WBS) for remnant ablation after thyroid hormone withdrawal were retrospectively reviewed. Successful ablation was defined as no visible uptake at WBS 6-12month after ablation with undetectable stimulated serum thyroglobulin. UIE < 66.2 ug/gCr at ablation was considered as adequate iodine restriction.

Results: Mean tumor size was 0.8cm and extrathyroidal invasion and lymph node invasion were observed in 13% and 60% of patients respectively. Median UIE at ablation was 34.1 ug/gCr, and 77% of patients had their UIE < 66.2 ug/gCr. Successful ablation was achieved in 72% of patients. Univariate analysis revealed that adequate iodine restriction was significantly associated with successful ablation. On the contrary, multivariate analysis failed to find out any significant factors associated with successful ablation including adequate iodine restriction.

Conclusion: Low iodine diet preparation for thyroid remnant ablation with low dose 131I in patients with PTC was not significantly associated with success rate of ablation in iodine-sufficient area.

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RELATIONSHIP OF CRIBRIFORM-MORULAR VARIANT OF PAPILLARY THYROID CARCINOMA WITH FAMILIAL ADENOMATOUS POLYPOSIS. REPORT OF THREE CASES WITH ANALYSIS OF MUTATIONAL STATUS OF BRAF GENE

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Objectives: The cribriform-morular variant (CMv) of papillary thyroid carcinoma (PTC) is a rare neoplasm that display distinctive morphological features comprising an intricate blend of cribriform, papillary, solid, tall, columnar, and morular areas. The cribriform-morular architecture makes this a separate entity which could be mistaken for an aggressive thyroid neoplasm. These lesions are usually associated with familial adenomatous polyposis (FAP), but rarely may be sporadic.

We describe three cases, two of which are FAP-associated. The BRAF mutational status is also investigated.

Methods: The clinical findings for the patients are summarized in the Table 1.

#	Gender/Age	FAP	FNAB (Class)	Surgical treatment
1	F, 44aa, mother	c.1917insA; exon 14	5	TT
2	F, 24aa, daughter	c.1917insA; exon 14	5	TT + cervical nodes
3	F, 35aa	negative	5	TT + central nodes

Results: Grossly, the size of the tumours varied from 1 to 2,4 cm in greatest diameter. Case 2 and 3 were unifocal with classical and CMv morphology, respectively. Case 1 harboured multiple and bilateral foci showing or follicular variant or CMv morphology. Immunohistochemically, CMvPTC was characterized by aberrant nuclear and cytoplasmic expression of β-catenin, focal staining for thyroglobulin and lack of immunoreactivity for HBME-1, galectin-3 and claudin-1. Conversely, the classical and follicular variant PTC showed the expected immunohistochemical profile.

Conclusions: The CMvPTC may be associated with FAP. When the CMv-PTC is diagnosed, the clinician should be alerted to exclude FAP along with appropriate family screening.

The prognosis of CMvPTC is similar to that of the classical type. Therefore, it is important to recognise this variant in order not to mistake it for other aggressive neoplasms.

FAP-related PTC usually belong to CMv-PTC, but classical and follicular variant PTC may be observed.

In agreement with previous reports, BRAF mutation was found only in conventional PTC but not in CMvPTC.

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TSH SUPPRESSION AND THYROXINE DOSE

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Objectives: To assess the effectiveness of current thyroxine dosing strategy for TSH suppression post I131Radio-iodine Ablation for Differentiated Thyroid Cancer.

Current practice in Leeds is for patients to commence thyroxine at a dose of 2.5µg/kg post radio-iodine ablation. TSH and freeT4(fT4) is rechecked at a 6 week clinic appointment. The dose of thyroxine is adjusted accordingly based on these results. The current dosing is based on a previous audit in 2008 which found that 66% patients needed a dose increase at 6 week appointment when dosed at 2µg/kg.This is a further audit to reassess dosing strategy.

Methods: Ninety patients treated with radio-iodine ablation from April 2008-Jan 2010 were retrospectively assessed. Information regarding gender, age, stage of disease, treatment received, starting dose of thyroxine, dose adjustment at the 6 week and subsequent appointments were collected and analysed.

Results: Thirty-five patients required a dose reduction of 25µg or more at the six week appointment based on TSH, fT4 measurement and symptoms of hyperthyroidism. Of those 35 with initial dose reduction, 23 required further subsequent dose reduction. Forty patients required no dose reduction at the initial 6 week appointment but 17 of these patients did eventually have dose reduction at later follow up. Overall more than half (58%) of the patients required a dose reduction at some point following initiation of thyroxine at a dose of 2.5µg/kg. There was no correlation with gender, age or starting dose of thyroxine on the dose adjustment required.

Conclusions: This re-audit confirms that finding the correct dose for the individual patient can be problematic and in many patients dosing at 2.5µg/kg may be too high. In some patients it can take even longer than 6 weeks for the TSH to fall. In light of these results we have changed our policy so that patients will receive 2.2µg/kg.

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SUPERIOR PARATHYROID GLANDS ARE LOCATED IN THE FLUID COLLECTION AROUND ZUCKERKANDLE TUBERCLE

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Background: Preservation of parathyroid gland is very important to prevent postoperative hypocalcemia in thyroid surgery. Superior parathyroid glands (SPG) are frequently found in the fluid collection around the Zuckerkandle tubercle (ZT) during thyroidectomy. However, this fluid collection has not been mentioned in the literatures. We named the fluid collection "Severance lake (S-lake)". The aim of this study is to evaluate the frequency and size of S-lakes, and the relationship between the S-lake and SPGs.

Materials and Methods: A total of 113 patients with total thyroidectomy between September 2010 and December 2010 were enrolled in this study. The frequency and diameter of the S-lake, and relation between the S-lake and SPGs were evaluated.

Results: Of the 113 patients, 96 (84.9%) had the S-lake. The S-lakes were examined on both sides in 56 patients (49.6%), and only one side in 40 patients (35.4%). The mean diameter of S-lake was 10.5mm. Of the 152 lakes, 128 (84.2%) SPGs were found in the S-lake; 109 (73.0%) were in the medial margin of S-lake and 19 (12.5%) in other area of S-lake. Remaining 24 (15.8%) were out of S-lake.

Conclusion: Majority of SPGs were located in the fluid collection (S-lake) around ZT. Therefore, fluid collection around ZT could be a landmark for the identification of the SPGs.

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DETECTION OF THYROGLOBULIN ANTIBODIES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA: BE AWARE OF INTERFERENCE OF SERUM THYROGLOBULIN

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Introduction: Thyroglobulin (Tg) is a specific tumor marker for differentiated thyroid carcinoma (DTC). However, interference of Tg antibodies (TgAbs) may hamper the detection of Tg and, consequently, may influence treatment decisions. In our clinic, TgAbs are measured using a luminescence immunoassay (TgAb-ILMA) and radioimmunoassay (TgAb-RIA).

The objectives were to evaluate the complementary value of our TgAb assays and to determine the relation between TgAb concentrations and interference in our Tg assay.

Methods: Between March 2006 and September 2010, TgAb concentrations were routinely measured in 3075 serum samples from 483 DTC patients using the TgAb-RIA (Brahms, Germany) and TgAb-ILMA (Abbott Laboratories, USA). Tg concentrations were measured using a sensitive immunoradiometric assay (Brahms). Additional Tg recovery tests were performed in selected samples to detect TgAb interference.

Results: Using the TgAb-ILMA and TgAb-RIA, respectively 8.5% and 10.1% of the samples were found positive. A strong positive correlation was found between TgAb concentrations measured by the TgAb-RIA and Tg concentrations ≥1078 ng/ml (rho=0.959, n=134, P< 0.001). Recovery tests of 39 samples with high TgAb-RIA, low TgAb-ILMA results and Tg concentrations ≥1078 ng/ml showed no interference of TgAbs. In sera with Tg concentrations < 1000 ng/ml, TgAb-RIA and TgAb-ILMA results were positively correlated (rho=0.386, n=2941, P< 0.001). Correlation of recovery percentages and TgAb concentrations revealed a 'grey area' of TgAb concentrations above the reference value that did not interfere in our Tg assay.

Conclusions: The results of the TgAb-RIA and TgAb-ILMA are correlated in sera with Tg concentrations < 1000 ng/ml. TgAb results of this TgAb-

RIA are false positive in sera with Tg concentrations ≥1078 ng/ml, which is lower than indicated by the manufacturer (1450 ng/ml). The TgAb-ILMA is a reliable method for TgAb determination and may be used in preference to Brahms' TgAb-RIA. Interference of low-positive TgAb concentrations in this Tg assay is negligible.

P139

CONCURRENT GRAVES´ DISEASE AND AGGRESSIVE BEHAVIOR OF THYROID CANCER: A CASE SERIES AND CONCEPT OF INTERRELATED PATHOGENETIC LINKS

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Background: Aggressively behaving thyroid cancer (distant metastases, dedifferentiation) associated with Graves' disease (GD) represents a clinical entity with remarkable pathophysiological interest but with many unanswered questions.

The objective of the present work is

- to present a case series with concurrent GD and aggressive thyroid cancer
- to provide potential common pathogenetic links supporting a hypothesised reciprocal association between GD and the initiation and progression of thyroid cancer
- to discuss the impact on clinical management.

Methods and Results: We describe 3 cases and review the literature with regard to autoimmune thyroid disease, TSH signaling and chronic inflammation in thyroid cancer.

The first case is 27yo female diagnosed with recurrent GD and a papillary thyroid cancer with diffuse iodine-sensitive pulmonary micrometastases. The second case is 63yo male simultaneously diagnosed with GD and poorly differentiated thyroid cancer of papillary origin, with iodine-refactory mediastinal and pleural metastases. The third case is a 66yo female, presenting with a rapidly growing painless neck mass and weight loss. She was simultaneously diagnosed with anaplastic thyroid cancer in the right thyroid lobe and GD in the left lobe.

Discussion: Based on the clinical course of the cases and the literature, we discuss the following issues (1) the epidemiological data on the frequency of the association and possibility of true co-existence (2) the role of stimulating TSH-R antibodies and relevance of TSH-R/cAMP/PKA signaling in thyroid cancer initiation and progression (3) the connection between autoimmunity, inflammation and thyroid carcinogenesis.

Conclusions: GD should be regarded a risk factor for thyroid cancer initiation and progression. Chronic inflammation might trigger mutagenesis and provide a pro-tumorigenic inflammatory microenvironment. TSH-R antibodies stimulate the mitogenic TSH-R/cAMP/PKA pathway, thereby potentially contributing to thyroid cancer progression. On the other hand, thyroid carcinogenesis with the induction of an anti-tumorigenic inflammatory program might induce autoimmunity.

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OUR EXPERIENCE WITH RECOMBINANT HUMAN TSH

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Background: Recurrence of differentiated thyroid cancer (DTC) may occur many years after initial treatment. Tyroglobulin (Tg) is a sensitive and specific marker of local recurrence or metastatic disease after appropriate initial treatment of DTC. The use of recombinant human TSH (rhTSH) allows rapid stimulation of potential existing thyroid tissue, which prevents the morbidity associated to clinical hypothyroidism.

Aims: To assess the potential and benefit from the use of rhTSH in the follow-up of patients with DTC.

Material and Methods: We evaluated the results of 451 patients, 85.6% female and 14.4% male, with a mean age of 51.9±13.8 (17-85) years old, with previous history of treated DTC, that were submitted to exogenous stimulation with rhTSH between January 2005 and December 2010. We administered two intramuscular injections of 0.9 mg thyrotropin alfa (Thyrogen ®) in two consecutive days. TSH levels, 24 hours after last injection and TSH and Tg levels, 72 hours after last injection were measured.

Results: TSH level was 97.2 ± 10.9 μUI/ml on the 3rd day and 22 ± 18.2 μUI/ml (1.95-100) on the 5th day. Mean Tg was 81 ± 849.8 ng/ml (0.2-12000 ng/ml); 51.1% had Tg < 0.2 ng/ml and 23.2% had a value above 2 ng/ml. Anti-Tg level was 14.5 ± 60.9 UI/ml (0.2-678.5). We did not detect relevant side effects and major changes in the ability to maintain business activities and activities of daily living were not pointed out. Those previously submitted to suspension of therapy with the same purpose felt satisfied with the difference in the sense of well-being and work capacity.

Conclusions: The use of rhTSH is safe and effective, and useful in monitoring patients with a previous history of DTC. It increases the sensitivity of Tg determination, avoiding the debilitating symptoms associated with withdrawal of therapy.

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THYROGLOBULIN MONITORING AFTER TREATMENT OF WELL-DIFFERENTIATED THYROID CANCER (WDTC)

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Objective: To optimize the approach to postoperative monitoring of serum thyroglobulin (Tg) in patients with WDTC

Design: 50 patients with WDTC underwent thyroidectomy and 131-I ablation without distant mts and signs of disease recurrence were included in the study.

TSH, fT4, Tg, TgAb were measured at baseline. All patients were examined by neck ultrasonography. L-T4 therapy was withdrawn in 18 patients. Serum samplings were obtained after 3 and 4-5 weeks of withdrawal; Tg values were measured by immunometric method with functional sensitivity ~1 ng/ml and 0,2 ng/ml.

The life quality of 50 patients was assessed by the SF-36 Health Status Survey at three time points: during L-T4 treatment, after 3rd and 5th weeks of L-T4 withdrawal.

Results: During suppressive therapy Tg values below 0,5 ng/ml were defined at 75,6%, between 0,7-0,9 ng/ml - at 24,4%. Prevalence of TgAb presence was 36%.

TSH concentration ≥30 mU/l had been reached by 21st±2 day of withdrawal at 98% of patients.

High-sensitivity (HS) Tg tests demonstrated low reproducibility for all TgAb-positive patients (43,4%), meanwhile in TgAb-negative patients (66,6%) all results were reliable.

TSH stimulation test detected disease recurrence in 2 patients, and meanwhile control 131I-TBS didn't show any foci of uptake in the neck.

Patients' LQ assessment after 4-5 weeks of L-T4 withdrawal demonstrated that level of physical functioning was significantly lower ($p < 0,05$) comparing to 21 days withdrawal.

Conclusion: Stimulated Tg is a reliable marker of disease recurrence.

Presence of TgAb reduces the clinical significance of Tg measurements by high-sensitivity test.

Short-term L-T4 withdrawal is a simple and sufficient method for TSH stimulation, which allows achieving of TSH ≥30 mU/l in most of patients without negative consequences of hypothyroidism and LQ reducing.

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PROGNOSTIC SIGNIFICANCE OF POST OPERATIVE CERVICAL ULTRASONOGRAPHY AND OUTCOME OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA TREATED BY RADIOIODINE ABLATION AFTER PREPARATION WITH RECOMBINANT HUMAN TSH

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Context: Although the efficacy of radioactive iodine ablation (RIA) after either recombinant human thyrotropin (rhTSH) or thyroid hormone withdrawal (THW) in patients with differentiated thyroid carcinoma (DTC) has been proved, little is known about the risk of recurrence and the prognostic significance of post operative cervical ultrasound (POCUS) examination.

Objective: To analyse the risk of recurrence and prognostic value of the POCUS examination in patients treated by RIA whatever the modalities of ablation.

Methods: We conducted a monocentric retrospective study of 195 patients treated by 3.7 GBq 131I ablation for DTC (stage pT1, pT2, pT3, N0, N1, M0): 93 patients (rhTSH group) were compared to 102 patients (THW group). US examination was performed after surgery and at 6 months after RIA with a real time US scanner (Toshiba; 7.5-13 MHz linear transducer). The disease free survival rate (Kaplan-Meier method) and the prognostic factors of recurrence (log-rank tests, uni and multivariate Cox model-based analyses) were analysed.

Results: POCUS results were abnormal in 9% and 13% in the rhTSH and THW groups respectively (p 0.4). Seventeen (8.7%) recurrences were observed. At 4 years, the disease free survival was 68% in the rhTSH group versus 93% in the THW group (p 0.18). In multivariate analysis, a suspicious result at POCUS examination or at 6 months after RIA ($p < 0.0001$), the presence of initial lymph node metastasis (p 0.0002) and the elevation of post surgical serum Tg concentration (p 0.0001) were significantly associated with recurrence, the modality of ablation was not.

Conclusions: The outcome after RIA of patients with DTC is good whatever the modalities of ablation. The proportion of recurrence remains unchanged after preparation with either rhTSH or THW. Besides the established factors of recurrence, suspicious POCUS features appear to be significant for predicting persistent disease or relapse in patients with DTC.

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USEFULNESS OF MEASUREMENT OF SERUM IODINE LEVEL TO ASSESS THE APPROPRIATE LOW IODINE DIET PREPARATION FOR RADIOACTIVE IODINE THERAPY IN THYROID CARCINOMA

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Background: Most patients with differentiated thyroid cancer (DTC) undergo radioactive iodine (RAI) therapy after thyroidectomy. Low iodine diet (LID) is generally recommended prior to RAI therapy to increase RAI uptake. For the evaluation of appropriate LID preparation, measurement of 24hr urinary iodine excretion is considered as a gold standard until now. However, 24hr urine collection is inconvenient for patients. Recently, we suggested spot urine iodine/creatinine (I/Cr) ratio as a good alternative method. However, there was no study which investigated usefulness of serum iodine level instead of urine level for evaluating LID preparation status.

Methods: We prospectively measured serum iodine and spot urine iodine concentration together in 852 patients; 419 DTC patients with LID and 433 patients with other thyroid disorder with normal diet. Poor LID preparation was defined as urine I/Cr ratio more than 66.2 ug/gCr.

Results: There were significant correlations between serum iodine level and the two spot urine iodine level; the correlation coefficient was 0.803 for urine iodine level and 0.841 for I/Cr ratio ($p < 0.001$). Calculated R2 after log-log transformation was 0.61 for urine iodine level and 0.70 for I/Cr ratio, respectively ($p < 0.001$). The cutoff of serum iodine level was 20.4 ug/L (sensitivity: 79% specificity: 82%) for the evaluation of appropriate LID preparation in DTC patients.

Conclusion: Measurement of serum iodine level may be useful as an adjunct parameter in estimating LID preparation status.

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CLINICAL FEATURES AND OUTCOME OF DIFFERENTIATED THYROID CARCINOMAS IN YOUNG ROMANIAN PATIENTS DIAGNOSED AFTER CHERNOBYL ATOMIC ACCIDENT

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Objectives: To present the clinical features and outcome of surgical and radioiodine treatment in young Romanian patients diagnosed with differentiated thyroid carcinoma after Chernobyl atomic accident.

Methods: Study group A consists of 27 patients (8M/19F), born between 1970-1986, diagnosed with differentiated thyroid carcinoma. Control group B consists of 13 patients (3M/10F), born between 1987-1999, diagnosed with differentiated thyroid carcinoma. Biochemical testing (TSH - immunochemiluminescence, thyroglobulin, antithyroglobulin antibodies - immunoradiometric assay), thyroid ultrasonography, ^{131}I thyroid, whole body scintiscan were performed.

Results: Gender distribution, iodine intake, tumor diameter at diagnosis, preoperative TSH levels were similar in both groups. Age at diagnosis was significantly higher in study group (26.8±5.4 years) than control group (18.8±4.7 years), $p < 0.001$. In study group there were 24 papillary carcinomas (5 papillary, 8 diffuse sclerosing variant, 11 follicular variant) and 3 follicular carcinomas. In control group there were 13 papillary carcinomas (3 papillary, 5 diffuse sclerosing variant, 5 follicular variant). All patients previously underwent total thyroidectomy. Multifocal carcinomas showed similar frequency (13/27 vs. 6/13 cases, respectively). Radiodiodine treatment (1-4 doses) was administered in all patients but 8, harboring microcarcinomas; mean cumulative radioiodine dose was 122.6±121 mCi ^{131}I in group A and 150±73.6 mCi 131I in group B. Median thyroglobulin levels after last radioiodine dose were similar (1.2 ng/mL in study group *vs.* 0.6 ng/mL in control group). Cure rate (final Tgl< 0.2 ng/mL, negative thyroid and whole body scans) was similar in both groups: 5 out of 27 cases in study group (18.5%) and 3 out of 13 cases (23.1%). in control group.

Conclusion: In our series, thyroid differentiated carcinomas occurring in patients exposed to Chernobyl radiation during childhood or adolescence showed similar clinical features and outcome with carcinomas occurring in patients born after 1987. Further follow-up and molecular studies are needed in order to identify specific differences.

P145

SEVERE DIFFUSE GLOMERULAR THROMBOTIC MICROANGIOPATHY OF THE VEGF-INHIBITOR ASSOCIATED TYPE FOLLOWING TREATMENT WITH XL184 OR PLACEBO

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Proteinuria and rare cases of nephrotic syndrome have been reported with several anti-VEGF agents. A role for additional pathogenic factors has been

suggested in patients treated with VEGFR signaling inhibitors who develop kidney damage.

We report a 23 year old patient with metastatic medullary thyroid carcinoma (MTC) who was treated with 4.4 GBq Y-90-DOTATE 10 months after surgery because of progressive MTC. Five months following treatment with 4.4 GBq Y-90-DOTATE which can further impair preexisting renal damage, the patient was enrolled in a blinded Phase 3 study comparing XL184, a Ret, MET, VEGFR2/KDR and KIT tyrosine kinase inhibitor to placebo. He received blinded treatment on study for 3 weeks with normal creatinine before the start of treatment. Five days after initiating study treatment, the patient received zolendronate 4 mg because of bone metastasis. A creatinine of 1.7 mg/dl and hypoproteinemia (48 g/l) was detected 14 days after his enrollment in the study and 9 days following zolendronate treatment. Subsequently, the patient developed hyperkalemia (6.3 mmol/l), LDH of 525 U/l, anemia, thrombocytopenia (76/nl) and nephrotic range proteinuria of up to 25 g/24 h. Renal biopsy on day 30 showed severe diffuse glomerular thrombotic microangiopathy of the VEGF-inhibitor associated type. Microangiopathic hemolytic anemia ameliorated spontaneously. The patient was discontinued from study treatment. Unfortunately, four months after initiating study treatment, the patient receives his first dialysis. The patient's treatment assignment (XL184 vs placebo) remains blinded.

The renal histology with diffuse glomerular thrombotic microangiopathy has been reported in patients treated with VEGFR signaling inhibitors. Bisphosphonates can act as epithelial toxins that target both the podocyte and the tubular epithelium at higher doses. Therefore, this patient's renal damage may have been precipitated by zolendronate. Given the findings of thrombotic microangiopathy, concomitant medications with possible renal damage should be discontinued during VEGFR-signaling inhibitor treatment.

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A GENERAL METHOD TO DERIVE ROBUST ORGAN-SPECIFIC GENE EXPRESSION-BASED DIFFERENTIATION INDICES: APPLICATION TO THYROID CANCER DIAGNOSTIC

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Differentiation is central to development, while dedifferentiation is central to cancer progression, hence a quantitative assessment of differentiation would be most useful. We propose an unbiased method to derive organ-specific differentiation indices from gene expression data and demonstrate its usefulness in thyroid cancer diagnosis.

We derived a list of thyroid-specific genes by selecting automatically those genes that are expressed at higher level in the thyroid than in any other organ across a collection of normal tissues genome-wide gene expression compendia. The thyroid index of a tissue was defined as the median expression of these thyroid-specific genes in that tissue.

As expected, the thyroid index was inversely correlated with meta-PCNA, a proliferation metagene (see companion paper), across a wide range of thyroid tumors. By contrast, the two indices were positively correlated in a time course of thyroid stimulation hormone (TSH) activation of primary thyrocytes. Thus, the thyroid index captures biological information not integrated by proliferation rates. The differential diagnostic of follicular thyroid adenomas and follicular thyroid carcinoma is a notorious challenge for pathologists. The thyroid index discriminated them as accurately as machine learning classifiers trained on the genome-wide cancer data. Hence, although it was established exclusively from normal tissues data, the thyroid index integrates the relevant diagnostic information contained in tumoral transcriptomes. These results were replicated in the classification of the follicular and classical variants of papillary thyroid cancers, i.e. tumors dedifferentiating along a different pathway.

Differentiation indices could in principle be derived for other organs and applied to other problems. Opportunities and limits are discussed.

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EPIGENETIC COMPOUNDS HAVE MINOR EFFECTS ON DIFFERENTIATION IN HUMAN THYROID CANCER CELL LINES BUT INDUCE EXPRESSION OF GENES INVOLVED IN *IN VITRO* ADAPTATION

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In thyroid cancer, lack of response to specific treatment, e.g. radioiodide, is generally caused by a loss of differentiation characteristics of tumor cells. It is commonly assumed that this loss is related to epigenetic mechanisms, which are reversible. Therefore drugs releasing epigenetic repression have been proposed to reverse this silencing. On the other hand, human cancer thyroid cell lines are often used as models of thyroid cancers. In this work we investigated by microarray and RT-PCR which genes are re-induced in cancer cell lines when treated with anti-epigenetic compounds. Most differentiation markers were not re-expressed, dual oxidases were most induced by 5-AzadC. Sodium iodide symporter (NIS) mRNA, a therapeutic target for thyroid cancer treatment, was only weakly induced after 5-AzadC treatment. The strongest NIS mRNA induction was observed when cells were treated with 5-AzadC combined with TSA and forskolin, the later being an activator of the cAMP pathway. However, this co-treatment did neither increase NIS protein expression nor iodide uptake, i.e. NIS function was not restored. Comparison of 5-AzadC induced mRNA expression profiles with primary cultured differentiated thyrocytes showed only few commonly regulated genes. This suggests that 5-AzadC had only a minor effect on the re-induction of differentiation. Whether this reflects an inadequacy of the model remains an open question. Most of the strongest commonly induced genes by 5-AzadC in cell lines were either not regulated or upregulated in anaplastic thyroid carcinomas. 5-AzadC negatively affected cell viability and microarray analysis showed induced pathways, including apoptosis, antigen presentation, defense response and cell migration. This suggests that the epigenetic control operating in the cell lines mostly represent adaptations of the cell lines to their culture conditions, rather than the initial cancer epigenetic silencing.

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ESTABLISHMENT AND APPLICATION OF CELL LINES FROM MEDULLARY THYROID CARCINOMA

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Objectives: Medullary thyroid carcinoma (MTC) originates from calcitonin-producing neuroendocrine C-cells in the thyroid gland. Activating mutations in the *RET*-proto-oncogene are associated with both familial and sporadic MTC development, but no additional genetic factors have yet been identified for non-*RET*-cases. The cytogenetics of MTC have been sparsely studied because the cells are difficult to grow in culture. As MTC is poorly responsive to chemo- and radiation-therapy, surgery is the only effective therapy. We have focused on the establishment of cell lines from MTCs as relevant models to study genetic properties and to search for potential treatments.

Methods: The maintenance of neuroendocrine characteristics was studied by immunocytochemistry, transmission and scanning microscopy and by tumorigenicity test in severe combined immunodeficient (SCID) mice. Cyto- and molecular-genetic analyses were performed in MTC-derived cell lines and compared to the tissue of origin using multiplex-FISH and array-CGH. Additionally, using assays for proliferation (WSt-1), necrosis and apoptosis

(Caspases 3/7), we examined whether selected plant-derived agents had anti-tumor activity specific for MTC. Normal skin fibroblasts served as controls.

Results: Nine MTCs were established as continuous cell lines. Each retained neuroendocrine characteristics, such as positive immunoreactivity with calcitonin. Neurosecretory granules were found in the cytoplasm. Tumorigenicity was positive in SCID mice and serial heterotransplantations were done. Genomic analyses showed that a subset of MTCs did not acquire chromosomal instability, although these cell lines were tumorigenic, indicating novel pathways in tumorigensis.

Treatment of MTC cells with plant-derived agents caused dose-dependent antiproliferative and pro-apoptotic effects while normal fibroblasts remained unimpaired, indicating a lack of side effects. Treatment of hetero-transplanted tumors produced a retardation of tumor growth thus confirming the *in vitro*-findings.

Conclusion: Our data suggest an improvement in the clinical outcome for patients with MTC when the diagnostic molecular markers that underlie its pathogenesis are identified.

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PROGNOSTIC VALUE OF BRAF MUTATIONS IN PAPILLARY THYROID CARCINOMA (PTC)

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Prognostic and predictive value of clinical, biological and histological features in PTC patients is still discussed. BRAF mutations, associated with more aggressive PTC course and higher risk of recurrence, are supposed to be one of these factors.

The aim of this study was to analyze the correlation between BRAF mutation and clinicopathological risk factors as well as to assess its value as a prognostic and predictive factor.

Material and Methods: A group of 330 PTC patients primarily operated between 2004 and 2006 in Oncological Surgery Clinic in Gliwice were analyzed. Up to now 106 PTC tumors were evaluated. Further analysis in the whole group is pending. DNA was isolated from tissue-paraffin blocks. The presence of V600E mutation was evaluated by sequence analysis performed using AbiPrism 377 and 3130 xl genetic analyzer (Life Technologies). Statistical methods based on SPSS12 software involved x^2 and Kaplan-Meier survival analysis.

Results: Frequency of BRAF mutation in the analyzed group of 106 PTC's was 42.5%

Mean tumor diameter in BRAF positive (BRAF+) subgroup was 21 mm, whereas in BRAF negative (BRAF-) 13mm. Tumors not greater than 1 cm were observed in 13 (29%) BRAF+ cases compared to 36 (60%) in BRAF-subgroup. The frequency of pT1a tumors was significantly higher in BRAF-group (p=0.02). One cancer-related death and two recurrences were observed in the BRAF+ group, whereas in BRAF- group only 1 relapse. The 5-year disease free survival was higher in BRAF- group than in BRAF+ group (98% and 95% respectively; ns.). In the analyzed group only older age positively correlated with the presence of BRAF mutation (p=0.0017). However, there were no correlation between BRAF status and lymph node/distant metastases, multifocality and extra-thyroid extension.

Conclusion: BRAF mutation is one of prognostic factor in PTC patients, but is too early to consider it as routine predictive one.

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FUNCTIONAL REDUNDANCY: AN ASPECT OF EPH RECEPTORS IN THE THYROID OF EPHA4 KNOCKOUT ADULT MICE

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Objectives: Eph receptors and their cognate ligands, the ephrins have been increasingly recognized as important cell membrane proteins regulating a wide range of physiological processes, including embryonic organogenesis and homeostatic maintenance of adult tissues. Both receptors and ligands possess the unique ability of bidirectional signaling, leading to activations of Eph and ephrin expressing cells. EphA4 is one of only two Eph receptors which is promiscuous and interacts with both class A and B ephrins. In the thyroid, EphA4 is continuously expressed from embryogenesis into adulthood. Recent findings indicate that in the developing thyroid, EphA4 is a novel regulator of thyroid morphogenesis, specifically in regulation of follicular genesis. However, functions of EphA4 in adult thyroid are less well understood.

Methods: EphA4-null and wild type (WT) adult mice were use to investigate expression patterns of ephrin ligands specific for EphA4 receptor. Using reverse transcription (RT) PCR, ephrinA1-4 and ephrinB1-3 gene expression in tissue homogenates from thyroid, brain, thymus and kidney were analyzed.

Results: RT-PCR analysis of mRNA expression of ephrinA1-4 and B1-3 ligands in tissue homogenates from thyroid, brain, thymus and kidney from EphA4-null and WT adult mice revealed considerable variations in levels of mRNA expression between different tissues, as well as between different ephrin ligands. Yet, when comparing within one specific ephrin, only modest variations in mRNA expression exist between EphA4-null and WT tissues.

Conclusion: We conclude that insignificant variations in mRNA expression of different ephrin ligands between EphA4-null and WT tissues strongly suggest the concept of functional redundancy. Compared with their WT counterparts, general deletion of EphA4 in adult mice did not show any significant down-regulation of ephrinA1-4 and B1-3. Therefore, indicating redundant effects of other Eph receptors interacting with ephrins ligands. These findings provide evidence of functional redundancy within Eph receptors expressed in the thyroid of adult mice.

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PREDICTIVE VALUE OF MOLECULAR MARKERS THAT INVOLVED IN A GENETIC SIGNATURE IN THYROID TISSUE AND THEIR INVOLVEMENT IN THE TUMOUR DEDIFFERENTIATION PROCESS

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Although the well-differentiated tumors (PTC or FTC) have a good prognosis, some of them can present a dedifferentiation process producing metastasis. In our previous results using microarray technology, we identified 23 genes as a genetic signature able to predict a worse prognosis in the patients.

Aim: Was to analyze this genetic signature in a cohort of patients that present well-differentiated tumors in other to identify molecular biomarkers with diagnosis value.

Material and Methods: FTC(n=7), PTC(n=12) were collected from unrelated patients. The normal RNA from thyroid tissue was obtained from Agilent. Total RNA was extracted from the tissues and cDNA synthesis was performed using High Capacity reagents which were used for TaqMan low-density arrays analyses. The Gene Expression Micro Fluidic Card was designed with the specific 22 genes obtained from Applied Biosystems Assays-on-Demand™ Gene Expression Products. Real-Time RT-PCR data were quantified by SDS203 software package and the statistical analysis using DataAssist™ software was preformed.

Results: Differential gene expressions were found in the comparisons of PTC and FTC series *versus* normal RNA from thyroid tissue as a control. In PTC, the expression of 13 genes was significant (P< 0.01), seven of

them were overexpressed (IL1RN, ORMDL3, PDK2, PTPRN2, SH3BGRL2, SIAH1, TWIST1) and 6 genes were underexpressed (ANLN, BIRC5, CCNB2, NUSAP, PRC1, RRM2). However in FTC, only 11 genes were significant ($P< 0.01$), 7 of them were overexpressed (APLP2, IL1RN, ORMDL3, PDK2, PPAP2B, SH3BGRL2, SIAH1) and 4 genes were underexpressed (BIRC5, CCNB2, CEP55, NUSAP1). Meanwhile, we found only of PTPRN2, TWIST1, ANLN, PRC1, RRM2 were differentially expressed in PTC. In contrast to FTC, APLP2, PPAP2B, SIAH1 and CEP55, genes were found.

Conclusion: These finding represent a helpful contribution to understand the molecular mechanisms involved in thyroid cell tumors. The next step will be to compare these results between well-differentiated and undifferentiated tumors.

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ACTIVITY OF NOVEL WATER SOLUBLE PORPHYRIN POR-EDTA AGAINST MEDULLARY THYROID CARCINOMA CELL LINES

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Objectives: Medullary thyroid carcinoma (MTC) is a calcitonin-producing neuroendocrine tumor arising from the parafollicular C-cells of the thyroid gland. It is noteworthy that MTCs are known for their poor response to standard chemotherapy and radiotherapy, and surgical intervention remains the only curative treatment. There is therefore a substantial need to establish new therapeutic options in the clinical treatment of these tumors. Recent studies have demonstrated antiproliferative and tumoristatic effects of novel porphyrin compounds in the MTC-SK cell line. We evaluated the effects of a novel water soluble porphyrin, Por-EDTA, in medullary thyroid carcinomas.

Methods: An A_3B-porphyrin bearing three pyridyl- and one nitro-phenyl substituent at the porphyrin's meso positions was prepared employing mixed aldehyde synthesis followed by reduction of the nitro group to the corresponding amine. Thereupon, an EDTA substituent was introduced via amidation of the amino functionality. Finally, the pyridyl subunits were methylated to ensure full water solubility of the derivative. MTC cell lines MTC-SK and SHER-I were incubated for 24, 48 and 72 hours at different concentrations of Por-EDTA, and cells were analysed with cell counting, WST-1 cytotoxicity assay, and DAPI staining.

Results: The fully water soluble porphyrin Por-EDTA showed antiproliferative effects in MTC-SK tumor cells. In both cell lines, MTC-SK as well as in SHER-I, an inhibition of cell proliferation as well as a decrease in cell viability was noted after treatment with 10µm Por-EDTA using cells with high passage numbers, while there were no significant alterations in treated HF-SAR human fibroblasts.

Conclusion: Novel porphyrin derivates could be a new option in the treatment of chemoresistant and radioresistant neuroendocrine tumors.

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EFFECTS OF CURCUMIN ON THYROID CANCER CELL LINES

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Objectives: Curcumin is a major phenolic antioxidant which is able to inhibit carcinogenesis in a variety of cell lines. However, little is known about its effects on thyroid cancer cell lines. In this study, we evaluated the effects of curcumin (10-50 µM) upon follicular thyroid carcinoma cell line FTC-133 and papillary thyroid carcinoma cell line K1.

Methods: Cell viability, cell apoptosis, the expression of apoptosis-related proteins Bcl-2 and PARP, intracellular Ca^{2+} concentration, mitochondrial membrane potential (MMP) and intracellular formation of reactive oxygen species (ROS) of both FTC-133 and K1 cells were investigated using MTT assay, Annexin V-FITC/PI, western blotting, Fluo-3 AM, rhodamine 123, and DCF-DA, respectively.

Results: Experiments showed that curcumin significantly inhibited FTC-133 or K1 cells proliferation and induced cells apoptosis in a dose-dependent manner. A decrease in expression of Bcl-2 and a cleavage of PARP were observed in FTC-133 or K1 cells after exposuring to 10~50 µM curcumin. Meanwhile, curcumin could also cause a rapid increase in intracellular free Ca^{2+} concentration and the disruption of mitochondrial membrane potential. Moreover, the intracellular production of ROS increased significantly and reached the peak within 5 min with 40 µM curcumin-treated and restored steadily to normal later.

Conclusions: These results may provide an explanation for effects of curcumin on the apoptosis of follicular and papillary thyroid carcinoma cells. The role of curcumin in inducing apoptosis of cells indicates that curcumin may be a potential chemotherapeutic agent for thyroid carcinoma.

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EXPRESSION OF SATB1 GENE IN THYROID CARCINOMA CELL LINES

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Special AT-rich sequence binding protein 1 (SATB1) is a genome organizer that controls chromatin structure and the expression of multiple genomic loci. Recently its gene has been reported to be upregulated in aggressive breast cancer emerging as a poor prognostic marker. Nevertheless, at the present time no data are available on SATB1 expression in thyroid carcinomas.

Aim of this study was to investigate SATB1 expression in a panel of thyroid carcinoma cell lines and compare it with the expression in carcinoma cell lines derived from other human cancers.

SATB1 expression was investigated by RT-PCR in a total of 24 cancer cell lines; 17 arising from thyroid tissue: 1 normal thyroid, 2 Papillary Thyroid Carcinomas (PTC), 2 Medullary Thyroid Carcinomas (MTC), 9 Anaplastic Thyroid Carcinomas (ATC), 3 Follicular Thyroid Carcinomas (FTC). The remaining 7 cell lines derived from: breast cancer (n=3), colon cancer (n=2), hepatocellular carcinoma (n=1) and melanoma (n=1).

Expression of SATB1 was not detectable in the cell line arising from normal thyroid (Nthy-ori3) but it was expressed in 1/2 (50%) PTC, 2/2 (100%) MTC and 3/9 (33%) ATC. No SATB1 expression was found in the 2 FTC cell lines. In non-thyroid cell lines, SATB1 was expressed in 2/2 (100%) colon carcinomas and in 2/3 (66%) breast carcinomas while no expression was detected in the hepatocellular and melanoma cell lines. Interestingly both MTC cell lines found to be positive for SATB1 expression harboured a mutation of RET gene and the PTC cell line (TPC1) positive for SATB1 harboured the RET/PTC1 rearrangement, suggesting a correlation between genetic alteration of the RET gene and the expression of SATB1.

In conclusion SATB1 is differentially expressed in thyroid cancer cell lines; the correlation between genetic alterations of RET and SATB1 expression suggests a link between these two events.

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PHARMACOLOGICAL CARDIOVERSION THERAPY FOR POST-THYROTOXIC PERSISTENT ATRIAL FIBRILLATION USING ANTIARRHYTHMIC DRUG; BEPRIDIL

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Objectives: Conversion to sinus rhythm is a treatment strategy for patients with post-thyrotoxic atrial fibrillation (AF). Several methods are available to convert AF to sinus rhythm, and pharmacological cardioversion is the method

of first choice. The multichannel blocker bepridil was first developed as an antianginal drug, and it was later found to possess an antiarrhythmic property, including conversion of AF. The objective of the present study was to assess the efficacy and safety of bepridil in patients with post-thyrotoxic persistent AF.

Methods: The records of 62 patients with post-thyrotoxic persistent AF who had been treated with bepridil (100-200 mg/day) were reviewed. Their conversion rate, sinus rhythm maintenance rate, and adverse events were examined. The thyroid function and cardiac condition of sinus converters (responders) and non-responders were compared to identify factors that might influence the outcome. Adverse effects were also examined.

Results: Oral bepridil therapy resulted in conversion in 32 (51.6%) of the 62 patients. There were no significant differences in clinical characteristics between the responders and non-responders. At the most recent follow-up examination (28.9±13.5 months) sinus rhythm was maintained in 26 (81.3%) of the 32 responders. The rates of sinus rhythm maintenance in the responder group, according to the Kaplan-Meier method, were 93.5% at one year, and 89.3% at 2 years. Adverse effects consisted of abnormal QTc prolongation in 3 patients and sinus bradycardia in 10 patients. These changes resolved after discontinuation of bepridil. There was one death in which a causal association with bepridil could not be ruled out.

Conclusions: Cardioversion remains a treatment strategy for post-thyrotoxic persistent AF, because once sinus rhythm has been achieved in such patients, the sinus rhythm maintenance rate is excellent. Bepridil is highly effective in converting post-thyrotoxic AF to sinus rhythm, but it should be used with caution to avoid serious side effect.

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LONG-TERM CLINICAL OUTCOME IN PATIENTS WITH THYROTOXICOSIS TREATED WITH A 60GY ABSORBED DOSE OF RADIOIODINE

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Objectives: The aim of this study was to evaluate the long-term outcome for patients with Graves' Disease treated with individually calculated radioiodine doses.

Methods: Previous work in this department suggested that an absorbed dose of 60 Gy to the thyroid offered a high probability for patients to achieve euthyroidism. We identified 133 patients who had been treated in this way and for whom we had a minimum of 5 years follow-up data. The subjects were categorised into two groups those with classic Graves' disease (97) and Graves' in a nodular goitre (32) as defined by homogenous uptake or heterogeneous uptake, respectively on radionuclide imaging.The activity required for each patient was calculated using the thyroid volume, the maximum uptake and the effective half-life of iodine in the thyroid. This resulted in a range of administered activities of between 21 and 707 MBq (mean 108 MBq).

Results: Table 1 shows the outcome of single 60Gy treatments.

	1 year (N=133)	1–5years (N=108)	5–10 years (N=89)
Euthyroid	70 (52.6%)	60 (55.5%)	13 (14.6%)
Thyroxine replacement	15 (11.2%)	29 (26.8%)	37 (41.6%)
Anti-thyroid medication	23 (17.2%)	0	0
Further Radioiodine	25 (18.7%)	16 (14.6%)	1
Lost/ discharged	0	3	38* (42.7%)

*discharged from follow up having been euthyroid for at least 3 years.

Conclusion: A substantial number (38%) of patients will achieve sustainable euthyroidism and the majority (66%) resolution of their hyperthyroidism following a single administration of a personalised radioiodine dose. The presence of nodules within the gland does not have a significant affect on outcome.

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EVALUATING THE RESULTS OF LONG-TERM TREATMENT WITH ANTI-THYROID DRUGS IN GRAVES´ DISEASE

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Purpose: This study was conducted to observe the results of long term treatment with antithyroid drugs in patients with graves´ disease and evaluate the factors affected the incidence ofhypothyroidisem and the relapse of hyperthyroidism after treatment.

Materials and Methods: Total of 268 patients with graves´ disease who had referred to Endocrinology clinic during 2005 - 2008 and were treated with long term anti-thyroid drugs, were studied. Data about the age, gender, estimated weigh of thyroid before and after the treatment, level of thyroid hormones, disease relapse, hypothyroidism and the side-effects resulting from the treatment were collected and analyzed.

Results: Total of 268 patients [82 (31%) males, 186 (69%) females, mean age of 35±27 and follow-up course of 31±16 months], were studied. After the end of treatment, 53% were affected with hyperthyroidism relapse, which 84% occurred at the first 12 months after the completion of treatment. The mean duration of hyperthyroidism relapse after the treatment was 8.3±7.3 months. The relapse in the treated patients in both ends of age spectrum was significantly high (P< 0.001). In male patients with massive thyroid and lower TSH level, the rate of relapse was higher. The rate of incidence of hypothyroidism after discontinution of treatment was about 6%. The mean duration of hypothyroidism incidence was 13.4±13.8. More decrease of thyroid size during the treatment, higher level of serum TSH after the treatment, and lower thyroid hormone levels before the treatment were some of the predictive factors of hypothyroidism incidence after the completion of treatment with antithyroid drugs (P=0.005, P< 0.001, P< 0.05 respectively). Of the 268 graves´ patients treated with antithyroid drugs, 104 patients (39%) remained euthyroid in the follow up course.

Conclusion: Using long term treatment with antithyroid drugs is still the first step in treating patients with graves´ especially in middle-aged women.

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RISK FACTORS OF DEVELOPMENT AND PERSISTENCE OF THYREOTOXIC CARDIOMYOPATHY

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It is known, that thyrotoxicosis (TT) causes cardiomyopathy which is accompanied with increasing heart rate (HR) and development of atrial fibrillation (AF) which, in turn, leads to development of heart failure(HF). Accordingly, the purpose of our study is carrying out step-by-step plural regressional analysis for definition of the contribution of various factors in AF development, decrease EF and reversibility of these changes.

The present study includes 254 patients with TT without any CVD before of treatment and in a year of therapy (mean age 41,3+1,2 years) (36 men and 218 women). The patients were examined echocardiography by standard method. Duration TT varied from 6 months to 5 years.

We showed, that the greatest influence on development AF rendered duration TT (p < 0,0001, 1-Toler=0,68), HR (p < 0,0001, 1-Toler=0,18), a male sex (p< 0,0001, 1-Toler=0,25), left atrial diameter (LAD) (p=0,0002, 1-Toler=0,48), left ventricular diameter (LVD) (p < 0,0001, 1-Toler=0,68) and left ventricular mass index (LVMI) (p=0,0001, 1-Toler=0,57). The account of all parameters (p < 0,0001), probability of correct classification - 91,2 %. For objective estimation of development HF values EF on Simpson (EFS) have been analysed by a method of plural regressional analysis. Plural factor of correlation R=0,76, p < 0,0001, SE=5,2. The same analysis has been executed for EFS. Plural factor of correlation R=0,52, p < 0,0001, SE=3,4. At step-by-step selection (with inclusion) 5 parameters have appeared to be highly significant: LVD (p < 0,0001), HR (p=0,01), duration TT (p=0,02), a level a sBP (p=0,0009), a level free thryiodthyronine (fT3) (p=0,005).

Thus, the duration TT for development AF was the most significant of all revealed factors. HR and a male sex were the most important predictors of AF development. Level a sBP and fT3 prior to the treatment TT and LVD were the most significant predictors for decreased EF.

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GRAVES DISEASE OF MEN AND WOMEN: COMMON AND DIFFERENT SIGNS

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Objectives: Graves disease (GD) managements are varying. More then 40% GD patients undergo surgery in Russia.

Methods: In the Centre 2920 GD patients were operated. They made 11.7% of 24934 thyroid (T) surgical cases during 1974-2009. This study includes 357 males (M) and 2527 females (F) observed 2-30 years after Dunhill-Drachinskaya operations (leaving 2-4 g. of T upper pole) or thyroidectomy.

Results: Average age made 46.2±2.5 years. M (43.2±1.5) were significantly (P< 0.05) younger then F (47.3±1.8). Age of GD beginning was about 39. Duration of diseases of M was much shorter (2.1±0.9r.) then F (7.2±1.9 r.). Cardiac fibrillation happened in 32.1% of M, 13.7% - in F, exophthalmia - in 44.4% of M, in 24.8% of F (P< 0.05). Deterioration of libido and potency has observed in 40.6% and 48.9% of M (39.1±0.4). Plasmapheresis was applied in 9.4% of M, 5.8% - of F. Thyroid has neck location in 55.0% of M, 62.0% - of F. T more often extended behind of sternum and trachea in M. The indication for operations: recurrent and complicated hyperthyroidism (47.0%); compression syndrome (27.0%); allergy (7.0%); oncological risk, pregnancy (19.0%). Postoperative unilateral RLN palsy was found at 0.9%, temporary hypoparathyroidism - at 1.7 %. T remnant function was stabilized per the first 12-18 months. In 2-5 years later euthyroid condition observed in 63.4%, postoperative hypothyroidism - at 29.8 %, subclinical hypothyroidism - at 5.4 %, the relapse of thyrotoxicosis - at 1.36 %. High-risk group of postoperative hypothyroidism included: patients over 55; high levels of "classical" antithyroid antibodies; expressed autoimmune inflammation; T remnant less 4 cm^3.

Conclusion: Clinical manifestations of M and F GD have essential differences with more aggressive course in M. Relapses of GD are rare after Dunhill-Drachinskaya T resection. Aggressive course of GD in M demands early surgical treatment.

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FUNCTIONAL SENSITIVITY OF A NEW ULTRASENSITIVE THYROID-STIMULATING HORMONE ASSAY: FROM INITIAL ASSESSMENT TO ROUTINE FOLLOW-UP

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Objective: TSH assays are the first-line thyroid function tests as they provide the most sensitive and specific means for detecting thyroid dysfunction. The level of sensitivity allows to distinguish euthyroid from hyperthyroid patients with suppressed serum TSH concentrations (< 0.02 mIU/L) and enables to detect early subclinical hyperthyroidism. Towards the clinical utility of low TSH measurements, the functional sensitivity of the new TSH third generation ultrasensitive assay (TSH3-UL) was evaluated on the ADVIA Centaur® analyzer (Siemens Healthcare Diagnostics). Thereafter, this assay was used for the routine and results of quality control (QCs) within- and between-lots of reagents over a period of twelve months were analyzed.

Methods: Before routine use, the functional sensitivity was assessed with different low-TSH human serum pools tested in 30 runs with 2 lots of reagents for 6 weeks. In routine, TSH assay precision was daily monitored with 5 different QCs: Lyphochek® Anemia and Immunoassay Plus Controls levels 1, 2 and 3, and a very low value human serum pool chosen to check the degree of reliability of values close to the functional sensitivity.

Results: TSH3-UL functional sensitivity was 0.0185 mIU/L in agreement with NACB guidelines (CV < 20 % for [TSH] < 0.02 mIU/L). QCs monitoring over one year showed acceptable precision except for the low TSH serum pool (mean 0.0252 mIU/L, CV 22%).

Conclusion: The good precision of low values obtained during the assessment has been thereafter affected by quite marked variations between reagent lots. This assay doesn't meet the specifications for a third generation test. In conclusion, manufacturers should compare the precision of low values on each reagent lots before their commercialization. Until adequate arrangements are made by the manufacturers, it can be useful for clinical laboratories to check between-lots precision with a low level QC close to the functional sensitivity value.

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THYROTOXICOSIS AND WPW SYNDROME: PROPRANOLOL IS CONTRAINDICATED

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Background and Aim: Beta -adrenergic blocking agents is widely administrated in treatment of patients with thyrotoxicosis. We have analysed the cases of thyrotoxicosis when propranolol administration must be contraindicated.

Materials, Methods and Results. The case history of two women with untreated thyrotoxicosis complicated by atrial fibrillation (AF) with ventricular rate (VR) more than 220/min.

1. M., 31 years, legs edema, tachypnea (22 min), BP 110/70mm, AF, VR -220 min. The diagnosis of diffuse toxic goitre was confirmed four month ago (T4 level - 369nmol/l), but patient didn't take methimazole prescribed. At admission 40 mg propranolole was given. Within 40 minutes BP decreased to 70/40 mm Hg, then - heart arrest. Resuscitation had been ineffective. 2. D., 71 years, with multinodular toxic goitre was admitted in ICU. Ten days ago she began to take methimazole 30 mg/day; at that time TSH level was 0.01 mU/l and T4 - 185nmol/l. In anamnesis was collapse episode after digoxin i.v. administration. Edema, ortopnoe, BP 110/70 mmHg, AF with VR 150-300min. Methimazole doses was increased to 50 mg/day. Because of tachycardia the first dose (40 mg) of propranolole was given. Within one hour shock developed; resuscitation was ineffective. Main pathology examinations data: myocardial dystrophy, heart weight - 325 and 380g. No significant signs of adrenal insufficiency were revealed.

Conclusion: The reason for this patients death was arrhythmogenic shock due to propranolol administration for thyrotoxic patients with undiagnosed WPW syndrome. The diagnosis of WPW syndrome on AF background is difficult and main marker in such situation is VR more than 210-220 min. To verapamile and digoxine known as agents contraindicated in WPW syndrome we add propranolol and recommend to diagnose this syndrome in thyrotoxic patients always.

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TREATMENT OF MILD GRAVES' HYPERTHYROIDISM WITH POTASSIUM IODIDE IN PATIENTS WITH MALIGNANCY REQUIRING ANTI-CANCER DRUG THERAPY

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Purpose: Potassium iodide (KI) therapy was tried in patients with Graves'hyperthyroidism complicated with malignancy.

Patients:

Case1: 34yo male was diagnosed as lung cancer (large cell ca, giant cell type). He lost 14kg body weight and small goiter was found. Serum fT_4 3.9ng/dl, TSH < 0.01mU/L, TBII 51.7%, TSAb 207%, RAIU 67.8%. He was treated with cis-diamminedichloro-platinum (CDDP), irinotecan and potassium iodide (KI) 100mg.

Case 2: 66 yo female became thyrotoxic when gastric ca relapsed. FT_4 2.5ng/dl TSH < 0.01mU/L, TBII 8.2IU/L, TSAb 953% RAIU 54.2%/5h, Estimated thyroid weight was 33g. She was treated with CDDP, tegafur gimeracil oteracil potassium (TS-1) and KI (100mg).

Case 3: 40 yo female was diagnosed as endometrial cancer and Graves'hyperthyroidism. FT_4 3.6ng/dl, TSH < 0.01mU/L, TBII 58.7%,TSAb 339%, ^{99m}Tc uptake 6.6%/30min. She was treated with 10-20mg methimazole and endometrial cancer was surgically treated. She became almost euthyroid but TBII and TSAb remained strongly positive. Before chemotherapy (paclitaxel and carboplatin), MMI was withdrawn and she was treated with 100-200mg KI.

Case 4: 47yo female. After hysterectomy for cervical cancer, pulmonary metastasis was found. Just before chemotherapy, Graves'disease was diagnosed and treated with 100-200mg KI.

Results: All the patients became euthyroid without escape during the period of chemotherapy. Slight leukocytopenia was observed in Case 3 and 4.

Discussion & Conclusion: KI therapy could be effective for the patients with mild Graves' hyperthyroidism who need chemotherapy for malignancy, without worrying about the possibility of leucocytopenia following the treatment with thionamide antithyroid drugs.

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EVALUATION OF RISK FACTORS IN GRAVES´DISEASE RECURRENCES IN PATIENTS WHO WERE TAKEN CARE IN THE REGIONAL HOSPITAL CENTER OF SAINT-PIERRE IN REUNION ISLAND FROM 1990 TO 2010 : A RETROSPECTIVE STUDY

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Objectives: Antithyroid drug therapy is the first line treatment for Graves´disease in Europe but it is the most provider of recurrence of hyperthyroidism. Our study was about 169 patients with Graves´disease,followed from 1990 to 2010 in our hospital.87 patients got recurrence.The aim of the study was to think about how to involve general practitionners to improve the prognosis of this disease during medical treatment. So, we studied all indicators such as different ways of take care, early parameters of recurrence and prognostic factors well known in the literature.

Methods: 599 hyperthyroidism records were reviewed; we found 262 Graves´disease but only 169 were selected; we made two groups:87 Recurrence and 82 without recurrence.We studied sexe, age at diagnosis,tobacco,3 delays of treatment: time from first signs to general practitionners examination and to endocrinologist examination and time between first signs of hyperthyroidism and the beginning of treatment,goiter,initial dose of antithyroid drug,duration of treatment, number of visits, initial biology, initial TPOAb level,compliance, time of efficiency on TSH value.

Results: Statistical processing of results showed significant relationship with tobacco (p=0,0228) and goiter (p=0,0053) but not with other well-known risk factor. However, it showed a significant relationship with duration of the first treatment (p=0,0094), delay from first signs of the disease to the beginning of treatment (p=0,0009), delay between firts signs and first endocrinologist examination (p=0,0053), compliance (p=0,0091), initial TPOAb level (p=0,0115) and the fact that TSH level was low again during treatment (p=0,0293).

Analysis of delay for take care revealed negligence from patients or practitionners,inconsistencies between biology and clinical signs (24% of records), no compliance.

Conclusions: We have to think about how to reduce the delay of take care when the first signs of Graves´disease appear: better informations to general practitionner and population, quick control when inconsistencies, good knowledge of all risk factors of Graves´disease.

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LITHIUM ASSOCIATED THYROTOXICOSIS: A BIPOLAR DIAGNOSIS

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Introduction: Lithium is a first-line treatment for bipolar disease, with potential side effects involving the thyroid. Although goiter and hypothyroidism during lithium therapy are well documented, thyrotoxicosis is uncommon. Incidence of thyrotoxicosis in lithium treated patients is 3 times higher than in the normal population.

The recommended conservative management is antithyroid medication and lithium continuation. Lithium should not be withdrawn because of several reports of thyrotoxicosis exacerbation. We report a case of lithium-associated hyperthyroidism treated with drug withdrawal, a treatment rarely documented in the literature.

Case report: A 48 year-old man, treated with lithium carbonate for affective bipolar disease, developed thyrotoxicosis. He had been previously diagnosed with degenerative Parkinsonism Syndrome with ataxia. A 14 pound weight loss, proptosis and enlarged thyroid were noticed. Lab tests reveale low TSH, increased free T4, normal free T3 and increased calcitonin levels. Anti-peroxidase, anti-thyroglobulin and anti TSH-receptor antibodies were normal. The US showed a diffusely heterogeneous gland with two nodules (13 and 16 mm), both of colloid nature on Fine-needle aspiration biopsy.

As a high therapeutic lithium level (3.12 mmol/L [normal range=0.50-1.50]) was observed lithium toxicity was suspected. Lithium was withdrawn, and the patient became asymptomatic with regression of the eye signs, with no need for anti-thyroid drugs.

Conclusion: The high incidence of thyroid dysfunction requires a careful thyroid examination before and during lithium treatment. Lithium induced thyrotoxicosis is probably underestimated.

This is a heterogeneous condition with differing underlying thyroid pathologies and uncertain mechanisms, including autoimmunity and direct toxic effect causing thyroid hormone release. Our patient's improval after lithium withdrawal, is consistent with the theory of lithium's direct toxic effect on thyrocytes. One could conclude that management of lithium-associated thyrotoxicosis differs, based on the etiology of thyroid overactivity. Our case suggests that patients who present with thyroiditis can be effectively treated with lithium withdrawal.

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ACQUIRED APLASTIC ANAEMIA WITH SUBSEQUENT AUTOIMMUNE HYPERTHYROIDISM

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Objectives: Acquired aplastic anaemia (AAA) is mostly caused by the autoimmune response against stem cells which leads to hematopoietic failure and pancytopenia. The overall incidence of AAA is relatively low, with an approximate incidence in both children and adults, in the U.S. and Europe, of 2-6 cases/million/yr. The incidence is higher in Asia, with as many as 14 cases/million/yr in Japan. Graves´ disease (GD) is also an autoimmune disorder caused by autoantibodies that activate the thyrotropin receptor (TSHR). GD is the most common cause of hyperthyroidism in both, children and adults. The incidence of GD is about 7/100000 per year peaking in late childhood (9-12yr) with female predominance 5:1.

Methods: We describe a girl in whom 12 months after stopping treatment due to AAA, GD developed. She was diagnosed with idiopathic severe aplastic anaemia (sAA) at the age of 6 years, when she presented with bruising and petechiae. Based on the performed tests (total blood count, peripheral blood smear, cytogenetic and immunohistochemical characterization of bone marrow aspirate) sAA was confirmed. She was treated with immunosuppressive therapy of anti-thymocyte globulin, prednisone and cyclosporine (CSA). Treatment with CAS was continued for 12 months.

Results: 1 year later the child was diagnosed with goiter, tremor, increased sweating and tachycardia. GD was confirmed by a low TSH (0,00 µIU/ml), elevated FT3 (7,9 pg/ml) and positive thyroid autoantibodies (TPOAb: 843 IU/mL↑, TgAb: 240 IU/mL↑, TRAb 7,6 U/L↑). FT4 was still normal (1,69 ng/mL). She was started on antithyroid drug (methimazole) and β-blocker. Complete remission was achieved and lasted 18 months. Afterwards a relapse occurred (despite the use of methimazole) and she underwent successful treatment with radioactive iodine (I^{131}).

Conclusions: There is a question whether the aggressive treatment of sAA triggered GD or whether we have two independent autoimmune disorders in a genetically predisposed individual.

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INSULIN RESISTANCE, LIPID PROFILE, HIGH SENSITIVITY C REACTIVE PROTEIN AND HOMOCYSTEINE IN PATIENTS WITH AUTOIMMUNE THYROIDITIS

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Objective: To evaluate the interrelationships between insulin resistance (IR), lipid profile and other cardiovascular risk factors, such as high sensitivity CRP (C reactive protein) and homocysteine in patients with AIT.

Patients and Methods: We analysed thyroid function, anti-thyroid antibodies, BMI, indices of IR, such as HOMA-IR, HISI (Hepatic Insulin Sensitivity Index), WBISI (Whole-Body Insulin Sensitivity Index), IGI (Insulinogenic Index), total cholesterol (TC), HDL-cholesterol, LDL cholesterol, triglycerides (TG), ApoB, ApoA1, Lp(a), homocysteine, CRP, folic acid and B12 vitamin levels in 354 patients with AIT 94% female, with a mean age of 47±16 years old. Each patient was submitted to an OGTI (75 g glucose) with measurements of glucose, insulin and C-peptide each 30 min, during 120 minutes (120'). Statistic analysis was done with Spearman` correlation tests. Results are expressed as mean±SD. A $p \leq 0.05$ was considered significant.

Results: Analytical results are presented: TSH (2.51±7.20 UI/ml); FT3 (2.98±1.41 pg/ml); FT4 (1.35±1.49 ng/dl); C-peptide120' (11.02±5.43 ng/ml); TC (198±41 mg/dl); TG (113±72 mg/dl); HDL-cholesterol (57±15 mg/dl); ApoA1 (144±26 mg/dl); ApoB (94±24mg/dl); Lp(a) (27±30 mg/dl); CRP (0.43±0.70 mg/dl). We found significant correlations between: TSH and Ins120' (r=0.13; p=0.03), Glucose120' (r=0.13; p=0.03), C-peptide 120' (r=0.12; p=0.04), HOMA-IR (r=0.14; p=0.01), QUICKI (r= -0.12; p=0.05), HISI (r= -0.14; p=0.01) and WBISI (r= -0.14; p=0.01). We also found correlations between T3 and HDL (r=0.11; p=0.02) and ApoB (r=0.12; p=0.02), and between T4 and homocysteine (r= -0.14; p=0.04)

Conclusion: The interrelationships between thyroid function, insulin resistance, lipid profile, homocysteine and inflammation may explain the increased cardiovascular risk associated with AIT.

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METABOLIC SYNDROME PARAMETERS AND INSULIN RESISTANCE IN DIFFERENTIATED THYROID CANCER

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Introduction: In this study we aimed to investigate the prevalence and relation of metabolic syndrome parameters and insulin resistance in differentiated thyroid cancer (DTC).

Materials and Methods: Forty one patients with DTC (Group I), and 41 patients with benign histopathology (Group II) were included in the study. Fasting plasma glucose (FPG), postprandial plasma glucose (PPG), insulin, postprandial insulin, lipid parameters were evaluated preoperatively. Metabolic syndrome criteria of Turkey Endocrinology and Metabolism Association adapted from NCEP-ATP III and IDF criteria were used for the diagnosis of metabolic syndrome.

Results: Mean age, sex distribution, height, weight, waist circumference and BMI were similar in two groups. Fourteen (34.1%) patients in each group met metabolic syndrome criteria. Insulin resistance evaluated with HOMA-IR was similar in two groups (p=0.80). Mean TSH was significantly higher in Group II compared to Group I (p=0.02), while fT3 and fT4 did not differ between groups. There was no statistically significant difference in terms of HOMA-IR between patients with microcarcinoma and macrocarcinoma (p=0.08). Presence of metabolic syndrome was determined as a risk factor for DTC with an Odds ratio of 0.227 in 95% confidence interval (p=0.047). Also, high TSH was determined as a risk factor for DTC with an Odds ratio of 0.581 in 95% confidence interval (p=0.029).

Conclusion: HOMA-IR values and prevalence of metabolic syndrome were similar in patients with benign and malignant thyroid nodules. We think further clinical studies with larger sample sizes are needed to investigate relation between obesity, insulin resistance, metabolic syndrome and thyroid cancer.

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THYROID STATUS IN OBESITY SUBJECTS

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The aim of this study is to identify the association of thyroid stimulating hormone (TSH) and thyroxin (T_4) levels with body mass index (BMI) and waste circumference (WC) in men and women with overweight and obesity.

Current study was performed within the HAPIEE. The sample of 280 subjects ((125 men (44,6 %) and 155 women (55,4 %)) was analyzed.

Results: TSH level was high in integrated subsample with II and III obesity degree (BMI≥35 kg/m^2). Average levels of general T_4 were significantly higher in abdominal obese women with BMI≥30 (according to NCEP-ATP III, 2001), than in subjects with normal weight and overweight. Significant decrease of general T_4 was detected in men with gross obesity (BMI≥35 kg/m^2).

In comparison with men women have positive correlation between general T_4 level and waist circumference.

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HYPOTHYROID TRH-R1 KNOCKOUT MICE EXHIBIT CENTRAL CHANGES IN LEPTIN SIGNALING

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As critical determinants of peripheral energy metabolism thyroid hormone (TH) levels are influenced by peripheral energy signals. For instance, leptin exhibits a strong dominant effect on the hypothalamic TRH neurons thereby adjusting the activity of the HPT axis to the peripheral energy state. Whether in return TH affects leptin signaling has not been sufficiently addressed yet.

Here, we analyzed leptin expression and signaling in TRH-R1 knockout (ko) mice which are hypothyroid due to diminished TRH stimulation of pituitary thyrotrophs. In our study, we also included TRH-R1 ko mice which were rendered euthyroid by TH treatment. Hypothyroid TRH-R1 ko mice exhibit decreased body weight and food intake that can be normalized upon TH treatment. Moreover, leptin transcript levels in white adipose tissue as well as leptin serum levels were strongly reduced in hypothyroid TRH-R1 ko mice and restored upon TH treatment. Most intriguingly, we detected increased leptin receptor levels in neurons of the PVN and the arcuate nucleus together with decreased mRNA levels for SOCS3 in hypothyroid but not euthyroid TRH-R1 ko mice. These changes imply an increased sensitivity of hypothyroid TRH-R1 ko mice towards leptin which may explain the decrease in food intake of these animals. To further evaluate the impact of TH on leptin downstream targets we generated TRH-R1/ob double ko mice by crossing TRH-R1 ko mice with the leptin-deficient ob/ob mice and monitored their response to leptin. Most surprisingly, compared to ob/ob animals, hypothyroid TRH-R1/ob double knockout mice showed decreased reduction in body weight and food intake following three days of leptin treatment. Moreover, phospho-Stat3 immunoreactivity in the arcuate nucleus was strongly reduced in TRH-R1/ob dko mice compared to ob/ob animals. Ongoing studies are expected to reveal the underlying mechanisms that cause the leptin resistance in the hypothyroid animals.

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REGULATION OF ADIPONUTRIN MRNA AND PROTEIN LEVELS BY T3 IN RAT BROWN ADIPOCYTES

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Introduction: Adiponutrin (PNPLA3) is a protein abundantly expressed in white and brown adipose tissues. Although its precise function is unknown, several studies suggest a dual role in lipid homeostasis with activities involved both in lipogenesis and lipolysis. The PNPLA3 mRNA is down regulated in humans on a low calorie diet and in starving animals, but in both cases the transcript increases after refeeding. We have previously shown that T3 increases the adiponutrin mRNA in white adipose tissue in vivo and in vitro.

Aims: To extend the study of the regulation of PNPLA3 by T3 in primary brown adipocytes at the mRNA and protein levels.

Materials and Methods: Brown adipocytes in primary culture have been used after differentiating them from their precursors from rat interscapular brown adipose tissue. We have measured mRNA levels by Northern-blots with radioactive probes and by in situ hybridization with digoxigenin labeled probes. After immunization of rabbits with a PNPLA3 peptide from the carboxyl end, we have obtained an antiserum to study the PNPLA3 levels by immunofluorescence.

Results: T3 increases the PNPLA3 mRNA levels with doses from 0.1 to 20 nM T3, although the maximal effects appear at physiological doses and between 20 and 28 hours. The effects by T3 are observed even in the absence of insulin. These results are confirmed by the in situ hybridization. The immunofluorescence with the antiserum against the protein shows that T3 or insulin alone increases the PNPLA3 levels, but the higher immunoreactivity appears in the presence of both hormones together.

Conclusion: T3 increases PNPLA3 mRNA and protein levels in primary brown adipocytes in the rat.

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3,5-DIIODOTHYRONINE (T_2) ADMINISTRATION TO HYPOTHYROID RATS ENHANCES THE OXIDATIVE CAPACITY OF BROWN ADIPOSE TISSUE

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Objectives: Brown adipose tissue (BAT) is a thermogenic tissue. BAT plays a role as energetic buffer in rodents and interesting data are emerging about an its possible role in adult humans. Thyroid hormone (TH) affects the thermogenic processes in BAT and now it is evident that some TH derivatives also possess metabolic properties. Among TH derivatives, 3,5-diiodo-L-thyronine (T_2) is able both to enhance the rat metabolic rate and to prevents the high fat diet-induced overweight, however a deep investigation on its effects on BAT is lacking. Because of this, we thought interesting to investigate about the involvement of the BAT in the metabolic effects of T_2.

Methods: The studies were performed on three groups of rats maintained at thermoneutrality (28°C): euthyroid (Eu), hypothyroid (Hypo) and T2-treated hypothyroid rats (HypoT2- 25 µg/100g bw for 1 week).

Results: Histological analysis of intrascapular BAT showed that in hypothyroid animals, lipid droplets were enlarged, and the number of unilocular cells within the tissue were enhanced, thus suggesting trans-differentiation of brown to white adipocyte phenotype. The administration of T_2 reversed the effect induced by hypothyroidism and enhanced the UCP_1 immunoreactivity in multilocular cells. At the functional level, BAT oxidative capacity (revealed as cytochrome-oxidase activity), that was reduced in hypothyroid rats (compared to euthyroid ones), was significantly enhanced by the in vivo administration of T_2. Interestingly, the stimulatory effect of T_2 on oxidative capacity was also observed following the in vitro addition of T_2 to BAT homogenate from hypothyroid rats. The maximum effect was reached at 10^{-7}M T_2 and the half-maximal effect was reached at a concentration of about 10^{-11}M T_2.

Conclusions: Our data show that BAT may underlie, at least in part, the metabolic effect exerted by T_2

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DOES THE AROMATIC L-AMINO ACID DECARBOXYLASE CONTRIBUTE TO THYRONAMINE BIOSYNTHESIS?

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Thyronamines (TAM) exhibit great structural similarity to thyroid hormones (TH) but metabolic actions markedly differ from T_3. Extrathyroidal TAM biosynthesis from TH precursors appears likely as recently shown by their elevated serum levels in thyroidectomized T_4 substituted patients compared to controls using a highly specific chemiluminscent immunoassay. A tentative biosynthetic pathway requires both decarboxylation and several deiodination steps to convert e.g. the pro-hormone T_4 into the most potent TAM, 3-T_1AM, which circulates in human serum.

Many researchers have reasoned that aromatic L-amino acid decarboxylase (AADC) mediates TAM synthesis via decarboxylation of TH. We tested this hypothesis by incubating recombinant human AADC, which actively catalyzes dopamine production from DOPA, with several TH. Products were analyzed by a sensitive liquid chromatography-tandem mass spectrometry method. Under all conditions tested, AADC failed to catalyze the decarboxylation of TH challenging the initial hypothesis. These *in vitro* observations are supported by our finding that 3-T_1AM is also detectable in plasma samples of patients with AADC-deficiency at similar levels (n=4, 46 ± 18 nM) as in healthy controls. Therefore, we conclude that TAM are formed by another decarboxylase.

Consequently, a search with bioinformatic methods for other candidate decarboxylases was performed. An interesting new candidate showing a very promising active site structure was identified. This active site exhibits, in comparison to AADC, two amino acid exchanges, which create an additional free space in the active center. This candidate enzyme might accommodate the second aromatic TH ring and thus catalyze TH decarboxylation. Experiments similar to those performed with the recombinant human AADC are now necessary to get any hints whether this candidate decarboxylase enzyme is involved in the postulated TAM production pathway.

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STRUCTURAL THYROID DISORDERS AND THYROID CANCER AT PATIENTS WITH ACROMEGALY

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In purpose to evaluate the prevalence of structural changes and thyroid cancer, we examined 78 acromegalic patients: 12(15.4%) male, 66(84.6%) female, age 54.9±13.8 years, duration of the acromegaly 4.5[3.0;6.0] years, GH levels 11.5[3.7;30.6] µUl/l, IGF-1 501[246.3;664] µg/l. All patients underwent thyroid hormone testing, thyroid ultrasound, aspiration biopsy of thyroid nodules.

Thyroid nodules were presented in 54(69.2%) patients (group1), among them 19(35.2%) patients had one nodule and 35(64.8%) had 2 nodules or more; thyroid volume was 20.6[15.6;27.5] ml. Diffuse goiter was found in 13(16.7%) patients (group2) and thyroid volume was 24.7[22.4;31.0] ml, what was significantly higher compared to group1 (p=0.03). GH and IGF-1 levels were slightly higher in group1 (15[3.7;33.0] µUl/l and 486[227.0;737.5] µg/l) compared to group2 (7.1[3.8;15.8] µUl/l and 384[231;535] µg/l), however the difference was not statistically significant. Normal thyroid structure was observed in 11(14.1%) other patients (group3), thyroid volume was 12.4[10.2;13.2] ml and it was considerably smoller compared to group1 and group2 ($p< 0.05$). There was no difference on acromegaly duration between all groups.

Papillary thyroid cancer (PTC) was observed in 5 patients: in 4 patients it was revealed at biopsy and 1 woman had thyroidectomy due to PTC before the acromegaly had been diagnosed. The diagnosis of PTC was confirmed histologically in all 5 cases. Patients with PTC were older (76[64;76] years) than other patients from group1 (55.6[49;61.3] years) and group2 (54[42;60] years, p=0.03). There was no difference on GH/IGF-1 levels, duration of acromegaly at patients with PTC and group1 or group2.

Thus, the prevalence of structural thyroid disorders was 67/78(85.9%) at patients with acromegaly. Moreover, the prevalence of papillary thyroid cancer was 5/78(6.4%) at these patients what is remarkably higher than in Russian population (0.006%). Careful screening for structural thyroid disorders and especially papillary thyroid cancer should be done in all cases of acromegaly.

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FOLLICULAR THYROID CANCER MOLECULAR MARKERS DISCOVERY

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Introduction: Malignant follicular thyroid tumors do not present any diagnostically useful change in cellular morphology compared to the benign ones. It is a matter of debate whether the gene expression-based markers may distinguish follicular thyroid carcinoma (FTC) from follicular adenoma (FA) and improve the relatively high misclassification rate in routine histopathological diagnosis.

Aim of the study: To analyze factors influencing the variability of gene expression in follicular tumors in the context of potential markers differentiating carcinomas from adenomas.

Methods: Gene expression profile was carried out in 52 samples (25 follicular carcinomas and 27 adenomas) by HG-U133 Plus 2.0 oligonucleotide microarrays (Affymetrix). Whole dataset was analysed by Singular Value Decomposition and Random Forests analysis to identify the major sources of variability. In the next step, on the subset of well-defined samples (concordance of diagnosis between two experts in thyroid pathology) the discriminating gene expression signature was derived; it will be validated on independent samples.

Results: The major source of variability in gene expression of follicular tumors was associated with immunity-related transcripts and it accounted for 14,5% of the total variance; this supergene distinguished between FTC and FA. The second important source of variability was proliferation-related signature.

At least 3 out of 6 most important sources of variance are potentially influencing FTC-FA gene expression differences. The discrimination between both groups based on gene expression is feasible: by leave-one-out cross-validation approach 77% of samples were correctly predicted. Gene predictor obtained from microarray analysis is currently validated by quantitative PCR on the independent dataset.

Conclusions: Follicular tumors differ in various aspects of gene expression, including immunity- and proliferation-related gene signatures. These sources of variability shall be taken into account in selection of potential molecular markers of malignancy.

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THYROID FUNCTIONAL AUTONOMY AND THYROTOXICOSIS AFTER UNIVERSAL IODINE PROPHYLAXIS: THE 2010 PESCOPAGANO SURVEY

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Objectives: To investigate if a program of voluntary iodine prophylaxis had increased iodine intake and modified the pattern of thyroid diseases, the results of 2 surveys performed in 2010 and 1995 in a same community (Pescopagano, Italy) were compared.

Subjects: 1194 subjects (92 children and 1102 adults) in 2010 and 1411 subjects (419 children and 992 adults) in 1995 were submitted to medical exam, thyroid ultrasound and measurement of serum FT4, FT3, TSH and urinary iodine excretion (UIE).

Results: Median UIE was significantly higher in 2010 than in 1995 (95µg/L vs 55µg/L). Functional thyroid autonomy (FTA), defined as subnormal serum TSH with normal FT4 and FT3, was not significantly different in 2010 vs 1995 overall (44/1194, 3.7% vs 67/1411, 4.7%), but was significantly lower in young (15-45 yr) adults, (3/507, 0.6% vs 22/591, 3.7%, p =0.001) and in older (46-75 yr) adults (29/502, 5.8%, vs 34/349, 9.7%, p=0.01). No difference in FTA frequency was observed in subjects older than 75 yr (15.7% vs 15.4%). Overt hyperthyroidism was detected in 18/1102 (1.6%) adults in 2010 and in 29/992 (2.9%) in 1995 (p=0.03), being the prevalence significantly lower in 2010 vs 1995 for non autoimmune hyperthyroidism (9/1102, 0.8% vs 20/992, 2.0% p=0.01), but not for Graves' disease (9/1102, 0.8% vs 9/992, 0.9%).

Conclusion: A significant increase of UIE excretion was observed in 2010 vs 1995. The overall frequency of FTA did not change, but it was significantly lower in young adults, suggesting that the increased iodine intake prevents goiter and development of FTA. A significant reduction of overt hyperthyroidism was observed, due to the disappearance of non autoimmune hyperthyroidism in young adults, while the prevalence of Graves' disease did not change.

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NODULAR DISEASE ASSOCIATED WITH CLINICAL AUTOIMMUNE THYROIDITIS HAS HIGHER RISK OF THYROID CANCER

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The association of differentiated thyroid carcinoma (DTC) and autoimmune thyroiditis (AT) has been widely studied with results that are often not univocal. The aim of this study was to evaluate the association between thyroid autoimmunity and DTC in a retrospective series of 567 patients (434 females and 133 males, mean age 52.6 ± 14.6 years) that underwent surgical thyroidectomy from January 2004 to December 2010. On the basis of clinical diagnosis the patients were divided in two groups: 1) Group A: 61/567 (10.8%) patients with AT [positive thyroid auto-antibodies associated with ultrasound (US) features]; 2) Group B: 506/567 (89.2%) patients with uni or multinodular goiter

not associated with AT. Indications for surgery were suspicious FNAC and/or compressive symptoms.

The prevalence of DTC in Group A was 62.2%, significantly higher than that observed in group B (36.9%, p=0.0001). Since thyroid auto-antibodies may be associated with nodular goiter without other (US) features of autoimmune thyroiditis, we assessed the frequency of DTC in Group B patients according to the absence [Group B1: 428/506 (84.5%)] or presence [Group B2: 78/506 (15.5%)] of thyroid auto-antibodies. The prevalence of DTC was not different between the two groups (36.6% and 38.4%, respectively, p= 0.79) and, in both groups, it was significantly lower than that observed in Group A (p = 0.0002 and p= 0.006, respectively).

In a multivariate logistic regression analysis including age, sex, preoperative TSH levels and the clinical diagnosis of AT, only preoperative TSH levels (OR=2.43; 95% CI, 1.49-3.98; p=0.005), age at thyroidectomy (OR=0.58; 95% CI, 0.40-0.83; p=0.001) and AT (OR=2.82; 95% CI, 1.64-4.85; p=0.0005) were independently associated with DTC.

In conclusion, our results show that the presence of clinical AT but not the mere positivity of thyroid auto-antibodies confers an increased risk of DTC.

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CAUSES OF INDIVIDUAL DIFFERENCES IN THYROID SIZE IN ADOLESCENTS: IMPACT OF BODY MASS INDEX

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Objective: Factors such as iodine nutrition, serum TSH concentration, and age are considered to influence thyroid size in adolescents. We aimed to determine the relative role of body-mass index (BMI) and other possible demographic factors on thyroid volume determined by ultrasonography in an adolescent cohort

Methods: Using the database of the study 'Thyroid consequences of the Chernobyl nuclear power station accident on Turkish population' (1680 adolescents aged between 14-18 years old), the euthyroid subjects were selected. An analysis of the associations between thyroid volumes and BMI, freeT4, TSH, urinary iodine concentrations (UIC), age, anti-tpo, anti-tg were determined. Subjects were also analysed in two cathegories (autoantibody positive:AP and negative:AN) based on anti-tg (>10 IU/mL) and anti-tpo (>15 IU/mL) levels.

Results: Of the euthyroid 1426 adolescents (Male/Female: 731/695), 288 (20.2%) had antibody positivity [Male/Female: 100 (13.7%) / 188 (27.1%), p< 0.001)]. Their BMI was 20.2±2.5 kg/m^{2,} their thyroid volume was 15.7±5.6 mL. Thyroid volume correlated with age (r=0.197, p< 0.001), UIC (r=-0.104, p=0.002), BMI (r=0.183, p< 0.001) in AN subgroup; and with freeT4 (r=0.163, p=0.004), age (r=0.195, p< 0.001), UIC (r=-0.154, p=0.013), and BMI in AP subgroup. A multivariate regression analysis demonstrated an independent correlation between thyroid volume and BMI (positively, p< 0.001), age (positively, p< 0.001), UIC (negatively, p=0.002) in both the AN and AP subgroups. Additionally, thyroid volume was independently associated with freeT4 (positively, p< 0.001), anti-tpo (positively, p=0.008), but not with anti-tg in the AP subgroup. There was no correlation between TSH and BMI in either subgroups.

Conclusions: Body mass index, age, and iodine status are predictors of thyroid volume in adolescents. In subjects with thyroid autoimmunity, freeT4 and anti-tpo concentrations also seem to predict thyroid volume in this population.

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THE ROLE OF GALECTIN-3, HBME-1, AND CYTOKERATIN-19 IN THE DIFFERENTIAL DIAGNOSIS BETWEEN FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA AND BENIGN THYROIDAL LESIONS: FOLLICULAR ADENOMA, HYPERPLASTIC NODULE, AND NODULAR HYPERPLASIA

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Objectives: We intended to evaluate the role of galectin-3, HBME-1, CK-19 in differential diagnosis between follicular variant of papillary thyroid carcinoma (FVPTC) and benign follicular patterned lesions such as follicular adenoma (FA), nodular hyperplasia (NH), and hyperplastic nodule (HN) of thyroid.

Methods and Results: A sum of 112 cases including FVPTC (n= 18), FA (n= 26), HN (n= 26), NH (n= 40) were retrieved from our archives where they have been deposited between 2005 and 2010. Immunohistochemical markers were performed both seperately and as a panel. Than, we evaluated them in the basis of their property of percentage and intensity of staining. There was no significant difference in FVPTC, and benign groups regarding both percentage and intensity of staining by the all markers. Galectin-3, HBME-1, and CK 19 were positive in 16 (88.0 %), 16 (88.0 %) and 18 (100.0 %) cases of FVPTC, respectively. We detected significant differences between FVPTC and the benign lesions. Sensitivities of the markers were higher than specificities. Specifities of three markers concerning percentage were higher than intensity of staining. HBME-1 was the most specific one which also had a high sensitivity.

Conclusions: Although positivity of three markers were significantly higher in FVPTC than the benign groups as studying seperately, no significant difference was detected when using them as a panel. Higher expression of them may refer to FVPTC, but lower one may not eliminate the malignancy. In our opinion, percentage should be considered when evaluating them and HBME-1 may be most useful marker among the others in the presented differential diagnosis.

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INTRANODULAR GLUCOSE LEVELS IN THE DIFFERENTIAL DIAGNOSIS OF THYROID NODULES: A PRELIMINARY STUDY

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Introduction: GLUT 1 expression in malignant cells increases glucose in to the cells. Detecting intranodular glucose amount might predict malignancy of thyroid nodules. The aim of this study was to evaluate the glucose content of thyroid nodules during fine needle aspiration biopsy (FNAB).

Patients and Methods: 42 nodules of 42 patients (39 female, 3 male, age range 24-71 years), detected during USG guided FNAB, were included in the study. The remaining of the needle used during FNAB, patient serum, remaining of the needle used in aspirating venous blood sample, the remaining of the needle used in aspirating serum and cytological examination was studied for each patient. The ratio of serum glucose level/glucose content of the nodule was determined for each patient.

Results: On cytological examination 21 of 42 nodules had benign, 8 nodules had malignant (proven histopathologically), and 13 nodules had nondiagnostic cytology. The cytological evaluation of 7 nodules with indeterminate cytology revealed colloidal material only, 11 nodules revealed colloidal material, few benign follicular epithelial cells. The ratio of serum glucose level/glucose content of the nodule which had benign, malign and indeterminate cytological results was 64.00±24.00, 52.02±22.00, 67.00±27.70 respectively (p=0,371). Although not statistically significant the ratio of serum glucose

level/glucose content of the malign nodules were lower than the other groups suggesting that the intrathyroidal glucose content was higher than serum glucose content in this group.

Conclusion: By measuring intranodular glucose content we have made an initial effort to evaluate the clinical significance of intranodular glucose content and to see if it may be possible to predict a nodule is weather benign, malign or nondiagnostic. This is a preliminary study. We think that this may be a new technique in the follow up of thyroid nodules and needs further investigation with a larger patient group with more standardized methods.

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REASON, PREVENTION AND SURGICAL TREATMENT OF BENIGN THYROID DISEASE RELAPSE PATIENTS

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Objectives: Clearing up of reasons, possibilities of prevention of postoperative recurrent goiter (PORG), indication for surgery, estimation of safety and efficiency of repeated operations.

Methods: During 1973- 2010 were operated on 1330 (5.2%) PORG pts among 25629 thyroid cases. 1246 (6.0%) PORG of 20776 operated for benign thyroid diseases (BTD) pts with known (4-30 years) follow up results were included in given research.

Results: We compared the structure of thyroid diseases (TD) for primary and repeated operations (RO). There were 3011 (16.5%) diffuse toxic goiter (DTG) of 19530 the first time operated on pts and 243 (18.2%) DTG relapse pts; 1532 (7.0%) nodular toxic goiter (NTG) and 106 (8.0%) NTG relapse pts; 13720 (70.2%) euthyroid nodular goiter (ENG) and 862 (69.2%) ENG relapse pts. Thus the structure of TD at the primary and repeated operations was almost identical. And opportunity of relapses after initial 19530 for BTD could made 6 - 8%. But only 100 (8.0%) of 1246 RO were underwent thyroid surgery in our clinic at first time. Those 100 pts made only 0.5% of 19530. It means that the main predictive factors of BTD renewing are rational volume and technique of surgery but no character of TD. We divided PORG according to 2 factors - time of the first time PORG registration ("false" and "new" relapses) and character of diseases of thyroid remnant (former or new). "False" relapse - is a continuation of pathological tissue growth after inadequate operation. "True" relapse is an appearance of the same or a new disease in unchanged thyroid tissue in later terms (in average 13.9 ± 3.15) after adequate surgery.

Conclusion: Thus, it is possible to allocate the following basic causes of PORG: technical (inadequate primary operations); pathogenetic - "true" relapse of the same or new diseases of a thyroid remnant.

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COEXISTING KIKUCHI-FUJIMOTO DISEASE AND HASHIMOTO THYROIDITIS IN A YOUNG WOMAN – A CASE REPORT

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Background: Kikuchi-Fujimoto disease (KFD) is a rare cause of enlarged lymph nodes in white population and the diagnosis of this entity remains highly difficult. The aim of this report is to present the case of a 24-year-old woman with local cervical lymphadenopathy and Hashimoto thyroiditis diagnosed before.

Material and Methods: A 24-year-old woman was admitted to the hospital with a history of fever, headache, coughing, loss of appetite, nausea, vomiting, weight loss and myalgia lasting for one month. On physical examination a right-sided lymphadenopathy in level V of the neck was revealed with tenderness and movable lymph nodes. Ultrasonography of the neck confirmed the presence of enlarged oval lymph nodes of 10-21mm in diameter within level V of the right neck. Most laboratory tests were normal except serum TSH level which was lowered (0.006 mU/L). An excision biopsy of one of the enlarged lymph nodes was performed.

Results: The diagnosis of KFD was established based on obliterated structure of the nodal architecture. The necrotic areas were surrounded by zone infiltrates composed of B CD20+ lymphocytes looking like large immunoblast-like cells and rarely CD3+ T-lymphocytes. The patient was treated with antibiotics, anti-thyroid drugs and non-steroid anti-inflammatory drugs. Lymphadenopathy resolved spontaneously after 6 months but anti-TPO serum level was elevated (415,61 IU/ml). Patient remains on l-thyroxin treatment with the dose adjusted to keep the serum TSH between 1.0-1.5 mU/L.

Conclusions: A close collaboration between expert panel of clinicians and pathologists as well as immunohistochemistry testing as an addition to standard histological evaluation are essential for accurate diagnosis. Reduced stress related to alarming symptoms and possible avoidance of unnecessary treatment can be considered the major benefits of early diagnosis of KFD. Nevertheless, all KFD patients require a life-long follow-up as other autoimmune diseases can become clinically apparent at any time.

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OUTCOME OF RADIOIODINE THERAPY IN AUTONOMOUS FUNCTIONING THYROID NODULES – A STUDY GROUP

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Thyroid autonomy is a common finding in iodine deficient areas; universal salt iodization was implemented in our country on Ianuary 1, 2003. A group of 25 patients (age range: 39 - 79 yrs, mean age: 58.1yrs; sex ratio (F/M): 7.3) with autonomous functioning thyroid nodules were treated with radioiodine; all of them were pretreated with methimazole. Overt thyrotoxicosis was found in 16 subjects (64%) and subclinical thyrotoxicosis was diagnosed in 9 patients (36%). Type 1 amiodarone induced thyrotoxicosis was revealed in 2 cases (8%).Thyrotoxic atrial fibrillation was diagnosed in 7 patients (28%) and sinus rhythm was restored in only one patient (14.2%) after achievement of euthyroidism. Before ablative treatment, diameter of toxic adenomas was between 2.8cm and 4.9cm; diameter of toxic adenomas was under 3cm in only one patient. In a male patient, thyroidectomy was contraindicated due to a major comorbidity (central core disease, a non-progressive congenital myopathy), associated with an increased risk for malignant hyperthermia; consequently, the only ablative therapy possible was radioiodine. Retreatment was required in 3 patients (12%).During a mean follow - up period of 5.5 years, prevalence of postradioiodine hypothyroidism (overt or subclinical) was 40%. At least in part, this increased prevalence of overt and subclinical hypothyroidism could be explained by partial suppression of the extranodular parenchyma due to pretreatment with methimazole. The risk of postradioiodine hypothyroidism is low only if extranodular uptake of radioiodine is prevented. After radioiodine therapy, a significant decrease (between 1cm - 2.5cm) in the greatest diameter of thyroid nodules was recorded in around one third (32%) of patients. None of our patients developed Graves disease after radioiodine therapy.

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INCREASING RADIOIODINE UPTAKE FOR THE TREATMENT OF NON AUTOIMMUNE MULTINODULAR GOITER

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Surgery is the optimum therapy for patients with compressive multinodular goiters (MNG). When it is contraindicated, 131-I would be the only alternative. MNG usually has a low radioiodine uptake (RU). Recombinant human (rh) TSH and a new formulation of modified release rhTSH has shown to increase the thyroid RU in this setting.

Objectives: To demonstrate the effect of metil-mercapto-imidazole (MMI) to increase RAI uptake in patients with MNG and to evaluate the outcome of the goiter size 12 months after 131-I dose.

Methods: Twelve female patients were prospectively included. Eight patients received the RAI dose until now. Each patient had a baseline thyroid profile, and thyroid RU (measured at 24 hours after 30 uCi 131-I administra-

tion) and a CT. MMI was prescribed 30 mg b/d. When TSH level was around 5 mUI/L, a new RU was performed and 30 mCi (1.11 Mbq) 131-I was then indicated.

Results: Mean baseline RU at 24 hours was 20 ± 8,9 %, which increased to 48 ± 16,8 % ($p < 0.001$) after the protocol. Mean time of follow-up for the 8 patients who received the RAI dose was 24,8 ± 14,6 months.

Outcome in thyroid function: In 4 patients hypothyroidism was observed. One patient developed a Graves' disease and 3 of them still remain euthyroid. *Outcome in thyroid size:* We observed a decrease of the MNG size, measured by tracheal cross sectional area (TCSA). Baseline TCSA was 191 ± 55,3 mm^2. It increased to 296 ± 63,3 mm^2 ($p=0.02$) after 12 months of follow-up in 6 of the 12 included patients. All subjects also referred a subjective amelioration of compressive symptoms.

Conclusions: This protocol would be an efficacious alternative to increase RU in patients with MNG in whom surgery is contraindicated or not accepted.

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HIGH RATE OF THYROID CANCER IN PATIENTS WITH THYROGLOSSAL DUCT CYST CARCINOMAS: A CASE SERIES

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Objectives: The incidence of cancer in thyroglossal duct cysts (TGDC) is low and management is controversial. Given the rarity of the disease and that every case may present in a different way, we report six cases of TGDC carcinoma, aiming to: (a) describe their special clinical features, surgical and post-surgical treatment and follow-up; (b) discuss management issues.

Methods: Medical files of patients with TGDC carcinomas treated at our hospital were reviewed. Tumour stage at initial diagnosis (tumor size, multifocality, local invasion, lymph node metastases), surgical treatment, treatment with radioactive iodine (RAI), local recurrence and follow-up were evaluated.

Results: A total of 6 patients (4 females, 2 males, average age 39.3 years) were treated for papillary carcinoma arising in a TGDC. All of them underwent total thyroidectomy and thyroid carcinoma was found in 5 of 6 patients (83%). One of the patients developed thyroid gland carcinoma 10 years after the diagnosis of TGDC carcinoma. RAI was administered to all patients. The most aggressive disease in terms of local infiltration, local recurrence and lymph node metastases was observed in our youngest patients (Table).

Conclusions: In view of the high incidence of thyroid cancer, we would recommend thyroid gland evaluation at initial diagnosis and at regular intervals thereafter. Therefore long term follow-up is necessary for these patients.

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STUDY OF MOLECULAR ALTERATIONS IN *SDHB, SDHD* AND *VHL* GENES IN FETAL ADENOMAS

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Background: Thyroid microfollicular fetal adenomas refer to benign tumours that resemble the formation of the gland from the remains of fetal structures, commonly with less colloid, abundant stroma and usually a prominent vasculature. There are several genes altered in cancer known to induce highly vascularized tumours through induction of a pseudo-hypoxic environment. Due to the prominent vascular structures observed in the fetal adenomas, we addressed some angiogenic-related genes that could be altered in these tumours.

Objective: The aim of the present work was to determine whether *SDHB, SDHD and VHL* mutations were present in our series of microfollicular fetal adenomas.

Material and Methods: Immunohistochemistry for endothelial markers CD105 and CD31 to confirm the augmented number of vessels. We performed PCR/direct sequencing of the genes *SDHB*, *SDHD* and *VHL* in our series of microfollicular fetal adenomas.

Results: The screening we performed did not reveal alterations in the studied genes.

Conclusion: Since no mutations were found we question whether the prominent vasculature is an end product of a mutated gene that was not addressed in this study or simply a paracrine effect resulting of an unveiled angiogenesis-prone mechanism.

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Table 1. Characteristics of patients (For Abstract P184)

Patient	Sex	Age	TGDC Ca size (mm)	Interval to thyroidectomy	Thyroid Ca size (mm)	Lymph nodes metastases	Local recurrence/ residual disease	RAI (mCi)	Follow up
1	M	18	8	10 years	9 invasive	no	yes	100	1 year
2	F	21	not available	Simultaneous removal	no malignancy	no	yes	250	9 years
3	F	18	not available	1 month	5-3 multifocal	yes	yes	250	2 years
4	F	68	6	Simultaneous removal	6	no	no	100	3 years
5	F	46	not available	3 months	10-3-1 multifocal	no	no	100	7 years
6	M	65	not available	6 months	2	no	no	100	1 year

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REAL-TIME, HIGH-RESOLUTION ULTRASONOGRAPHY OF THE VOCAL FOLDS IN PATIENTS BEFORE AND AFTER THYROID SURGERY - ADVANTAGES AND DISADVANTAGES

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The aim of the study was to evaluate the function of vocal folds by real-time, high-resolution ultrasonography and to correlate the imaged features to results of laryngological examination. Subsequent analysis of obtained results was performed to evaluate advantages and disadvantages of the technique in patients before and after thyroid surgery.

Methods: The study group comprised 72 patients (61 females and 11 males), qualified to thyroidectomy. All the patients had laryngoscopic and ultrasound examination before and two days, and three months after the surgery. We used high resolution US-imaging to identify vocal folds, and subsequently a pulsed Doppler and Doppler gate to quantify the tissue displacement velocity in the vibrating vocal fold section. Moreover, color Doppler examination of vocal fords was performed.

Results: Laryngological examination revealed unilateral vocal fold paralysis in seven patients. Vocal folds dysfunction was diagnosed in other ten subjects. In simultaneously performed US-examination, changes in vocal folds displacement velocity were observed in twenty patients. Both US-imaging and laryngological examination, performed after the three months follow-up, confirmed the transitional character of the above-mentioned pathologies.

Conclusions: US-imaging of the vocal folds correlated with laryngological examination results, while being a minimally invasive, easily reproducible and inexpensive method of examining vocal folds function. Thanks to many recording options, it may soon become a perfect tool for an early identification of postoperative dysfunction of the vocal folds with its later monitoring. However, an analysis on a larger group of patients is necessary to standardize the technique and precise diagnostic criteria, in order to introduce it into diagnostic algorithm.

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USEFULNESS OF REAL-TIME DYNAMIC SONOELASTOGRAPHY IN NON-INVASIVE DIFFERENTIATION OF BENIGN AND MALIGNANT THYROID AND PARATHYROID LESIONS

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Introduction: Sonoelastography is a novel technique, providing an objective estimation of tissue elasticity. Neoplastic transformation is often associated with changes in mechanical properties of the lesion, thus decreased elasticity should raise suspicion of malignancy. The aim of the study was to assess the usefulness of real-time dynamic sonoelastography in non-invasive evaluation of thyroid and parathyroid lesions.

Materials and Methods: Sonoelastography with the use of AIXPLORER equipment by Supersonic Imagine was performed preoperatively in a group of 115 patients, admitted for thyreoidectomy and/or parathyreoidectomy. The elasticity of nodules was subsequently correlated with the results of histopathological examination of the resected specimens. The elasticity was expressed in kilopascals (kPa) and in 5-point Ueno Scale.

Results: 408 thyroid and parathyroid lesions were evaluated with the use of sonoelastography. Histopathologically thyroid cancer was diagnosed in 23 cases. The mean stiffness of nodules was significantly higher in neoplastic lesions in comparison to benign nodules (156.2±81.3 vs 39.9±36.5 kPa, p=0.0002). The obtained sensitivity, specificity as well as positive and negative predictive values of sonoelastography in detection of malignant lesions are presented in the table below. All diagnosed 8 parathyroid adenomas presented high elasticity (1 according to Ueno scale).

Elasticity	≥2	≥3	≥4
Sensitivity	92.3%	84.6%	69.2%
Specificity	39.2%	79.4%	98.0%
Positive predictive value	16.2%	34.3%	81.8%
Negative predictive value	97.6%	97.6%	96.1%

Conclusions: Real-time dynamic sonoelastography may be a useful tool in non-invasive differentiation of benign and malignant thyroid and parathyroid lesions. Due to high negative predictive value sonoelatography may reduce the amount of unnecessary thyreoidectomies, however, because of moderate positive predictive value it does not allow to eliminate fine-needle aspiration biopsy from diagnostics of thyroid nodules.

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DO ULTRASOUND AND ELASTOGRAPHIC PATTERNS OF THYROID CARCINOMAS VARY WITH THEIR SIZE?

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Objectives: To determine if the ultrasound appearance and stiffness of thyroid carcinomas vary with their size.

Methods: We conducted a retrospective study on 514 patients having a thyroid nodule, divided into three groups according to the tumor size : 1 to 10 mm (group A), 11 to 20 mm (group B) and more of 20mm (group C), corresponding respectively to 58, 58, and 55 carcinomas and 43, 177 and 123 benign nodules. All the ultrasound and Doppler parameters were studied and the absolute quantitative elastographic score obtained by manual compression recorded. Within every group, carcinomas were compared with the benign nodules and then the three groups of carcinomas between them. The odds-ratio (O.R.) was calculated for each sign.

Results:

1. In group A, microcarcinomas and benign nodules do not show significant difference of vascularization (p 0.56), whereas central vascularization is more frequent in group B (64% against 29% in group A) and even more in group C (76%) and significantly differs in those two groups (p< 0.0001) from benign nodules (O.R. respectively 4.5 and 12.4).
2. The "taller-than-wide" sign is more frequent in group A than in groups B and C (p=0.05).
3. The average quantitative elastographic score was respectively 0.04, 0.07 and 0.06 for the carcinomas of group A, B, C against 0.07, 0.11 and 0.13 for benign nodules : the three groups of carcinomas had a lower strain value than benign nodules of the same group (p< 0.005). There was no difference of stiffness between the three groups of carcinomas.

Conclusions: Ultrasound screening to detect thyroid carcinomas should take into account that shape and vascularization vary with the size of the tumor. Elastography is a valid tool, being useful even for microcarcinomas and should be used regardless of the size of the lesion.

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EMPIRIC HIGH DOSE IODINE THERAPY IN THE ERA OF FDG PET/CT: IS IT STILL USEFULL?

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Background: The follow-up of patients with differentiated thyroid cancer (DTC) treated with surgery and radioiodine (131-I) is based on serum thyroglobuline (Tg) measurements and neck ultrasonography. In case of suspicion of recurrence/persistent disease, it is recommended to administer an empiric 131-I treatment (3.7 GBq after thyroid hormone withdrawal) in order to localize and treat the disease.

Objective: To evaluate whether the administration of empiric 131-I in patients with DTC and a suspicion of recurrence/persistent disease remains a standard of care to localize the disease in the era of fluorodesoxyglucose (FDG) PET/CT.

M**ethod:** This is a single centre retrospective study. Thirty four consecutive patients (12M, 22F; mean age 53 years), treated for papillary TC (n=32) or follicular TC (n=2) with a suspicion of recurrence/persistent disease, based on an increasing Tg levels or on the persistence of TgAb who underwent empiric 131-I treatment between March 2003 and December 2008 were included. All had a FDG PET/CT performed and a previous normal postoperative 131-I ablation WBS. FDG PET/CT and 131-I whole body scans (WBS) were blindly analyzed by two readers.

Results: Twenty-two (64%) patients had evidence of disease on FDG PET/CT or WBS with both FDG PET/CT and WBS being abnormal in 5 cases, FDG PET/CT being the only abnormal examination in 17 cases and WBS being the only abnormal examination in 1 case.

A total of 71 lesions in 36 organs were depicted. The sensitivities for the detection of distinct lesions and the diagnosis of metastatic organs were 92 and 97% for FDG PET/CT and 13% and 22% for WBS, respectively. All lesions detected on WBS were also detected on the FDG PET/CT, except one.

Conclusions: FDG PET/CT is much more sensitive than empiric WBS to localize recurrence/persistent disease in DTC patients with a previous normal post-ablation WBS.

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EVALUATION OF THYROID UPTAKE IDENTIFIED BY 18-F-FDG PET/CT FOR NON-THYROIDAL ILLNESS

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Background: Fluorine-18-fluorodeoxyglucose positron emission tomography/ computed tomography (18-F-FDG PET/CT) is now widely being used for the evaluation of malignant diseases. The number of incidental thyroid incidentalomas identified by FDG-PET is increasing among patients who have no history of thyroidal diseases.

Objective: To investigate the clinical significance of incidental focal or diffuse FDG uptake in the thyroid gland on PET/CT scan

Methods: 52 subjects with increased FDG uptake of thyroid gland were enrolled to the study. All participants were evaluated by thyroid ultrasonography (US) and US elastography as well as Tc-99m thyroid scintigraphy. Fine needle aspiration and cytological examinations (FNAC) were applied to all thyroid nodules detected by US. Of these subjects, the uptake patterns on FDG PET/CT were classified as diffuse, focal or diffuse plus focal. The FDG uptake pattern, maximum standard uptake values (max SUV), scintigraphic images, both grey scale US and US Elastography findings were compared with the cytological results of the thyroid nodules.

Results: In the focal FDG uptake pattern cases (n=39), the mean max SUV of malignant cases was significantly higher than that of benign cases (6.3 ±8.97 vs. 4.3±3.04, p< 0.05). In addition, there was a significant correlation between suspicious US features and malignant FNAC results (x2=1.44, p< 0.05). US elastographic score of 4-5 was observed in six of eleven (54.5%) patients with carcinoma on cytology. 48% of the having focal uptake pattern cases (n=12), Tc-99m scintigraphy was significantly showed no hypofunctioning (cold) nodule (p=0,022).

Conclusions: FDG uptake of the thyroid nodules is not a useful tool in absolute discrimination between malignancy and benignity. Therefore we suggest that the thyroid incidentalomas detected on FDG PET/CT should be further examined with USG and scintigraphy. If hypofunctioning thyroid nodules are detected on scintigraphy and/or suspicious features are detected on USG, FNAC should be performed.

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PROSPECTIVE ASSESSMENT OF HARMONIC TISSUE DOPPLER IMAGING ELASTOGRAPHY IN THYROID FOCAL LESIONS

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Aiming at the highest specificity in differentiating benign from malignant thyroid nodules effects in new diagnostics development. Recent technologies such as elastography enable determination of tissue elasticity difference between focal lesions and surrounding thyroid tissue. This method is based on quantifying the stiffness of the lesion - the malignant lesions show decreased elasticity, when compared to adjacent tissue. In order to estimate stiffness of the examined lesion, most of the available ultrasound applications require external tissue compression, made by the researcher by means of the transducer. In this method, due to individual examination technique differences, some artifacts interfering the diagnosis may occur.

The aim of the study was to assess a potential role of harmonic tissue doppler imaging elastography in the diagnosis of thyroid lesions.

76 thyroid focal changes in 68 patients were examined. Patients were qualified for surgical intervention, due to nodular goiter (63 lesions) and papillary thyroid carcinoma (PTC) (13 lesions). All final diagnoses were obtained from histological evaluation. Each case of PTC was confirmed in histological evaluation. There were no malignant lesions in the remaining probes.

Elastography revealed higher stiffness of malignant than of benign lesions (4,6-15,7, median value 7,8 versus 0,2-2,8, median value 2,4). We observed an evident impact of examination technique (thyroid compression, localization/ dimension of lesions) on test outcomes. Proper examination technique and adequate reference tissue selection enables the decrease of artifacts frequency or their elimination.

The performed analysis has revealed higher stiffness in PTC cases in comparison to benign lesions, what may indicate usefulness of elastography in distinguishing benign from malignant lesions. Due to lack of other types of thyroid carcinomas in the examined material, we are not able to estimate an application of elastography in their diagnostic.

The awareness of conditions generating artifacts and correct examination technique are crucial for proper results interpretation.

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NOVEL APPLICATION OF SONOELASTOGRAPHY IN DIAGNOSTICS AND TREATMENT MONITORING OF DE QUERVAIN THYROIDITIS

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Objectives: Sonoelastography is a novel technique, providing an objective estimation of tissue elasticity. To date, there were no reports on application of sonoelastographic examination in de Quervain thyroiditis (dQT). The aim of the study was to prospectively assess the role of sonoelastography in diagnostics and treatment monitoring of dQT.

Methods: Studied group consisted of 13 patients newly diagnosed with dQT, aged 48.3±14 years (2 men, 11 women). In all patients, sonoelastographic examination with estimation of tissue stiffness was performed at baseline, at a 4-week follow-up during anti-inflammatory treatment and in remission after treatment. Thyroid tissue stiffness in dQT was compared to a group of 18 patients with chronic autoimmune thyroiditis (CAT) and a control group of 40 subjects without thyroid pathology (CS), matched for age and gender.

Results: Thyroid tissue stiffness in dQT was as follows: 211.16±36.6 kPa at baseline, 39.68±21.8 kPa at a 4-week follow-up and 21.13±5.0 kPa in remission. Patients with CAT presented tissue stiffness at the level of 38.36±19.3 kPa while CS at the level of 16.18±5.4 kPa. A significant difference between thyroid stiffness in above mentioned three phases of dQT ($p< 0.001$) was demonstrated. Thyroid tissue stiffness in dQT at baseline differed significantly if compared to CAT ($p< 0.0001$) and CS ($p< 0.0001$). No significant difference between thyroid tissue stiffness at a 4-week follow up in dQT if compared to patients with CAT was noted, however, there was a significant difference if compared to CS ($p=0.0026$). Thyroid stiffness in remission of dQT was significantly lower than in CAT ($p=0.0038$), while higher than in CS ($p=0.0135$).

Conclusions: dQT is associated with increased stiffness of thyroid parenchyma, which is restored with treatment to values close to normal. Sonoelastography might be useful in diagnostics and treatment monitoring of dQT as well as differentiation between dQT and CAT.

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THE VALUE OF SPECT/ CT EXAMINATIONS FOR THE DETECTION OF THYROID FOCAL LESIONS AND RETROSTERNAL GOITER

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Objectives: The most common thyroid diagnostic modality is ultrasonography. In some well-established cases a thyroid scan is performed. In recent years three dimensional, hybrid SPECT/CT imaging has become available for the examination of lesions situated in the neck region. To assess the value of SPECT/CT examination over planar scintigraphy in patients suspected of having focal neck lesions like retrosternal goiter and focal thyroid gland abnormalities.

Methods: Group of 31 patients (28F, 3M, age 45-76 years, average 62.9 years) who were suspected of having multinodular goiter and/or retrosternal goiter were investigated. After an i.v. injection of the radiopharmaceutical: Tc99m in 3 patients, Tc99m and MIBI-Tc99m in 2 patients, MIBI- Tc99m in 26 patients - the same day planar and SPECT/CT examination of the neck were performed. Obtained images were analyzed to find out the focal areas of abnormal accumulation of the tracer and its localization. The scintigraphic results were related to computer tomography and ultrasound of the neck region. It was analyzed if SPECT/CT images provided additional information in relation to planar scans.

Results: All together 28 focal abnormal lesions were found in 25 (81%) patients. In 12 (39%) patients 15 lesions not visible on planar scintigraphy were revealed with SPECT/CT examination. In 13 (42%) patients there was no additional information gained from SPECT/CT over planar study. In 6 (19%) patients there was normal planar and SPECT/CT result. In 3 cases retrosternal goiter was found.

Conclusions:

1. SPECT/CT examination of the neck region is the better then planar for detection of tracer focal abnormal accumulation. Additionally, it allows for its anatomical localization.
2. SPECT/CT enables diagnosis of retrosternal goiter, provides its very good functional and anatomical information.

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CAN WE USE TC-99M MIBI SCINTIGRAPHY FOR THE DIFFERENTIATION OF MALIGNANT AND BENIGN THYROID NODULES?

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Technetium-99m-methoxyisobutylisonitrile (MIBI) has been proposed to characterize thyroid nodules preoperatively. The aim of this study was to find out which thyroid nodules retain MIBI and whether preoperative detection of malignancy is possible.

Methods: Over a period of 36 months, 48 patients (36 women, 12 men; aged 47 ± 12.8 (mean ± S.D.) (24-75.yr) with thyroid nodules were studied. All patients underwent thyroid ultrasonography with 7 MHz transducer, 99mTc-pertechnetate thyroid scanning and single injection-dual-phase (30 min and 2 hr) tumor scintigraphy with 99mTc-MIBI. MIBI scans were considered positive if there was focal tracer retention in the thyroid nodule on the delayed SPECT image.

Results: In the following months 21 patients underwent surgery. Histopathological diagnoses revealed a total of 8 thyroid carcinomas. 6 were MIBI positive and 2 were MIBI negative (one papillary microcarcinoma and one patient with Multi Drug Resistance (MDR) positive tumor). 6 and 2 patients had papillary and follicular carcinoma respectively. Thirteen patients had benign adenomas on histological examination. Of these, 5 and 8 were MIBI (+) and (-) respectively. 25 patients who did not have surgery were followed up for a mean period of 12 months (3-24). Twelve of them were MIBI positive and 13 were negative. Control physical exam and USG did not reveal any evidence of enlargement of the nodule or malignant characteristics on USG. The positive and negative predictive values of MIBI scintigraphy for the detection of thyroid cancer was 26 % and 95 % respectively.

Conclusion: These results indicate that although MIBI accumulation and retention in the thyroid nodule is not tumor specific, absence of Tc-99m MIBI retention drastically reduces the probability of malignancy, however, papillary microcarcinoma or tumors with MDR protein cannot be excluded.

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THE COMPARISON OF TC-99M AND I-123 UPTAKE IN PATIENTS WITH THYROID AUTONOMOUS TISSUE

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Purpose: In patients with thyroid autonomy (TA) the estimation of iodine uptake is needed to assess thyroid function, particularly before treatment with radioiodine-131. While the method using technetium-99m-pertechnetate (Tc-99m) is quicker, cheaper and easily accessible, the radioiodine-123 (I-123) represents the radionuclide of choice due to physiological behaviour in thyroid. Therefore, the aim of this retrospective study was to compare the uptake of Tc-99m and I-123 in patients with different types of thyroid autonomy.

Methods: Unifocal, multifocal or disseminated TA were diagnosed on the basis of biochemical hyperthyroidism, ultrasonographically detected thyroid nodules and by thyroid scintigraphy. All patients were negative for thyroid antibodies. At the time of diagnosis thyroid uptake of Tc-99m was measured. Before treatment with radioiodine-131, performed on average 9.2 weeks later, we determined also 2-hours and 20-hours uptake of I-123 using collimated scintillation detector.

Results: We evaluated 133 patients with TA, 112 females and 21 males, aged between 18 and 90 years (mean, 67.1±14.3). Among them, 61 (46%) were diagnosed with unifocal, 32 (24%) with multifocal and 40 (30%) with disseminated TA. The patients did not differ with respect to thyroid function or time period between Tc-99m and I-123 scintigraphy. In unifocal, multifocal and disseminated TA an excellent correlation between 2-hours and 20-hours I-123-uptake was established (R, 0.68, 0.84 and 0.58, respectively, $p< 0.001$). The correlation of Tc-99m-uptake with 2-hours I-123-uptake was highly significant in all types of TA (R, 0.61, 0.53 and 0,60, respectively; $p< 0.002$). The correlation of Tc-99m-uptake with 20-hours I-123-uptake was significant

only for unifocal and multifocal autonomy (R, 0.51 and 0.60, respectively, p< 0.001), but not for the disseminated autonomy.

Conclusion: Our results indicate a strong correlation of Tc-99m-uptake with both 2-hours and 20-hours I-123-uptake in patients with unifocal and multifocal TA, but not in patients with disseminated TA.

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SOLITARY THYROID NODULES INCIDENTALLY DETECTED BY PET/CT

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Thyroid nodules are often encountered in clinical practice and its prevalence is 4% - 50% of general population depending on age, diagnostic method and race. Thyroid nodules and their prevalence increases with age. Thyroid incidentalomas are characterized as focal impalpable intrathyroidal new nodular lesions detected by imaging modalities during study for non-thyroidal disease. These nodules are usually impalpable and benign, with an associatiated risk of cancer ranging from 1.5% to 10%.

Positron emission tomography (PET) using F18- fluoro-D-glucose (FDG) a valuable functional imaging modality that has demonstrated distinguished capabilities in fields of primary cancer detection, planning and monitoring treatment, prognosis prediction, early detection of recurrent disease, and the diagnosis of regional lymph node and distant metastasis.

Subject of our study was four patients with different oncology diseases: the first patient was with cervical cancer, the second with chronic lymphocytic leukemia, the third was with breast cancer and the fourth with pulmonary metastasis and not clear localization of the primary tumor.

Methods: All four patients underwent 18F- FDG PET/CT whole body scan, high-resolution thyroid ultrasound and ultrasound guided fine needle aspiration.

Results: The PET/CT whole body scan revealed solitary hypodence nodular lesions in the thyroid gland with focal increased uptake in them at the fourth patients.The result of fine needle aspiration biopsy showed a papillary thyroid cancer in patients with breast cancer and chronic lymphocytic leukemia, medullary thyroid cancer in patient with cervical cancer and low differentiated thyroid cancer in patient with pulmonary metastasis.

Conclusion: FDG PET/CT is playing an increasingly important role in the evaluation of thyroid cancer. Focal thyroid lesions incidentally found on 18F-FDG PET/CT have high risk of thyroid malignancy.

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THE ROLE OF THE CONTRAST ENHANCED ECHOGRAPHY IN THE DIAGNOSIS OF THYROID NODULES

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Objectives: our purpose was to evaluate the role of elastosonography (ELX) and Contrast enhancement with ultrasound (CEUS) in the diagnosis of citologically dubious thyroid nodules.

ELX has been recently extended to the evaluation and discrimination between hard and soft nodules. CEUS, wich assesses the degree of blood flow in a organ, seems to be applicable to thyroid nodules, as well.

Methods: 19 patients with indeterminate cytology (Thy3 n=12) or suspicious for malignancy (Thy4 n=7) were evaluated. All subjects underwent ELX (Esaote Mylab 70) and CEUS. The numerical quantification of nodular vascularity was performed by Q-Contrast software V 4.00 (Bracco). All patients were then referred for surgical approach to obtain a correlation between histology, cytology, ELX ratio between nodular and non-nodular tissue (ELX2/1) and indexes of CEUS - peak (P) and time to peak (TTP) - expressed as P and TTP index between extra-nodular tissue and nodule. These parameters of Thy2 nodules (n=8) were considered as control.

Results: The values of ELX2/1 ranged between 0.8 and 3.3; no difference were observed in mean (± SEM) of ELX between Thy2 (1.62 ± 0.22) and Thy3-Thy4 nodules (1.59 ± 0.16). No correlation emerged between histology and ELX. No significant difference between TTP and P index of Thy2 and Thy3-Thy4 nodules was detected. CEUS showed that nodules proved malignant by histology had a lower peak than the surrounding parenchyma (P index>1). A significant correlation was found between histology and P index (Sr 0.56, P=0.05). No correlation was showed between histology and TTP index.

Conclusions: Although based on a limited case number, our study suggested that ELX2/1 did not provide meaningful data. CEUS, instead - especially concerning P index - seems to be a valid and promising technique in the discrimination of nodules.

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THE ANALYSIS OF THYROID ULTRASOUND ECHOGENICITY IN THE PATIENTS WITH HASHIMOTO´S DISEASE

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Background: Ultrasonography is an approved diagnostic method in Hashimoto´s disease (HD) based mainly on subjective estimation of thyroid hypoechogenicity. The aim of our study was objective ultrasound parameters analysis for discrimination the patients with HD. Different types of echogenicity measurements were analysed to find the proper area of differentiation of HD from normal thyroid gland. Selected neck muscles were also tested.

Material and Methods: Ultrasound echogenicity parameters for right and left thyroid lobes: proximal part, distal part, sternocleidomastoid muscle and infrahyoid muscles, respectively, were obtained from 62 patients (42 with new diagnosed HD and 27 controls). All scans were performed using GE Logic5 scanner with 11MHz linear array transducer; average estimation of echogenicity during preprocessing was maintained. The tested area was pointed manually. Two-sided t-Student test was applied, sensitivity and specificity were assessed using ROC test.

Results:

	t-Student test			roc test		
Echgenicity(dB)	Study group mean (SD)	Control group mean (SD)	p	Sensitivity	Specificity	cut off (dB)
RP - proximal part of right lobe	–70,9 (4,1)	–64,8 (3,0)	<0,001	76%	80%	–68
TP - total proximal part of lobe	–71,6 (4,5)	–65,3 (2,8)	<0,001	73%	89%	–68,25
TD - tptal distal part for both lobes	–74,5 (4,4)	–70,5 (4,2)	<0,001	68%	67%	–72,2
TL - SCMM (total lobe - sternocleidomastoid muscle)	0,6 (6,5)	6,9 (6,5)	<0,001			
TL-IM (total lobe - infrahyoid muscle)	–1,1 (4,5)	3,7 (5,6)	<0,001			

Conclusion:

- The highest level of sensitivity and specificity was observed for echogenicity of the proximal part of one lobe and for average of proximal parts of both thyroid lobes. Evaluation of lobe's distal parts was not such discriminating.
- We did not confirm correlation between thyroid hypoechogenicity related to neck muscle echogenicity in HD, unlike different authors.
- The point of references for thyroid echogenicity in differentiation of Hashimoto's disease was estimated for -68dB. We are planning further, larger studies to verify this finding.

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IS SUBTRACTION PROTOCOL FOR PARATHYROID HYPERTHYROIDISM NOT MORE USEFUL IN SPECT/CT ERA?

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Objectives: Progress in hybrid nuclear medicine techniques may influence protocol type dedicated to exam patient with hyperparathyroidism. Comparison between Technetium and MIBI-Tc99m subtraction protocol (SUB-p) and MIBI-Tc99m washout protocol (WASH-p) both performed with three dimensional scintigraphy was performed. It was analyzed which method allows better visualization of the lesion for the surgeon.

Methods: 18 patients (14F and 4M, aged 17-76 years, av. 57 years) with P-HPT and 40 patients (21F and 19M, aged 23-81 years, av. 58) with S-HPT had early and delayed planar study. Delayed SPECT/CT study was done in all 58 patients but early SPECT/CT was done only in those with WASH-p. Each of SPECT/CT finding was presented to the surgeon as transverse, sagital and coronal fusion scans. After an inconclusive subtraction protocol result, washout protocol was employed in seven cases.

Results: In P-HPT 12 patients and S-HPT 8 patients had SUB-p. In 3 patient of P-HPT group and 4 patients with S-HPT group examinations had to be repeated due to possible blurring of Tc99m in three dimensional presentation. Due to possible relatively smaller size of parathyroid adenomas in S-HPT overlapping of Technetium 99m activity on MIBI-Tc99m activity turned to be crucial factor for repeating study with another protocol. All of them underwent surgery and histological examination was performed. In 6 of these patients surgeon removed the whole thyroid gland due to its nodular appearance. One thyroid papillary cancer and one follicular tumor and one parathyroid cancer was found in histopathology.

Conclusions:

1. Subtraction protocol with Technetium and MIBI-Tc99m is more time consuming in comparison to washout protocol.
2. It is difficult to differentiate parathyroid adenoma from non-parathyroid adenoma due to presence of Technetium-Tc99m in 3D modality.
3. An examination performed with SPECT-CT subtraction protocol does not facilitate localization of suspected parathyroid adenoma in S-HPT.

P200

UTILITY OF SERUM THYROGLOBULIN, TC-99M THYROID SCINTIGRAPHY, NECK I-131 UPTAKE AND ULTRASONOGRAPHY FOR THE EVALUATION OF PATIENTS WITH THYROID CANCER AFTER SURGERY

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Aim: To evaluate the correlation between ultrasonography (USG), Tc-99m thyroid scintigraphy (TS), 24 hour radioiodine I-131 uptake (RAIU) and serum thyroglobulin (Tg) in patients with differentiated thyroid carcinoma (DTC) after surgery.

Methods: 29 patient with a mean age of 45.89±11.85 years (range 15-74) with DTC treated with total thyroidectomy were prospectively studied. Patients with metastases and anti-Tg antibodies were excluded. After optimal TSH stimulation (> 30 mU/ml), TS, RAIU, USG, serum thyroglobulin and antithyroiglobulin antibody measurements were obtained.

Results: Out of 23 patients with papillary, 2 patients with follicular and 4 patients with mixed tumors, 6 had thyroiditis on the histological examination (21%). The mean remnant thyroid volume was 0.283 ml (0-1.89 ml). Tg values after surgery were in the range of < 0.2 and 84 ng/ml (median:4.93). RAIU varied between %0.1 to %16.4 (median2.9, mean:4.42). USG and TS detected residual tissue in the neck in 18 and (%62) and 25 patients (%86) respectively. TS was significantly more sensitive than USG for the detection of remnant thyroid tissue ($P < 0.005$). When RAIU was ≥ 0.9 %, all patients had tracer uptake in the thyroid bed on TS. Correlation between thyroid bed iodine uptake and remnant volume was poor. ($r = 0{,}26 = p < 0{,}05$). The RAIU in patients with thyroiditis was not different than those without thyroiditis. In 4 patients whose Tg values were above 25ng/ml extrathyroidal uptake was seen on the postablation scan.

Conclusions: For the postoperative evaluation of patients with well differentiated thyroid cancer 1) The sensitivity of TS is higher than USG for the detection of residual thyroid tissue 2) When remnant volume does not correlate with Tg levels, metastases are likely 3) Postoperative RAIU correlates poorly with remnant volume 4) No relation was found between IU and presence of thyroiditis on the surgery specimen.

P201

FDG PET/CT IN DIAGNOSTICS OF DIFFERENTIATED THYROID CANCER (DTC)

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Introduction: FDG PET, playing an important role as a diagnostic tool in oncology, is also used in DTC, mostly to evaluate disease staging or to localize metastases in subjects with elevated serum thyroglobulin (Tg) level.

Aim: The aim of the study was to evaluate the usefulness of FDG PET/CT in DTC.

Material and Methods: Up to now 74 PET/CT examinations, among them 34 after TSH stimulation, were analyzed. The study group comprised 48 women and 26 men. In 55 patients papillary thyroid cancer was diagnosed, whereas follicular in 10, oxyphylic in 4 and poorly differentiated thyroid cancer in 5 cases. PET/CT was performed to evaluate the final DTC staging (24 pts with persistent disease), to confirm complete remission after treatment (7 pts) or to clarify diagnostic problems such as non-specific 131-I uptake in whole body scan or ambiguous CT (17 pts) or to localize cancer foci (26 pts with hyperthyreglobulinemia).

Results: In 24 patients with persistent disease new lesions were detected in 9 cases (38%), whereas in 6 (24%) tracer uptake in known metastases was confirmed and in 9 no specific uptake was observed (38%). In the subgroup with FDG uptake in known metastases and new detected lesions half of the examinations were done under TSH stimulation and the other half under TSH suppression. However, false negative results were mostly observed under TSH suppression (89%).

Among 26 cases with hyperthyreglobulinemia alone PET/CT allowed to localize the disease in 15 patients (57%). However, in 9 (34%) of them no specific uptake was noticed and in two cases the PET/CT results were equivocal. The source of elevated Tg level was detected significantly more often when PET/CT was done under TSH stimulation (89%).

Conclusion: The findings confirmed usefulness of PET/CT in DTC diagnostics and monitoring, especially in cases when all other procedures failed.

PO19 Trace Elements and Environment

P202

EFFECT OF HAND SCRUBBING ON URINARY IODINE CONCENTRATIONS OF OPERATING ROOM STAFF

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Background: It is well known that excessive iodine exposure is associated with thyroid dysfunction and thyroid autoimmunity. Some of the surgical hand scrub solutions contain huge amounts of iodine.

Table 1. UIC among study subjects

	N	Mean Age	UIC† (min-max)	P value*
HSG from hospital-1	39 (F:13 M:26)	32±6.5	126.0 (12-345)	.014
HSG from hospital-2	78 (F:24 M:54)	33±9.3	165.5 (12-822)	<.001
HSG (total)	117 (F:33 M:84)	32±8.6	142.0 (12-822)	<.001
Control group	92 (F:50 M:42)	31±9.5	89.0 (1-429)	

HSG: Hand scrubbing group. † Median of urinary iodine concentrations. *when compared to the control group.

Objective: To explore the effect of hand scrubbing, by using iodine containing surgical hand scrub solutions on urinary iodine concentrations (UIC) of the operating room staff.

Methods: 117 surgeons, anesthetists and surgical nurses who used surgical hand scrub solutions from two different hospitals (iodine exposure group) and 92 age matched hospital staff from non-surgical units of the hospitals were used as healthy controls. In the iodine exposure group, 39 subjects (from hospital-1) used iodine containing hand scrub solutions occasionally, and the remaining 78 surgical staff (from hospital-2) used only iodine-containing hand scrub solutions. Morning spot urine specimens were collected from all participants for the analysis of UIC.

Results: This study demonstrated that the operating room staff (together and separately analyses of the hospital-1 and hospital-2 groups) had significantly higher levels of UIC compared to the control group (table 1).

Occasionally, especially among the staff using only the iodine containing scrub solutions for scrubbing, UIC may reach to levels of higher than 500 µg/day, far over the recommended daily intake.

Conclusion: Scrubbing by iodine-containing solutions could lead to iodine excess among surgical staff.

P203

MULTIPLE PESTICIDES – ENDOCRINE DISRUPTORS- EXPOSURE OF GREENHOUSES WORKERS AND THYROID PARAMETERS AS WELL AS MARKERS OF THYROID AUTOIMMUNITY

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Objective: The persistence of high prevalence of thyroid pathology (goiter, nodules) in our population, despite the correction of iodine deficiency, determined us to evaluate the impact of factors different than iodine intake on the thyroid gland as environmental endocrine disruptors. We studied the potential correlation between pesticide exposure and parameters of thyroid function, autoimmunity and morphology in a group of greenhouses workers (GHW) exposed to multiple uncontrolled pesticides across agricultural season.

Materials and Methods: We studied a group of 72 farworkers, aged 15 - 78 y.o, from a plain village with normal iodine intake, who enrolled voluntary in the study. In biological samples (urine, blood) collected 4 times across agricultural season from GHW exposed to multiple pesticides, as toxicological inquiry confirmed, we determined thyroid parameters, chlorpyrifos, its metabolite trichlopyridinol (TCP), dimetoat, cypermetrin and carbofurane. It was also assayed cholinesterase activity. Thyroid echography was performed.

Results: Median TSH 3.37±4.25 mcUI/mL, range 0.0051 - 21.50; TSH higher than 4.2 in 13% of subjects. Median FT4 16.68 pmol/l. Positive ATPO in 16% of subjects. Thyroid nodules were found in 32,75% and echographic pattern suggestive for chronic thyroiditis in 18% of subjects. TCP, the metabolite of chlorpyrifos, was detectable in proportion of 64,70% (mean TCP10,5 µg/l) and of 100% (mean TCP 57,3 µg/l) respectively, in different time season exposure. Cypermetrin and dimetoat concentration in the majority of samples was under the quantification limit. Carbofurane was present in 71,4% of samples with concentrations range from 0,03 µg/ml to 0,50 µg/ml.

Conclusions: The incidence of thyroid pathology in studied group, in conditions of normal iodine intake, was much higher than the known epidemiology of thyroid disease. The most frequently encountered pesticide (70-90%) was chlorpyrifos with concentrations significantly higher than the known concentrations for exposure background. It is necessary to complete and control these preliminary data.

P204

RECOMMENDED NUMBER OF SAMPLES FOR MONITORING OF IODINE NUTRITION AFTER IODINE SUPPLEMENTATION

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Background: Iodine fortification of food has been applied in many iodine deficient regions. As both iodine deficiency and excess are unfavourable, it is recommended to monitor the iodine intake of the target population by measuring the median urinary iodine excretion (UIE) in groups of people. It remains to be elucidated if an iodization program affects the size of the subpopulation to study for estimating iodine intake of the population with a certain precision.

Aim and Method: We describe variations in UIE as measured in spot urine sampled in each participant once monthly for 13 months. Group 1 (G1, n=16) was studied before and G2 (n=21) after implementation of the Danish iodization program

Results: G1 / G2 (208 / 273 samples) mean (SD) UIE were 57 / 112 (14/41) µg/L. Median individual coefficients of variation (CV) were G1 / G2: 39 / 43% (p=0.92), and the group based CV 57% in both groups. No trend was seen between mean UIE during the year and individual variation (Spearmans Rho 0.01, p=0.54) or at a group level (Jonckheere-Terpstra p=0.37). The number of samples needed to reliably estimate the UIE level of a population was estimated to 122 in G1 and 126 in G2.

Conclusion: The iodization program led to a considerable increase in UIE, but variations in UIE were unchanged both at the individual and the group level. Consequently, the number of samples needed to reliably estimate the UIE level of a population did not differ between these populations with a two-fold difference in mean UIE levels.

P205

VARIATION IN THYROID FUNCTION TESTS AMONG INUIT AND CAUCASIANS IN LIVING IN AN ARCTIC ENVIRONMENT

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Background: Variation in thyroid function tests influences their interpretation. Genetics may influence variation in thyroid function tests. Inuit is a genetic entity and the influence on variation in thyroid function tests remains to be detailed.

Aim: To obtain data on variation in thyroid function tests among Inuit and Caucasians living in an Arctic environment.

Methods: Repeated sampling among Inuit and Caucasians living in North Greenland. Participants answered a questionnaire regarding thyroid disease, dietary and lifestyle factors. Specimens were collected for measurements of TSH, fT4 and fT3 in serum, and iodine in urine at winter, spring, autumn and summer. Samples were collected, stored and transported under similar conditions, and mixed for analysis.

Results: Participants were 33 Caucasians, 39 Inuit in a town and 25 Inuit in a settlement. Inuit counted more alcohol abstainers than Caucasians (26% vs 3%, p=0.002) and had a higher intake of traditional Inuit foods (p=0.02). The median of individual average fT4 was lower in Inuit than in Caucasians (p=0.006) while median fT3 and TSH were similar. Inuit and Caucasians differed in variance for TSH (Bartletts test, p< 0.01) and fT4 (p=0.03) while not

for fT3. Ethnicity influenced CV for TSH (p=0.029) and fT4 (p=0.006) while not fT3 when adjusted for age, gender and smoking habits and alcohol use.

In conclusion ethnicity may influence variation in thyroid function tests among Inuit and Caucasians living in the same environment.

P206

LOW URINE IODINE CONCENTRATION IN MIDDLE AGE WOMEN IN THE NORTHERN SWEDEN

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Introduction: In 1936, a voluntary iodine fortification program was introduced in Sweden. Since 1966 50 mg sodiumiodide/kg is added to table salt. A national investigation in 2006, performed according to the WHO guidelines in 857 school-children, confirmed iodine sufficiency (median urinary iodine concentration, UIC: 125 µg/l). Is the iodine intake sufficient among adults?

Method: From the 2009 MONICA Survey (multinational MONitoring of trends and determinants in CArdiovascular disease) 325 subjects from the two most northern counties in Sweden (targeted population 312000) were randomly selected from population registers, stratified for age (25-74 years) and gender. Patients from four groups were studied: younger men (YM, n=65), younger women (YW, n=88), older men (OM, n=84) and older women (OW, n=87). Cost registration and UIC, measured by a modified Sandell-Kolthoff method, were collected once in February-May. Estimated 24 h UIC (E24-UIC) was calculated from a morning urine sample.

Results: Median UIC in the whole group was 105 µg/l and median E24-UIC 102 µg/l. Women (n=175) had lower median UIC than men, 96 µg/l and 113 µg/l, respectively, p=0.025. OW group had lower median UIC (82 µg/) than OM (122 µg/L) and YW (110 µg/l), p< 0.001. Analyses of E24-UIC confirmed lower levels in OW (median 96 µg/l) but also in YW (96 µg/l) and YM (85 µg/l) than in OM (122 µg/l), p< 0.05).

Conclusion: Despite a national UIC in the range recommended by WHO (100-200 µg/l) subsamples of adults in Northern Sweden have an iodine excretion below 100 µg/l, which may indicate mild iodine deficiency. This may be attributable to Swedish food patterns were 50% of the iodine intake comes from milk, cheese and bovine meats, 30% from butter, bread and 20% from table salt. In the north hunting of elks is very common, which may lead to decreased consumption of bovine meat.

P207

EFFECTS OF SELENIUM SUPPLEMENTATION ON TPOAB IN ACTIVE AUTOIMMUNE THYROIDITIS

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Objective: In several prospective randomized trials it has been shown that selenium supplementation in patients with autoimmune thyroiditis (AIT) significantly reduces serum thyroid peroxidase antibody (TPOAb) concentrations after 3 and 6 months treatment.The effect of selenium (Se) supplementation was more pronounced in patients with higher TPOAb concentrations (>1200 U/ml).The aim of our study was to investigate the effects of Se tretmant on patient with newly developed or active AIT and high TPOAb titers.

Methods: Forty AIT female petients(aged 23 - 56 years) with elevated plasma TPOAb above1200 U/ml and basal TSH within the normal range were included in the present study.All patients received 200 µg sodium selenite per day orally over a period of 3 months.TPOAb,TSH,and free thyroid hormones were determined by commercial assays.All patients underwent ultrasonographical histogram analyses under standardized conditions.Mean densities of the thyroid tissues were determined in grey scales(GWE).

Results: No significant difference in the TPOAb levels was found after Se administration(1972 ± 1055 vs. 1953 ± 1054 U/ml; p=0.055).Also,we found no differences of thyroid echo levels (17.04 ± 2.07 GWE vs. 17.01 ± 2.05 GWE; p=0.166)

Conclusions: We demonstrate that Se administration in our AIT patiens with high disease activity does not induce significant changes of TPOAb levels and sonographic echogenicity of the thyroid gland.

P208

TIROKID STUDY: STATUS OF IODINE NUTRITION OF SPANISH INFANTS (PRELIMINARY RESULTS)

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Introduction: Iodine déficit (ID) is associated with psychomotor disorders and intellectual disabilities. Iodine déficit has been endemic in several spanish regions. Studies have been conducted locally or in different communities but to date, there have been no studies which have evaluated the status of iodine nutrition of global Spanish infants.

Objectives: Primary endpoint of the study is to assess iodine nutrition status and secondary endpoint is to estimate thyroid disfunction prevalence in Spanish schools population aged 6 - 7 years.

Methods: Multicenter, observational, transversal study in spanish schooling population aged 6 - 7 years, The estimation of iodine deficit prevalence < 100 mcg/l in 20.0% of the population with precision 1.5%, it was estimated a sample size of 2.500 schooling children. Multistage, stratified, random sampling according to Autonomous Regions and type of population. Urine iodine was measured using Benotti method and the TSH levels using Whatman 903 filter paper (normal range 0.4 - 4.0 mcU/L).

Results (preliminary): So far first 474 samples have been analyzed (Andalussia, Aragon, Asturias, Balearic Islands, Castilla La Mancha and Castilla León).Urine iodine median was 172.8 mcg/L (min 10.0 - max 605). Urine iodine < 100 mcg/L was shown in 20.0% of the population, < 50 mcg/L in 5.4% and > 500 mcg/L in 0.63%. TSH median was 2.12 mcU/L. The prevalence of TSH < 0.4 mcU/L was 1.7% (IC 95% ±0,038) and the prevalence of TSH > 4.0 mcU/L was 6.2% (IC 95% ±0,7). It has not been detected any association between urine iodine concentration and TSH levels.

Conclusions: These preliminary results show a good iodine nutritional status within the studied population, supporting a significative change in the historical iodine deficiency in Spain. A highly hypothyroidism prevalence has been observed in this study which may require further confirmation.

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P209

ASSESMENT OF IODINE AND SELENIUM SUPPLEMENTATION IN DIFFERENT REGIONS OF BELARUS

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The objective of the work was to study iodine and selenium supplementation in some regions of the Republic of Belarus according to the data of 2010.

Methods and Subjects: Iodine content was determined in morning urine samples taken from 464 schoolchildren and adults living in different areas of the country (Mozyr, Stolin, Pinsk, Minsk) using the cerium-arsenic method. Selenium was determined in the blood serum by spectrofluorimetry. More than 250 residents aged 18-40 years from Brest, Gomel, Mogilev, Minsk regions of Belarus and from the city of Minsk have been examined.

Results: In all the examined settlements, median urine iodine concentrations were within normal range (145-190 µg/l). There were no significant differences among the regions.

Low urine iodine concentrations (below 20 µg/l) have been observed only in isolated cases. The iodine levels corresponding to moderate iodine deficiency (20-50 µg/l) have been detected in 2-10% of cases. Mild iodine deficiency (50-100 µg/l) was registered in 11-18% of cases, while normal urine iodine concentration (above 100 µg/l) - in 76-85% of cases. Iodine levels about 300-500 µg/l have been found in 7-11% of cases, with isolated cases amounting to more than 500 µg/l. Medians of selenium content in blood serum ranged within 89-110 µg/l in people living in different regions of Belarus, which is slightly lower than the optimal level (118 µg/l).

Conclusions: Thus, the obtained results testify to a satisfactory iodine supplementation in the examined regions of Belarus due to an effective strategy for iodine deficiency elimination. Median blood serum selenium concentration may indicate a light selenium insufficiency in the studied areas of the Republic.

P210

THE ACTIVITY OF NA, K-ATPASE OF PLASMA MEMBRANES OF LIVER, KIDNEY, AND HEAD OF RAT BRAIN WITH DIFFERENT IODINE IN THE DIET

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Objective: To study the activity of Mg and Na / K-ATPase in plasma membranes of brain, liver and kidneys in rats with different iodine.

Materials and Methods: The experiments were 144 albino rats, 2-nd generation of at different times after birth (5, 10, 15, 30, 60 and 120 days of life), always contained in the face of declining to provide 85-90% of iodine (4,3 mg / day) from normal control rats were receiving 34,3 micrograms of iodine per day.

Results: In rats of all ages iodine deficiency group noted the suppression of the activity Na / K-ATPase activity in the brain by an average of 22,0%, and in the liver and kidneys - 37,5%. The obtained data show a decrease of adequate supply of thyroid hormone-governmental, in conditions of iodine deficiency.

There is a tendency to increase the activity of Na / K-ATPase with age in all the organs, as in rats with normal iodine and iodine deficiency in, with significant changes in the activity of this enzyme are still present between these groups of animals.

Parallel investigated Mg-ATPase activity, an enzyme that does not found the dependence on thyroid status. Experiments have shown that the active sequence Mg-ATPase of plasma membranes of liver, kidney and brain in rats with iodine deficiency in nutrition is not changing, its concentration did not change, depending on the age of animals.

Conclusions:

1. There is a direct relationship between the concentrations of thyroid hormones and activity Na / K-ATPase in plasma membranes, depending on the thyroid status of the organism.
2. Experiments have shown that the activity of Mg-ATPase activity does not depend on a thyroid status, this fact confirms the purity of the experiments.

P211

THYROID FUNCTION- AND SELENOPROTEIN P STATUS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Introduction: Chronic Kidney Disease (CKD) impacts on thyroid hormone (TH) metabolism resulting in low T3 concentration in patients with a low glomerular filtration rate (GFR). As deiodinase selenoenzymes metabolise T4 to T3 and degrade rT3 in kidneys, CKD might affect both pathways. Selenoprotein P (SEPP) contributes the majority of serum selenium and acts as selenium transport protein for the kidneys. Data on selenoprotein status in CKD and its implication on TH metabolism in renal tubular epithelium are rare. Therefore we studied serum TH and SEPP in patients with different CKD stages (1-5, not yet on dialysis) and in chronic hemodialysis patients (CHD) (3 times/week).

Methods: 180 CKD patients and 72 CHD patients were prospectively investigated for clinical data, renal function parameters, serum thyroid hormone parameters (TSH, T4, fT4, T3, fT3, rT3, TBG), C- reactive protein (CRP), and SEPP.

Results: Decreasing renal function (GFR) was associated with increasing SEPP concentrations (r= -0.17 *). T4 and fT4 were positively correlated with renal function (r= 0.16 *; r= 0.18 *). SEPP was negatively correlated with T4 and fT4 (r=-0.17 *). There was no correlation of SEPP with T3, fT3, rT3, TSH, TBG or CRP.

T4 (median 81.0 vs 87.0 nmol/l *) and fT4 (median: 13.2 vs 16.0 pmol/l*) were significantly lower in the CHD group compared to patients with CKD stage 4 and 5 (GFR < 30 ml/min); SEPP concentrations were lower in the CHD group (median 2.50 mg/l) vs the GFR < 30 ml/min group (3.26 mg/l*). *: significant at level p< 0.04 or higher

Summary: Patients with normal renal function show low but still normal SEPP concentrations in the presence of normal T4 and fT4 concentrations, whereas patients with end stage kidney disease undergoing CHD have low T4- and fT4 values in the presence of low SEPP concentrations.

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P212

THE USE OF AN ULTRASENSITIVE THYROGLOBULIN ASSAY IN THE FOLLOW-UP OF PATIENTS WITH THYROID CARCINOMA REQUIRES A REVIEW OF ITS CUT-OFF

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Serum thyroglobulin (Tg) is the marker of persistence/recurrence of differentiated thyroid carcinoma (DTC) after surgical treatment and radioablative therapy. The sensitivity of the assay improved by thyrotropine (TSH) stimulation which, nowadays, is performed by administrating the recombinant human TSH. A more sensitive Tg assay might avoid the rhTSH stimulation but it is known that the highest is sensitivity the lowest is specificity.

Objective: We compared two serum Tg assays (Immulite and Beckmann) which have functional sensitivity of 0.5 and 0.1 ng/ml, respectively. To this end, we measured serum Tg with both methods in 273 patients (pz) with DTC and followed up at our Department.

Results: In 255/273(93.4%) pz, the Tg-I was < 0.5 ng/ml. Of these 255 pz, considered in clinical remission based on the values of Tg-I and other clinical and instrumental data, 163/255(63.9%) showed Tg-B< 0.1 ng/ml, 83/255(32.6%) showed a Tg-B between 0.1 and 0.5 ng/ml and 9/255(3.5%)

showed Tg-B>0.5 ng/ml. Finally in 18/273(6.6%) pz, the Tg-I was >0.5 ng/ml and Tg-B ranged from 0.1 ng/ml to 6.65 ng/ml.

Conclusions: This study showed that the two assays have several discrepancies and confirms that the greater sensitivity of Tg-B is accompanied by a reduced specificity since 36.1% apparently disease free pz would be defined as still affected when considering Tg-B >0.1ng/ml and therefore these patients would be submitted to further investigations. Thus, whenever we would routinely use the Tg-B assay but, at the same time, avoid inappropriate treatments it needs to reconsider the cut-off of negativity for Tg-B to at least < 0.5 ng/ml: in this case only 9 of the 255 subjects who were considered as cured would result "positive" and submitted to further investigation.

P213

THORACIC 131-I UPTAKE AFTER PREVIOUS PNEUMONECTOMY IN PATIENTS TREATED FOR DIFFERENTIATED THYROID CANCER

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Introduction: In patients treated for differentiated thyroid cancer (DTC), the presence of an abnormal uptake of radioiodine (131-I) on the whole body scan (WBS) considered as local recurrence and/or distant metastases leads to repeated administration of 131-I. Uptake not linked to thyroid cancer but to other conditions should be recognized in order not to overtreat patients.

Case report: We describe 3 cases of unilateral thoracic uptake of 131-I in patients previously treated by pneumonectomy for lung cancer. Patients were diagnosed for a papillary cancer after at least 7 years of complete remission of lung cancer. After initial surgery, they received repeated administration of 131-I because of abnormal or suspicious 131-I neck uptake on the postablation WBS. In 2 patients the 131-I thoracic uptake was unilateral, diffuse and homogeneous and in the remaining patient it was restricted to the upper left thorax, at the exact location of the pleural cavity following pneumonectomy. In all patients, 131-I thoracic uptake remained identical on subsequent WBS. It was isolated in 2 cases, both patients with undetectable serum stimulated Tg levels, and it was associated to neck and mediastinal lymph node uptake in the remaining patient who had a low detectable Tg level. Chest CT scan only showed sequellae of previous surgery. FDG PET/CT, performed in 2 patients was normal in both cases. The abnormal thoracic uptake was attributed to 131-I accumulation in the pleural cavity after pneumonectomy.

Conclusion: Benign thoracic 131-I uptake can be seen in patients treated for DTC after previous pneumonectomy.

P214

THE ADDITIONAL VALUE OF A SECOND HIGH-DOSE ^{131}I THERAPY IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA WITH THYROGLOBULIN ANTIBODIES

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Introduction: International guidelines for differentiated thyroid carcinoma (DTC) differ in their recommendations for the management of patients with thyroglobulin antibodies (TgAbs), especially in the long term follow-up. Also, this applies to the decision about a second ^{131}I therapy.

The objective of this study was to evaluate the additional value of a second high-dose ^{131}I therapy in DTC patients with positive serum TgAb levels.

Methods: TgAb concentrations were routinely measured using a luminescence immunoassay (Abbott Laboratories, USA) in sera from 117 DTC patients diagnosed and treated in our clinic between March 2006 and September 2010. According to our institutional protocol, TgAb-positive patients received a second ^{131}I therapy of 150 mCi six months after ^{131}I ablation. Post treatment scans were performed ten days after ^{131}I therapy and were scored either as positive (pathological) or negative (none or physiological ^{131}I uptake). All patients with a positive post treatment scan after the second ^{131}I therapy received a MRI.

Results: Twenty-four (median follow-up 35.7 months) out of the 117 patients (20.5%) showed positive TgAbs. Twenty-one patients actually received a second ^{131}I therapy. For different reasons, three patients did not receive this therapy. Four out of the 21 patients with a second ^{131}I therapy showed pathological ^{131}I uptake on the post treatment scan. In one of them persistent disease was confirmed. In this patient, disease activity was already detected with a MRI performed before the second ^{131}I scan because of evidence of neck metastases and an inconclusive ultrasound. The other three patients with a positive post treatment scan (follow-up respectively 49.3, 40.9 and 38.3 months) showed no localization of disease on MRI and were considered to be disease free.

Conclusion: The additional value of the second high-dose ^{131}I therapy in TgAb-positive patients seems to be limited. However, this finding needs to be confirmed in larger series.

P215

OUTCOMES FOR PATIENTS WITH ANAPLASTIC THYROID CARCINOMA RECEIVING DIFFERENT TREATMENT MODALITIES

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Objectives: To evaluate outcomes for patients with anaplastic thyroid carcinomas receiving different treatment modalities.

Methods: The outcomes of 20 patients with histologically confirmed anaplastic thyroid cancer from 2004 - 2010 were retrospectively analysed using case notes and hospital records.

Results: 20 patient's notes were reviewed; 9 female and 11 male (ratio 1:1.2) with the median age being 69.5 years (mean 69.7; range 56.3-80.56 years).

19 patients died due to the anaplastic thyroid carcinoma or as a consequence of its complications, 8 of whom died specifically from asphyxiation.

13 patients received radiotherapy. Doses ranged from 2436cGY to 6500cGY; fractions ranged from 6 to 30 (median 8). The response to radiotherapy at one month was: partial response-5 people (38.5%); stable-1 person (7.7%); progression-2 people (15.4%); death-4 people (30.8%); unknown-1 person (7.7%).

10 people had radiotherapy only; 3 people had chemotherapy only; 3 people had radiotherapy and chemotherapy; 4 people had no treatment.

Median survival for all cases was 59 days from initial consultation with the oncologist/diagnosis (range 32 to 350 days; mean 117.4). The mean and median survival for different treatment modalities is shown in table 1.

Conclusion: Anaplastic thyroid cancer remains a diagnosis with poor prognosis with current treatment modalities. Outcome is not significantly improved with any of the usual treatments and so more research into alternative therapies is recommended.

Table 1. Means and Medians for Survival Time (for Abstract P215)

Treatment	Mean				Median			
	Estimate (days)	Std. error	95% Confidence interval		Estimate (days)	Std. error	95% Confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
None	85.000	51.020	.000	184.998	32.000			
Radiotherapy only	141.600	42.476	58.346	224.854	59.000	37.947	.000	133.377
Chemotherapy only	117.667	39.872	39.518	195.816	137.000	78.384	.000	290.632
Radiotherapy and chemotherapy	207.333	86.258	38.268	376.399	220.000	137.171	.000	488.856
Overall	136.550	27.057	83.519	189.581	59.000	53.666	.000	164.185

P216

COMPARISON OF PROCALCITONIN STIMULATION TESTS WITH PENTAGASTRIN (PG), AND HIGH-DOSE CALCIUM IN PATIENTS WITH MEDULLARY THYROID CARCINOMA (MTC)

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Introduction: In clinical practice it is becoming more common to use procalcitonin levels to monitor the course of MTC patients.

Objective: The aim of the study was to compare procalcitonin concentrations after stimulation with Pg and calcium.

Materials: The study used both methods of stimulation in 6 surgically treated MTC patients with persistent disease.

Method: Procalcitonin secretion stimulation tests were performed in patients first using Pg, and after 6 months using high-dose calcium. Recorded data were analyzed.

Results:

1. Procalcitonin concentration at time zero
   · Test using Pg 1,483(±1,0812)
   Test using calcium 2,908 (±3,5385).
   Procalcitonin concentration differences at time zero in both tests were not statistically significant.
2. Procalcitonin concentration 3 minutes after stimulation
   · After Pg stimulation 6,460 (± 7,2560)
   After calcium stimulation 5,624 (± 7,9128)
   Differences in procalcitonin concentrations at 3 minutes in both tests were not statistically significant.
3. Procalcitonin concentration 5 minutes after stimulation
   · After Pg stimulation 6,505 (± 7,0589)

After calcium stimulation 5,846 (± 8,2360)Differences in procalcitonin concentrations at 5 minutes in both tests were not statistically significant.

Conclusions: In post surgery MTC patients with persistent disease the procalcitonin concentrations after Pg and calcium stimulation were comparable.

P217

CEREBRAL FOLLICULAR THYROID CANCER METASTASIS. WHEN NEUROSURGERY?

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Objective: To evaluate the neurosurgical moment in cerebral metastases of a follicular thyroid cancer (FTC), in relation to radioiodine treatment.

Methods: A woman aged 55 was diagnosed with a 4.4/ 3.8/5 cm FTC and lung metastases. She underwhent total thyroidectomy with neck dissection, with staging at that time of pT3, PNx, ST3, G2, R1,V1.

One month after surgery, thyroglobulin was above 1700 ng/ml, TSH 43 mU/L. Whole body I^{131} scan showed lung and right parietal metastases, and anterior cervical rezidual uptake, therefore she received 100 mCi I^{131} and then restarted 150 ug LT4 /d. After several months, she developped a sincopal episode; cranian MRI showed a 3.2/3.5 parieto-occipital mass. Neurosurgery was scheduled and an FTC metastasis was documented, with TGL and TTF2 immunoreactivity. Additional radiiodine treatment was given in several instances after 2 years, at a total dose of 660 mCi, with partial control of disease.

Results: At 2 years after the neurosurgery, she presents residual lung FTC uptake but no cranian or cerebral and increased tyroglobulin at 2569 ng/ml. Further radioiodine treatment was scheduled.

Conclusions: In the presence of FTC cerebral metastasis, the neurosurgical approach should precede the radioiodine treatment, in order to avoid cerebral radionecrosis lesions.

P218

ION- IS ABLATIVE RADIO-IODINE NECESSARY FOR LOW RISK DIFFERENTIATED THYROID CANCER PATIENTS?

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Background: Most patients with differentiated thyroid cancer have surgery followed by TSH suppression and radioactive iodine (RAI) ablation. However, the American Thyroid Association are unable to recommend either for or against RAI ablation in low-risk patients because the evidence comes from observational studies only. Among patients with a low risk of recurrence, RAI ablation in addition to thyroidectomy and TSH suppression, may represent over-treatment and therefore patients may undergo hospital isolation and the risk of short- and long-term side effects (eg second malignancies) unnecessarily. IoN will be the first ever randomised trial to address this issue.

Trial design: Low-risk eligible patients are those with R0 total thyroidectomy (previous 6 months), and the following features. Papillary thyroid cancer with non-aggressive histological features: pT1b (1-2cm); pT2 (2-4cm); pT3, intrathyroidal only; multifocal microcarcinoma; pN0; pN1a; pNX. Follicular

thyroid/Hürthle cell cancer (minimally invasive with capsular invasion only); primary size 1-4cm intrathyroidal; pN0; pN1a; pNX.

Patients will be randomised to receive RAI ablation (1.1GBq) or not, following surgery. All will go on a low iodine diet and have a pre-ablation Technetium 99m scan (for remnant size). 6-9 months later, they will have an I131 scan, neck ultrasound and stimulated thyroglobulin (Tg). For the following 5 years: Tg every 6 months, and neck ultrasound every 6 months in year 1 then annually. The main objective is to determine whether 5-year disease-free survival is no worse in the no-RAI ablation group, compared to RAI ablation.

Target: 570 patients are planned across the UK National Cancer Research Network: 3 years accrual and 5 years follow-up. IoN has been approved and funded by Cancer Research UK, and is the next national UK trial. It is the natural successor to HiLo, which showed that 1.1GBq is as effective as 3.7GBq. We will provide further details of the IoN trial.

P219

BURKITT LYMPHOMA OF THE THYROID IN A PATIENT WITH AUTOIMMUNE THYROIDITIS

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Objectives: To present a rare case of Burkitt lymphoma of the thyroid.

Methods: M.R, female, 62 years old, resident in an iodine sufficient area; biochemical testing (TSH - immunochemiluminescence, TPO Abs - immunoradiometric assay), thyroid ultrasonography, immunohistochemistry were performed.

Results: The patient presented with rapid thyroid and left lateral cervical lymph nodes enlargement, within the last 4 months. Biochemical data showed: normal thyroid function (TSH=0.4 mIU/L, FT4= 15.2 pmol/L), positivity of thyroid autoimmunity markers (TPO Abs=146 IU/mL, antithyroglobulin Abs=261 IU/mL), normal calcitonin (< 2 pg/mL). Whole blood count, alkaline phosfatase (84 IU/L), lactate dehydrogenase (408 IU/L), calcium, phosphorus, albumin were normal. ESR was slightly increased. Thyroid ultrasound revealed small goiter (thyroid volume= 18.4 mL) with 2.4/1.8/1.55 cm left thyroid nodule and numerous lateral cervical and supraclavicular hypoechoic lymph nodes, confirmed by cervico-thoracal CT scan. Fine needle aspiration biopsy raised the suspicion of thyroid lymphoma. Total thyroidectomy and extensive lymph nodes dissection was performed. Postoperatively, PET/CT scan showed stage II non-bulky disease, with intensely FDG-avid involved bilateral neck and anterosuperior mediastinal lymph nodes. There was no evidence for pulmonary, hepatic gastrointestinal or renal lymphoma. On pathology, a diffuse population of monomorphous, medium and large sized lymphoid cells was shown. Admixed numerous apoptotic figures and mitosis are present. The infiltrating lymphoid cells have round to oval nuclei and prominent nucleoli. On immunohistochemistry, these cells show CD20, CD10 and BCL-6 expression. IRF 4/MUM1 and BCL-2 were negative. CD3 was negative in thyroid tumor, but positive in reactive lymphocytes. EMA was negative in the tumor, but positive in epithelial structures. Ki67 proliferation index was 90-95%. FISH analysis showed c-Myc chromosomal translocation, confirming the diagnosis of Burkitt lymphoma. Chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, intrathecal methotrexate was started recently.

Conclusion: Even rare, thyroid Burkitt lymphoma should be suspected in patients with rapidly growing thyroid mass.

P220

INFLUENCE OF SMOKING AND ALCOHOL ON SERUM CALCITONIN VALUES

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Aims: Previous studies have shown that smoking and alcohol may have influence on serum calcitonin levels. However, no data is available about the effects of smoking and alcohol on the serum calcitonin in patients of Vienna population. In this study we evaluated serum calcitonin in smoking and alcoholic patients of Vienna population.

Materials and Methods: 50 smoking patients and 50 alcoholic patients (daily alcohol consumption > 100 g) were included in the study. 250 non-smoking patients with daily alcohol consumption less than 10 g were used as control. The basal serum calcitonin, free triiodothyronine (fT3), free thyronine (fT4) and TSH were measured in all patients.

Results: Compared with control group (serum calcitonin: 2.6 ± 0.3 pg/ml), no significant difference (p=0.14) was found in basal serum calcitonin values in smoking patients (1.9 ± 0.4 pg/ml). There is also no significant difference (p=0.42) in basal serum calcitonin values between alcoholic patients (2.2 ± 0.4 pg/ml) and the control group. No significant change (p=0.47) was demonstrated between smoking patients and alcoholic patients.

Conclusion: Our preliminary results suggest that no significant effects of smoking and alcohol on basal serum calcitonin values were found in the patients of Vienna population. However, studies with larger numbers of patients of Vienna population are needed.

P221

TUMOR FORMATION OF THE THYROID GLAND ON THE BASE OF AUTOIMMUNE THYREODITIS

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Autoimmunization elements may be present in the pathogenesis of many pathological states and is the cause of diffuse, nodular and diffuse nodular-hyperplasia body as well as a risk factor for cancer study localization. The purpose of this study is to assess the cytological and histological research, defining tactics surgeon. Retrospective analysis of the results subjected to examination and treatment of 164 patients operated on with a diagnosis of follicular neoplasm of thyroid gland disease whose background was autoimmune tireodit (AIT) in the department of endocrine surgery MUZ GB №2 from 2007 to 2010 years performed after fine-needle aspiration biopsy (FNA). Among the patients were women aged 19 to 71 years. The most frequent indication for FNA when AIT was the presence of nodules in the thyroid, requiring differential diagnosis with adenomas or cancer. Follicular adenoma is a tumor of follicular structure, without typical signs of follicular cancer capsule invasion and (or) blood vessels. Cytological study can not distinguish follicular adenoma from follicular carcinoma. That is why they combine into a single category of cytology (follicular neoplasm). With such a cytologic picture showed operative treatment. Gistological material obtained after surgery performed with a diagnosis of follicular neoplasm on the background of autoimmune tireodit divided into two categories:

1. Benign changes - a group of patients whose amounted to 72,5%. Follicular adenoma met with (62,8%) patients operated with the cytological picture of follicular neoplasm. Tireodit was (6.1%), toxic adenoma (1.2%), as well as onkotsitarnuyu adenoma (2.4%).
2. Malignant changes were detected in 27.5% of patients. Proportion of follicular cancer was (14.07%), follicular-papillary (9.83%), papillary (2.4%) and medullary (1.2%).

The results of our investigations show that any nodules in the thyroid gland against the background of autoimmune tireodita may be cancerous. This category of patients must be active diagnosis using FNA.

P222

DELAYED TRACHEAL NARROWING SPECULATED TO BE DEVELOPED AFTER ENDOTRACHEAL INTUBATION INJURY IN ROBOT-ASSISTED THYROIDECTOMY

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Objectives: Tracheal complications after thyroidectomy such as perforation or stenosis are rarely present. Moreover, a delayed tracheal narrowing after robot-assisted thyroidectomy has not been reported. We experienced a case which the patient developed a delayed tracheal narrowing after thyroid operation.

Case report: A 43 year-old female patient received the robot-assisted hemithyroidectomy with central compartment node dissection due to papillary thyroid microcarcinoma. She was discharged without any postoperative complications or discomfort at postoperative day (POD) 4. On POD 18, she came to our emergency room with dyspnea, sputum and cough. On neck CT and bronchoscopy, we found a tracheal narrowing with luminal irregularity accompanying submucosal edema. However, we were not able to find any specific anatomical injury related to airway problems. We reviewed the recorded operation video and were not able to find any evidence of intraoperative tracheal injury. The patient eventually recovered through conservative management with antibiotics, steroid and nebulizer with bronchodilators treatment.

Conclusions: We were not able to find the specific cause of the delayed tracheal narrowing and speculated that the luminal irregularity accompanying submucosal edema were developed due to endotracheal intubation injury with subsequent secondary infection. In such case, conservative management was enough, instead of operative care.

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P223

SALVAGE TOTAL LARYNGECTOMY FOR INVASIVE THYROID CANCER; TWO CASE REPORT

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Introduction: For the patients with well-differentiated thyroid cancer, invasion of the aerodigestive tract is uncommon but worsens its prognosis. Investigation of 314 cases of thyroid tumor resections, which were performed at our faculty in recent 11 years, revealed two cases of salvage laryngectomy after first shaving operation. We report these cases with our treatment strategy.

Case 1: The patient was a 67-year-old woman, who was introduced to our hospital as suspicious esophageal cancer. At the first examination, computed tomography (CT) indicated a low-density mass behind the trachea, which measured 35mm in diameter, and endoscopic survey revealed submucosal tumor with strong erosion. Fine needle aspiration (FNA) cytology showed papillary thyroid carcinoma (PTC). At first, tangential tumor excision with shaving technique was executed, but most of tumor remains attaching firmly to the esophagus and trachea. After 13 months follow-up, residues of PTC grew invading the larynx and esophagus. So that, with patients' admission, salvage total laryngectomy was performed. Radioactiveiodine (RAI) therapy was executed subsequently and 1-year follow-up study proves no recurrence.

Case 2: 83-year-old man was referred to our department for recurrent PTC. He had clinical histories of PTC (T3N0M0) which had been totally resected 8 years previously in another hospital. In 13 months after tangential tumor excision (shaving), rest of tumor regrew invading the skin and larynx. A salvage total laryngectomy with deltopectoral (DP) flap reconstruction was performed and subsequent RAI therapy is scheduled in a few months.

Discussion: The management of invasive thyroid cancer remains controversial. Several studies have shown no significant difference in survival between radical and conservative resection. Honings J et al. recently reviewed contemporary literatures about this issue and concluded that tracheal or laryngotracheal resection should not be avoided. Although long-term prospective studies are still required, salvage total laryngectomy is still necessary based on our experiences.

P224

DIAGNOSIS OF THYROID CARCINOMA IN A TERCIARY CENTER OVER A PERIOD OF FIFTEEN YEARS

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Introduction: Differentiated thyroid carcinoma is by far the most common primary malignancy of the thyroid gland. Papillary carcinomas constitute the vast majority and follicular carcinomas have been reported as 10% to 15% of cases.

Aims: To present the frequency and distribution of histological subtypes of thyroid cancer diagnosed at our institution and to analyze it´s evolution during this period.

Methods: We did a retrospective evaluation of histopathological data of all patients operated on for thyroid cancer at our hospital between 1996 and 2010. Statistical analysis was done with SPSS 18.0 for Windows.

Results: During this period a total of 1885 patients (271 males and 1614 females with a mean age of 51.9 ±15.2 and 49.9±14.5 years old, respectively) were diagnosed and treated for thyroid cancer at our institution. Histological subtypes distribution was: Papillary 1785 (91.9%), Follicular 101 (5.2%), Medullary 30 (1.5%), Poorly differentiated 6 (0.3%), Anaplastic 4 (0.2%), primary thyroid Lymphoma 2 (0.1%), Metastasis 1 (0.1%), Leyomiosarcoma 1 (0.1%), Uncertain malignancy 13 (0.6%). During this period the proportion of patients with papillary carcinoma increased from 86.8% in 1996 to 90.2% in 2010 while follicular carcinoma decreased from 11.3% in 1996 to 3.6% ($p< 0,05$). The highest rate of increase was for papillary carcinomas less than 2 cm (50% in 1996 versus 77,6% in 2010; $p< 0,05$).

Conclusion: Our series confirm that papillary thyroid carcinomas are the most common form of thyroid malignancies and the percentage of follicular cancers is less than traditionally reported. As expected the incidence of papillary thyroid carcinoma increased with the decrease of follicular cancers over this 15 year period. This may be explained by an increased incidence of papillary cancers and modifications of the histologic criteria used for classification of encapsulated follicular lesions.

P225

FREQUENCIES AND LEVELS OF ANTI-THYROGLOBULIN ANTIBODY OF PATIENTS WITH I-131 RADIOACTIVE IODINE TREATMENT FOR THYROID CANCER METASTASES

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Introduction: The thyroglobulin (Tg) level in blood is commonly used to evaluate the effectiveness of I-131 radioiodine therapy for thyroid cancer metastases. However, the measured Tg levels are lower than the actual Tg levels when anti-Tg antibody is present in the serum. We investigated whether the serum anti-Tg antibody is indicative of the level of Tg.

Methods: Ninety-eight patients (34 men, 64 women; mean age, 60.5 years; age range, 19-82 years) with thyroid cancer who were monitored after I-131 radioactive iodine treatment from January 2009 to December 2010 were reviewed for this study. The serum thyroid stimulating hormone, Tg, and anti-Tg antibody levels of all the patients were regularly measured.

Results: The serum anti-Tg antibody levels were positive in 26 (27%) patients (7 men, 19 women; mean age, 57 years). The mean serum anti-Tg antibody level was 371 ± 1067 U/ml (range, 0.3-5278 U/ml). These patients were divided into 2 groups according to the anti-Tg antibody threshold level, which was set at 1 U/ml. The mean Tg value was 677 ± 1404 ng/ml ($n = 14$) in the group with anti-Tg antibody levels under 1 U/ml, and it was 13.8 ± 17.5 ng/ml ($n = 12$) in the group with anti-Tg antibody levels more than 1 U/ml. There was strong significance ($P = 0.0014$) between both groups. In 13 patitens of the positive 26 patients, Tg levels just after 3 weeks stopping of thyroid hormone medication were evaluated. The mean Tg value was 7269 ±

9374 ng/ml (n = 9) in the group with anti-Tg antibody levels under 1 U/ml, and it was 10.65± 10.97 ng/ml (n = 4) in the group with anti-Tg antibody levels more than 1 U/ml. There was significance (P = 0.01) between both groups.

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A CASE OF APLASTIC ANEMIA FOLLOWING THE RADIOACTIVE IODINE THERAPY FOR THYROID CARCINOMA

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Radioactive iodine therapy is a major therapeutic agent in patient with thyroid carcinoma. Radioactive iodine ablation for thyroid carcinoma has a beneficials: decrease the recurrence and mortality rates and facilitates the early detection of recurrence based on serum thyroidglobulin measurement and ^{131}iodine scan. Although this therapy was performed safely more than 60 years, it may produce side effects. The accumulation of radioactive iodine can cause the various solid cancer and leukemia. We recently experienced aplastic anemia which was rare complication for radioactive iodine therapy for thyroid carcinoma.

A 58-year-old female patient presented with fever, easy bruising and bleeding tendency. The patient had no medical history. The patient underwent a total thyroidectomy along with right modified radical neck dissection under the diagnosis of thyroid carcinoma. One month after the operation, the patient received radioactive iodine therapy with 250mCi, and second radioactive iodine therapy with 250mCi was performed after six months. In laboratory findings at presentation, white blood cell count 420/uL (normal, 4,000-10,800/uL), platelet count 21,000/uL (normal, 150,000-400,000/uL) were noted. The patient was diagnosed as aplastic anemia based on the laboratory and clinical findings.

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MANAGEMENT OF ANAPLASTIC THYROID CARCINOMA IN OUR HOSPITAL

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Introduction: Anaplastic thyroid carcinoma (ATC) is a relatively rare but show very aggressive malignancy; almost 80% death within a year. We report six clinical cases of ATC at our hospital in these 7 years.

Methods: Retrospective analysis revealed six ATC cases in a total of 205 cases of thyroid carcinoma from 2004 to 2010. Statistical data was as follows: age; 44-81 years (median: 63.0), sex; three males and three females, stage distribution: IVA/IVB/IVC=2/2/2.

Results: In all cases, radiotherapy (RT) or chemoradiotherapy (CRT) was executed. Total radiation dose were 39-60 Gy (median: 46.9Gy). The five cases were treated by surgery and subsequent RT/CRT. In two cases, the local tumors were totally resected and they could have long-time survivals. Otherwise one case was treated only by RT because of emergency admission. The female patient was referred to our institution with dyspnea caused by tracheal compression by suspicious ATC. Emergent tracheotomy and emergent RT was executed immediately after admission.

Postoperative pathology revealed anaplastic inversion from papillary thyroid carcinoma (PTC) in two cases. They were treated by subsequent radioactive iodine therapy, but one case showed sudden anaplastic inversion 3 years after PTC operation. Multimodal treatments including RT and chemotherapy (CBDCA/THP) are still going on for this case.

Conclusion: Golden standard of ATC treatment is still discussed. We treat ATC mainly by surgery if total resection is possible, but if not, we choose RT/CRT as second-line treatment. From these cases, we suggest that multimodal treatment is important. Especially chemotherapy is one of the multimodal treatments.

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BONE METASTASES FROM FOLLICULAR THYROID CARCINOMA. CASE REPORT

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Introduction: Distant bone metastases(BM) in follicular thyroid carcinoma(FTC) have a bad prognosis. Usually bone metastases have a low capacity to trap the iodine, however when there is sufficient uptake, radioiodine could be a important therapeutic weapon. The metastatic tissue of differentiated thyroid carcinoma can also have the capacity to produce thyroid hormones

Material and Methods: We describe a case of a patient with extensive metastatic disease of a FTC A 53 years old woman with back pain. Surgery 3 years ago to a discal hernia L4-S1. Due to the pain exacerbation a spine CT scan disclosed a huge lytic mass at left pelvis. A biopsy was consistent with a metastases of a FTC.The study revealed a volumous thyroid nodule and multiple lesions in the lungs suspicious of metastases. A total thyroidectomy with lymph node dissection was performed. Histopathology showed a 7 cmT4N1M1. One month after surgery,without T4 the TGB levels were 74560 ng/ml(TSH-8,9uU/ml), antibody anti TGB negative. At this time she received 200 mCi I131 The post therapy WBS reavealed diffuse uptake in the thyroid bed region, lungs and very intense at the left pelvis. Three 3 months later a debulking surgery with stabilization of the pelvis was done and.after a 2nd iodine therapy with 200mCi. At this time the TGB was 4735ng/ml with a TSH 78 uU/ml

Conclusions: Radioiodine therapy can be a very effective treatment even in bone metastatic FTC. Clinically the patient improve a lot and the TGB levels marked decrease. Due to the burden of the metastatic disease with some production of thyroid hormones there was only a slight increase of TSH one month after thyroidectomy. The fact that in the 2nd iodine therapy the TSH marked increase, after withdrawing T4, indicates that the thyroid - pituitary axis is intact.

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MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES TREATMENT: ONE CENTER EXPERIENCE

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Results: 9(0.04%) cases of MEN of 24934 operated in 1973 - 2009. 6(2.6%) MEN-2a of 226 medullar thyroid cancer patients. Were performed 23 operations.

1. MEN-1: female, 29. Pancreatic insuloma, nodular goiter, prolactinoma and parathyroid adenoma. Hemithyroidectomy (2001),Transsphenoid adenomectomy (2003), subtotal resection of pancreas (2003), parathyroid adenomectomy (2004). Recovered.
2. MEN-1: female, 59. Pituitary adenoma, nodular goiter, parathyroid adenoma, type-2 diabetes. Conservative pituitary adenoma and diabetes treatment, subtotal thyroid resection and parathyroid adenomectomy (2006). Recovered.
3. MEN-2a: female, 40. Bilateral Pheochromocytoma, medullar thyroid cancer (MTC), parathyroid adenoma. Bilateral adrenalectomy (1989), relapse of left adrenal tumor adrenalectomy (1992) thyroidectomy, central and lateral neck dissection in another clinic (2003), repeated central and lateral neck dissection, parathyroid adenomectomy in our clinic (2003). Recovered.
4. MEN-2a: female, 43. MTC, left low parathyroid adenoma. Thyroidectomy, central neck dissection (CND), parathyroid adenomectomy (2005). Recovered. Observation.
5. MEN-2a: male, 25. MTC, left pheochromocytoma. Thyroidectomy, central and lateral neck dissection (1998, 2004), adrenalectomy (2000). Recovered.

6. MEN-2a: №5 brother, 23. Congenital right hydronephrosis, MTC, right pheochromocytoma. Right nephrectomy (1981), thyroidectomy (1998, 2010), right adrenalectomy (2003). Recovered.
7. MEN-2a: №5 & 6 father, 54. MTC, 1 kg pheochromocytoma. Thyroidectomy (1969), refused of adrenalectomy. Suddenly died. Clinical -morphologic diagnosis: hypertonic crisis, pheochromocytoma rapture, retro-and intraperitoneal bleeding (2000).
8. Boy, 5. Son of №6. Has defective gene [mutation in T1900C (C634R)] in 11 exon gene RET). Prophylactic/curative thyroidectomy, CND (2007). pT1N0M0.
9. MEN-2b: male, 47. MTC, marfanoid habitas and mucosal neuromas. Thyroidectomy, central and lateral neck dissection. Recovered.

Conclusion: MEN syndrome should be excluded in all of parathyroid and medullar cancer patients.

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RADIOIODINE REFRACTORY, POORLY DIFFERENTIATED METASTATIC FOLLICULAR CARCINOMA OF THE THYROID

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55-year-old female initially presented in 2003 with a left sided thyroid mass which proved to be a benign colloid nodule on FNA (AC2). 2 years later she represented with a 5 month history of hoarseness of voice. Examination revealed large multinodular goitre with a dominant 30x28mm nodule in the left lobe; there was also evidence of left vocal cord palsy. FNA confirmed a follicular neoplasm (AC3). Histological appearances post left hemithyroidectomy were in keeping with a widely invasive, poorly differentiated follicular cell carcinoma with a frequent vascular invasion(pT4 Nx Mx).Completion thyroidectomy ws carried out in July 2006. Shortly after ablation therapy with RAI in February 2007 (3.7 GBq ^{131}I) she developed a parietal patch of hairloss and pain in left shoulder and arm. Imaging confirmed a large extradural metastatic deposit within the parietal bone, abutting the sagittal sinus. There were further deposits within left clavicle and proximal humerus. In August 2007 she underwent parietal craniotomy and resection of the metastasis, completed with an acrylic cranioplasty. Whole body scan following second RAI ablation (5.0 GBq ^{131}I) revealed persistently increased uptake within the clavicle and humerus, markedly reduced uptake within the skull and new area of increased uptake in the thyroid bed. The latter proved to be a 2cm mass consistent with a local recurrence on FNA. Subsequently the patient underwent 3 radioiodine ablation therapies with persistently increased uptake in the neck, clavicle and humerus on the post ablation scans, in the setting of rising thyreoglobulin. The mass in the neck was resected in May 2010 but further local recurrence was noted 6 months later. In December 2010 the patient underwent sixth RAI and post ablation scan demonstrated markedly increased uptake in the lungs raising suspicion of pulmonary metastases, confirmed on the CT. Should we consider treatment with TKI at this stage?

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PARATHYROID CARCINOMA WITH LUNG METASTASIS IN A FOURTEEN-YEAR-OLD GIRL

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Parathyroid carcinoma is a rare disease in pediatric patient. We present the case of a 14-year-old girl who presented to the thyroid clinic for palpable neck mass for 1 year. The high level of calcium, ionized calcium, parathyroid hormone level and parathyroid scintigraphy suggested primary hyperparathyroidism and parathyroid carcinoma was confirmed by pathologic examination after operation. Six month later persistent hypercalcemia and multiple lung metastases were presented and then bilateral lung wedge resection was done but the metastasis was persistent in computed tomography. Four year later, her calcium and parathyroid hormone level increased to 12.4 mg/dl, 191.5 pg/ml withiout any other symptoms. However, en bloc resection of primary parathyroid cancer and aggressive resection of metastatic parathyroid cancer is the most effective treatment to control of hypercalcemia.

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THYROID DYSFUNCTION IN NON-THYROID CANCER PATIENTS TREATED WITH SUNITINIB

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Sunitinib is increasingly used in oncology, particularly patients with metastatic renal cancer and GIST. Thyroid dysfunction, particularly hypothyroidism is reported in 85% of patients with renal cancer being treated with sunitinib.

Objectives: To assess the impact of sunitinib on thyroid function in a cohort of patients with cancer in our centre and evaluate how dysthyroidism was managed.

Methods: Patients commenced on sunitinib between November 2007 and December 2010 were identified from the hospital pharmacy database. The medical records were reviewed and data extracted for analysis.

Results: 81 patients were identified, median age 63 (range 29-81), 65 male. Metastatic renal cell carcinoma was the commonest diagnosis (82.7%). The incidence of thyroid dysfunction before commencing Sunitinib was 11%. The median follow-up after commencing sunitinib was 176 days (12-1141). 7 patients died, 40 patients stopped treatment after a median 41 days (range 31-342) because of cancer progression, 7 patients were lost to follow-up and the remaining 27 patients are still on treatment. The median number of thyroid function tests (TFT) per follow-up year was 7.4 (0-61).

The incidence of new abnormal TFT after starting treatment with sunitinib was 39.2% (subclinical hypothyroidism 85%, subclinical hyperthyroidism 11%, hyperthyroidism 4%). Only 53% of patients with abnormal TFTs were treated. 8 patients with thyroid dysfunction were documented to have persistent subclinical thyroid dysfunction, but no action was taken. Only 9% of patients who developed thyroid dysfunction after sunitinib treatment were referred to endocrinology.

Conclusions: The incidence of thyroid dysfunction after sunitinib treatment is high, though in our centre it was half of that reported in the literature, suggesting that different patient populations may have variable susceptibilities. A watchful approach to managing subclinical thyroid disease is acceptable in otherwise healthy populations, however the impact of subclinical thyroid disease in patients with cancer is unknown and worthy of further research.

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EXPRESSION OF APOPTOSIS-RELATED MOLECULES (GALECTIN-3, BCL-2, BAX AND SURVIVIN) AND APOPTOTIC CELL DEATH IN PAPILLARY VERSUS ANAPLASTIC THYROID CARCINOMA

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Papillary carcinoma of the thyroid (PTC) is slow-growing tumor with favorable prognosis, while anaplastic thyroid carcinoma (ATC) is highly aggressive tumor with rapid fatal outcome. It is assumed that genetic defects in apoptotic pathways may contribute to differencies in their biological behavior.

We used archival tissue sections of PTC (n=69) and ATC (n=30) and analysed in situ apoptotic cell death (TUNEL method) and immunohistochemical expression of apoptosis related molecules: galectin-3, Bcl-2, survivin (anti-apoptotic) and Bax (pro-apoptotic).

The rate of apoptotic cell death was found to be low in the investigated carcinomas, especially in ATC. Mean galectin-3 staining scores (individual grading from 0-3) significantly differed between PTC and ATC (2.261 and 1.100, respectively, $p< 0.05$). Similarly to galectin-3, high expression levels

of Bcl-2 were found in PTC (1.971), but low levels in ATC (1.067), $p< 0.05$. The Bax score was similar in PTC and ATC (2.188 and 2.233, respectively, $p>0.05$). The mean survivin staining score was higher in ATC (2.462) than in PTC (1.696), $p< 0.05$. Thus, the trends of down regulation of galectin-3 and Bcl-2 during the progression of malignancy from PTC to ATC were similar. The ratio between galectin-3 and Bax, as well as between Bcl-2 and Bax decreased from PTC to ATC, while survivin/Bax ratio increased in ATC in favor of survivin.

In Conclusion: Transition from well differentiated (PTC) to undifferentiated carcinoma (ATC) is followed by down-regulation of anti-apoptotic molecules, galectin-3 and Bcl-2. This down-regulation is counterbalanced with up-regulation of survivin, which may overcome the effects of high Bax expression, and, at least partly, explain the low apoptosis rate and high biological aggressiveness of ATC.

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CROSSTALK BETWEEN THE TRANSCRIPTION FACTORS: ZEB1 AND TWIST AND THE TRANSCRIPTIONAL REGULATION OF E-CADHERIN AND SNAIL1 GENES USING A FOLLICULAR TUMOUR CELL LINE WRO ENRICHED FOR ABCG2/BCRP1 TRANSPORTER

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Epithelial Mesenchymal Transition(EMT) has been described in the dedifferentiation process in thyroid carcinoma. The EMT process is characterized by a down regulation of adhesion molecules, such as E-cadherin and the upregulation of myofibroblastic genes. Follicular cell as well stem cell population remaining in the adult tissue can be involved. Most of follicular thyroid carcinomas are considered well-differentiated with a good prognosis, however, some of them presented a desdifferentiation process. In our previous results using WRO/ABCG2 cell line, we observe a high expression of Zeb-1 and vimentin genes whereas not E-catherin and NIS expression were observed.

Aim: siRNA were used to inhibit Zeb1 and Twist expressions in order to investigate the crosstalk with Snail1, ABCG2 and E-catherin genes expression in the WRO derived from ABCG2 resistant sublines.

Methods: The cells were transfected in 24 and 48h with different siRNA: Zeb-1, Twist or both. Gene expression of Snail1, ABCG2 and E-cadherin were measured by means of the cDNA analysis through the qRT-PCR. The relative expression levels were determined by the CT Method. The protein expression of E-cadherin was analyzed by immunocytochemistry technique.

Results: are shown in the table:

Fold change (RQ)

	ABCG2	E-catherin	Zeb1	Twist	Snail1
24h	x3.3	No expression	Inhibition 80%	No change	x1.5
	x2.4	No expression	No change	Inhibition 81%	x1.8
48h	x1.8	x7.3 Nuclear stain	Inhibition 80%	No change	x1.4
	x2.0	No expression	No change	Inhibition 62%	x1.4

No changes were observed when the inhibition with both siRNA was preformed. NIS was not re-expressed in any condition studied; in contrast, vimentin expression was decreased when Zeb1 siRNA was preformed at 48h.

Conclusion: Zeb1 gene can regulate epithelial and stem cell genes, such as E-catherin, vimentin and ABCG2 independent of Twist gene. However, further experiments may be required to investigate the nuclear E-catherin finding.

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HYPOXIA EFFECTS INDUCED BY $COCL_2$ ON HUMAN THYROID CARCINOMA FTC-133 CELLS

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Objective: To investigate the change of the cell proliferation, hypoxia inducible factor-1α(HIF-1α) expression and mitochondrial membrane potential (MMP) under hypoxia condition induced by $CoCl_2$ in follicular thyroid carcinoma FTC-133 cells in vitro.

Methods: $CoCl_2$, a chemical inducer of hypoxia, was used to induce chemical hypoxia in FTC-133 cells. The cell viability (IC50), reflecting the cytotoxic effects of $CoCl_2$ on cells, was investigated by the MTT assay. The expression of the HIF-1α protein was detected by immunocytochemistry and western blotting. And the MMP was measured using Rh123 staining by flow cytometry (FCM) analysis.

Results: We found that $CoCl_2$ could significantly inhibit the growth of FTC-133 cells after treatment for 72h, and the IC50 was 1.69 μmol/L. Immunocytochemistry and western blotting assay indicated that the expression level of HIF-1α protein was induced with the treatment of different concentrations of $CoCl_2$. When its concentration rised to 150 μmol/L, the expression of HIF-1α increased significantly and reached the peak after 4h treatment and then decreased steadily with the incubation time. FCM showed that the MMPs of FTC-133 cells declined during the initial period after incubation with 100~200 μmol/L $CoCl_2$ and restored to normal 4h later.

Conclusion: $CoCl_2$ could exert direct cytotoxicity to FTC-133 cells at high concentration for longer time periods. However, the expression of HIF-1α increases after 4h treatment of $CoCl_2$. At meantime, HIF-1α may improve cells survival under hypoxic conditions and restore MMP.

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RET/PTC REARRANGEMENTS IN FOLLICULAR HüRTHLE CELL CARCINOMAS

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Follicular Hürthle cell carcinomas (FHCC) are differentiated thyroid carcinomas that are not well characterized from the genetic standpoint. Controversies on the molecular alterations underlying this type of thyroid tumour still persist. In particular, it remains unclarified if RET/PTC rearrangements can play a role in their neoplastic development.

We investigated a series of 17 follicular Hürthle cell tumours (14 FHCC and 3 follicular Hürthle cell adenomas (HCA)) for *RET/PTC* rearrangements and point mutations in exon 15 of *BRAF* gene, and exon 2 in *H-RAS* and N-*RAS* genes.

The 17 follicular Hürthle cell tumours were from 13 females and 4 males with a mean age of 60years (29-81years), and the mean size of tumours were 3.8cm (1.5-10cm).

RET/PTC rearrangements were found in 1 out of the 3 HCA (33%), and in 8 out of the 14 FHCC cases (57%). In 6 out of 8 *RET/PTC* positive FHCC (75%) had a solid pattern of growth. One FHCC (7%) scored positive for *N-RAS* mutation. All the investigated tumours scored negative for $BRAF^{V600E}$ and *H-RAS* mutations. The genetic alterations detected in 9 Hürthle

cell tumours were mutually exclusive, i.e. no tumour displayed more than one alteration.

We confirmed the presence of RET/PTC rearrangement in HCA and FHCC, as previously advanced by other groups. This study reveals the association between the presence of RET/PTC rearrangements and the FHCC, raising the possibility that tyrosine kinase inhibitors may now become a treatment option for patients with this kind of tumour.

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SCREENING OF THE *RET* PROTO-ONCOGENE IN CZECH PATIENTS WITH MEDULLARY THYROID CARCINOMA

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Objectives: Medullary thyroid carcinoma (MTC) occurs in a sporadic form and less commonly in an inherited form comprising multiple endocrine neoplasia (MEN) types 2A and 2B, and familial MTC. Germline point mutations of the *RET* proto-oncogene are responsible for these genetic disorders.

Methods: Screening of the *RET* proto-oncogene was performed in 361 patients with MTC and 344 their at-risk relatives. The cohort of MTC patients consisted of 14 MEN2A, 8 MEN2B and 12 FMTC families, and 329 apparently sporadic MTC patients. Six risk exons were sequenced in each patient. Families with familial MTC without detected mutation in risk exons were also tested in other exons. We used single strand conformation polymorphism method to detect eventual appearance of minor mutations and verified it by sequencing.

Results: We detected 18 different germline mutations in the *RET* proto-oncogene. The mutation Met918Thr was found in all 8 MEN2B families, one family had a double mutation Met918Thr+Tyr791Phe. In 13 MEN2A families (93%), *RET* mutation was detected (Cys620Arg, 8x Cys634Arg, 2x Cys634Ser, Cys634Tyr); a double mutation Cys620Phe+Tyr791Phe was revealed in one MEN2A family. Seven FMTC families (58%) were analyzed to have *RET* mutation (Arg321Gly, Cys618Arg, Cys634Trp, Glu768Asp, 2x Tyr791Phe, Val804Met). In addition, 13 patients (4%) with apparently sporadic MTC had a germline *RET* mutation (Cys609Tyr, Cys611Tyr, Cys634Phe, Cys634Ser, Leu790Phe, 3x Tyr791Phe, Val804Leu, 4x Val804Met). Genetic testing confirmed *RET* mutation in 60 at-risk relatives and 94 of them could be excluded from biochemical screening due to negative *RET* analysis results.

Conclusions: This study summarizes the results of 15-year-screening of the *RET* proto-oncogene in the Czech Republic. Molecular genetic analysis was beneficial not only for patients, but also for their family members. Genetic testing had a significant impact on reducing the incidence of MTC, and contributed to better prediction of the disease.

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VARIABLE MODULATION BY CYTOKINES AND THIAZOLIDINEDIONES OF THE PROTOTYPE TH1 CHEMOKINE CXCL10 IN ANAPLASTIC THYROID CANCER

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Objective: Until now, no data are present in literature about the prototype Th1 Chemokine (C-X-C motif) ligand 10 (CXCL10) in anaplastic thyroid cancer (ATC).

Methods: This study aimed to test in "primary human ATC cells" (ANA) *vs* "normal thyroid follicular cells" (TFC): a) CXCL10 secretion basally and after interferon (IFN)gamma and/or TNFalpha stimulation; b) PPARgamma activation by thiazolidinediones (TZDs), rosiglitazone or pioglitazone, on CXCL10 secretion, on proliferation and apoptosis in ANA.

Results: We demonstrate that: a) ANA produced basally CXCL10 in a 50% of cases, while TFC did not produce it; b) IFNgamma stimulated dose-dependently CXCL10, in ANA and TFC; c) TNFalpha did not induce CXCL10 secretion, in ANA and TFC; d) IFNgamma+TNFalpha induced a synergistic but variable release of CXCL10 in the different ANA preparations, while it was more reproducible in TFC; e) rosiglitazone exerted an inhibition of CXCL10 release in 2/6 ANA, stimulated it in 1/6 and had no effect in the others, while inhibited it in TFC; f) rosiglitazone inhibition of proliferation in ANA was not associated with the effect on CXCL10; g) nuclear factor-kappa B and ERK1/2 were basally activated in ANA, increased by IFNgamma+TNFalpha, and rosiglitazone inhibited that activation.

Conclusions: On the whole, the present data first show that ATC cells are able to produce CXCL10, basally and under the influence of cytokines. However, the pattern of modulation by IFNgamma, TNFalpha or TZDs is extremely variable, suggesting that the intracellular pathways involved in the chemokine modulation in ANA have different types of deregulation.

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ANTITUMOR EFFECTS OF NOVEL AGENTS IN HUMAN NEUROENDOCRINE TUMOR CELLS: AN IN VITRO STUDY

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Objectives: Neuroendocrine tumors (NET) are rare neoplasms that secrete neuropeptides and hormones. Medullary thyroid carcinoma (MTC) is a calcitonin-producing neuroendocrine tumor arising from the parafollicular C-cells of the thyroid gland and representing one of the malignancies of the endocrine system. The establishment of new treatment options is very important as MTCs respond poorly to radiation therapy and conventional chemotherapy, and surgical removal of all neoplastic tissue is, to date, the only curative treatment. Medicinal herbs are of high interest in drug research due to their potential antiproliferative effects against MTCs.

Methods: In this study four plant extracts and two isolated pure substances of *Christia vespertilionis* (CV), a southeast Asian Fabaceae, were tested for their antiproliferative and proapoptotic effects in the medullary thyroid carcinoma cell line MTC-SK, established at our institute.

Results: The data show that cell growth as well as enzymatic activity of mitochondrial dehydrogenases was inhibited by treatment with 10µg/ml of the ethylacetate extract of *Christia vespertilionis* (CV-45). Furthermore, CV-45 did not affect normal human fibroblast HF-SAR cells at the same concentration. Treatment with CV-45 also exhibited apoptotic effects in MTC-SK. Activity of the effector caspases 3 and 7 was increased after 3 hours of CV-45 treatment and DAPI® staining displayed apoptotic effects in nuclear morphology shown with fluorescence microscopy. Flow cytometry analysis showed decreased G1-phase cell population after treatment with CV-45. Studies on gene expression level of apoptosis related genes TNFRSF10b, PDCD5 and metadherin showed altered gene expression in treated MTC-SK cells in contrast to control cells.

Conclusion: These results indicate the antiproliferative and pro-apoptotic potential of *Christia vespertilionis* plant extracts for therapy against MTCs and other neuroendocrine tumors.

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ESTROGEN-RELATED RECEPTOR ALPHA MODULATES A KEY ENZYME OF GLYCOLYSIS : THE LACTATE DEHYDROGENASE

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Tumour cell metabolism is adapted to support their growth and survival that should be considered as a crucial hallmark of cancer. Multiple molecular mechanisms converge to alter cellular metabolism and provide supports for the three basic needs of dividing cells: rapid ATP generation to maintain energy status; increased biosynthesis of macromolecules, and maintenance of appropriate cellular redox status. The aim of this study was to identify the role of Estrogen-related receptor alpha (ESRRA) in the regulation of glycolysis metabolism especially by controlling lactate deshydrogenase A and B (LDHA, LDHB) activities.

We explored three thyroid cell lines FTC-133, XTC.UC1 and RO 82 W-1 each well characterized for their metabolic status. We identified multiple cis-acting promoter elements including functional sites for ESRRA. The interaction between ESRRA and promoters of LDH genes was confirmed by chromatin immunoprecipitation and in vitro analyses for LDHB but not for LDHA. Overexpression of ESRRA decreased the LDH activity whereas inhibition by XCT790 or siRNA increased it.

Warburg effect which shift tumor cell metabolism from oxidative phosphorylation to glycolysis is inadequate to explain conserve metabolism in the three thyroid cell lines. We therefore hypothesize that ESRRA favours oxidative metabolism by inhibiting glycolytic pathway trough modulation of LDH expression and activity in cells whith preferentially oxidative metabolism. All these data suggest that ESRRA and its regulating pathways could be potential therapeutic targets for thyroid tumors.

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ROLE OF GH AND IGF-I ON ONCOGENESIS OF PAPILLARY THYROID CARCINOMA

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Objectives: Prevalence of thyroid carcinoma is high in patients with acromegaly. We established a novel cell line derived from papillary thyroid carcinoma (PTC) with acromegaly patient, and compared with other PTC cell line to elucidate the role of growth hormone in oncogenesis of PTC.

Case: 85 year-old man with PTC and also with acromegaly had PTC metastasis observed at cervical lymph nodes. The metastasis tumor was used as the sample for establishment of cell line.

Methods: The sample was cut into small pieces and dispersed. The dispersed cells were cultured with growth medium, which was DMEM/Ham's F 12 medium supplemented with 10% FBS. The colonial cloning was performed, and a novel cell line was established. The cells were treated with GH or IGF-I, and concentrations of thyroxin and thyroglobulin in conditioned medium, and TSH receptor (TSHR) on cells were measured. The results were compared to two PTC cell lines, which were with or without metastasis.

Result: The cell line derived from PTC with acromegaly patient was consisted of small size of epithelial cells and has a lot of lysosome. The secretion of fT4 and thyroglobulin were increased by GH and IGF-I treatment. The cell line derived from PTC with no metastasis was consisted of middle size of epithelial cells and has a little lysosome, and showed pavement structure. The secretion of fT4 and thyroglobulin were increased by TSH, or GH and IGF-I treatment. The cell line derived from PTC with metastasis was consisted of small epithelial cells and has lysosomes, and showed floating cluster. The secretion of thyroglobulin was slightly increased by TSH, or GH and IGF-I treatment.

Discussion: GH stimulated fT4 and thyroglobulin secretion and TSHR protein level. The data suggested that GH might be related to oncogenesis of PTC.

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LONG TERM OUTCOMES OF TREATMENT WITH ANTI THYROID DRUGS, RADIOACTIVE IODINE AND SURGERY IN HYPERTHYROID PATIENTS

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Introduction: This study was disigned to evaluate long term outcomes of different type of treatment in graves disease,toxic multi nodular goiter and toxic adenoma.

Material and Method: In this study 1022 hyperthyroid patients reffered to endocrinology clinic between 1999-2005 and treated and follow uped there were evaluate for long term outcome. A questioner include age, sex, cause of hyperthyroidism, treatment modality, recurrence of disease after treatment, incidence of hyporthyroidism, complication of each treatment and follow up term were filled out for each patient.

Results: In 580 graves patients after long term treatment with anti thyroid medication, rate of euthyroidism with out adverse drug reaction was 39.5% (during follow up period of 31 ± 16 months.), this rate after radioiodine therapy (during 30 ± 11 months follow up) was 18% and during 13 months follow up period after surgery was 7% which these differences were significant ($p < 0.001$). Among TMNG cases (354 patients) rate of euthyroid cases after a period of 29 ± 19 months follow- up with radioiodine therapy was 33% and after 18 ± 12 months post surgical follow up was29%(P=0.368). The surgical complication rate in TMNG was 36%. Among toxic adenoma cases (88 patients), rate of euthyroidism cases after radioiodine therapy and 27 ± 10 months follow-up was 70% and after surgery during 16 ± 8 months follow-up was 75% (p= 0.502). Surgical complications were not seen in toxic adenoma.

Conclusion: Anti thyroid therapy is the best treatment modality in graves disease and radioactive iodine therapy is the prefered treatment in toxic multi nodular goiter and toxic adenoma according to long term outcomes.

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THE CLINICAL IMPORTANCE OF SUPERIOR THYROIDAL ARTERY MEAN PEAK SYSTOLIC VELOCITY IN DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS IN KOREA

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Background: Thyrotoxicosis can be devided into Graves' disease (GD) or destructive thyroiditis (DT) depending on the pathophysiology. As treatment modality and prognosis for GD or DT are different, rapid and correct differential diagnosis is very important. Doppler ultrasonography is a noninvasive and cost-effective method rapidly contribute to useful information in discriminating thyrotoxicosis. High intrathyroidal blood flow and increased mean peak systolic velocity (PSV) of the thyroid artery are well known characeristics of GD. In this study, we evaluated the superior thyroidal artery-mean peak systolic velocity(STA-mean PSV) as a clinical marker to differentiate types of thyrotoxicosis in Korean patients.

Methods: The study had been conducted with newly diagnosed thyrotoxic patients (age>18, M & F) who visited Pusan Paik hospital from Feb. 2010 to Dec. 2010. Blood samples were taken to evaluate thyroid function and thyroid autoAbs. Tc 99m pertechnetate scan was done to confirm GD or DT. STA-mean PSV was measured by Doppler ultrasonography and were analyzed with each parameters.

Results: Total 35 patients with thyrotoxicosis were enrolled in this study. 25 patients were diagnosed as untreated GD, 10 paitents with DT and 20 subjects without thyroid disease as control. The STA-mean PSV was the highest in the untreated GD group, followed by treated DT group and then those with controls (GD: 76.44 ± 32.35 cm/sec, DT: 23.58 ± 6.68 cm/sec, control: 21.67 ± 9.04 cm/sec). The optimal sensitivity and specificity to differentiate untreated GD from DT were 92 % and 90 %, respectively, using 36.7 cm/sec as a cut-off value.

Conclusion: Measurement of peak systolic velocity of the superior thyroid artery by doppler ultrasonography is useful for the diagnosis of thyrotoxicosis in Korean patients

Keywords: Graves disease, Superior thyroidal artery-mean peak systolic velocity, Thyrotoxicosis

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P244

CHARACTERISTICS OF THE CARDIOVASCULAR SYSTEM AND MICROCIRCULATION IN PATIENTS WITH UNCOMPENSATED THYROTOXICOSIS

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Objective: The purpose of this study was to define the cardiovascular and microcircovascular manifestations in patients with decompensated thyrotoxicosis.

Methods: 30 patients with diffuse toxic goiter (mean age 47, 31±10,74 yr.) with mean disease duration (4,52±3,05 yr.) were investigated. The diagnosis of thyrotoxicosis was based on clinical, instrumental and laboratory values. The TSH level in patients was 0,005 mIU/L at the time of investigation. We performed ambulatory blood pressure monitoring (ABPM) and ECG monitoring by Holter (Holter ECG). Indirect cold stress testing and wavelet-transform analysis of skin temperature oscillations were performed to evaluate endothelial, neurogenic and myogenic components of microcirculation.

Results: Patients with decompensated thyrotoxicosis receiving thyrostatic therapy had mean heart rate 71,85±11,46 bpm. Paroxysmal atrial tachycardia with HR 115-130 bpm occurred in 3 patients. Supraventricular and ventricular extrasystoles were obtained in all participants. ABPM showed no optimal ABP reduction at night time due to diastolic BP mostly (daily index SBP 3%, daily index DBP 6.2%). Indirect cold stress results show no reaction on temperature changes in comparison with healthy people.

Conclusions: Patients with decompensated thyrotoxicosis are «non-dippers». They have pathological reaction of endothelial and neurogenic microcirculation components.

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URGENT THYROIDECTOMY IN A PATIENT WITH SEVERE AMIODARONE-INDUCED HYPERTHYROIDISM

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Amiodarone is an iodine-rich antiarrhythmic drug that causes thyroid dysfunction in 15-20% of cases. There are two main forms of Amiodarone-Induced Thyrotoxicosis: type 1, a form of iodine-induced hyperthyroidism, and type 2, a drug-induced destructive thyroiditis. However, mixed/indefinite forms exist that may be caused by both pathogenic mechanisms.

We present a case of a 60-year-old man, hospitalized at the Department of Endocrinology of the University Hospital in Krakow for severe amiodarone-induced hyperthyroidism. He had a history of 3 years of amiodarone therapy for atrial fibrillation. In the previous 3 months he complained of weight loss, tachycardia, palpitations, diaphoresis, and insomnia. Serum biochemical test were: TSH < 0,005 μIU/ml (normal values 0,3-4,3), free T4 >100 pmol/ml (normal values 11-22), free T3 10,1 pmol/ml (normal values 2,8-7,1). Amiodarone was withdrawn and as we classified the patient with the mixed/indefinite form of hyperthyroidism, he was started on thiamazole, steroids and sodium perchlorate. Despite treatment, we observed an increase in serum concentrations of thyroid hormones. During the 5th week of thyreostatic treatment, the patient developed thiamazole - induced agranulocytosis that led to the withdrawal of the thyreostatic. The agranulocytosis was treated with Neupogen® (filgrastim). Contraindications to further treatment with antithyroids, the worsening condition of the patient and his unresponsiveness to medical treatment prompted a consultation with a cardiologist and an anaesthestesiologist, and an urgent thyroidectomy was successfully performed.

Conclusion: Total thyroidectomy performed in a severe amiodarone - induced hyperthyroidism is highly risky, yet remains a procedure worth undertaking.

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TOWARDS EVIDENCE-BASED DOSAGE OF ANTITHYROID DRUGS AND OF THYROXINE IN GRAVES' PATIENTS WHO DISPLAY A SUPPRESSED TSH-LEVEL - THE CASE FOR A TREATMENT GUIDELINE

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Problem: In Graves' patients, the TSH-level can remain suppressed for a long time, despite normal FT3- and FT4-levels. As measured by the TSH-level, this situation can be regarded as "subclinical hyperthyroidism", which suggests to increase dosage of anti-thyroid drugs (before definitive treatment) or to reduce dosage of thyroxine (after definitive treatment). Yet this dosage approach can lead to symptoms of hypothyroidism, thus reduced well-being of patients, including possible exacerbation of endocrine orbitopathy. This raises treatment costs. - In contrast, according to existing empirical evidence, TSH-receptor autoantibodies (TRAb) can suppress the TSH-level. In light of this evidence, a long-term suppressed TSH-level in otherwise euthyroid Graves' patients should not be interpreted as "subclinical hyperthyroidism". However, this evidence does not seem to have been received comprehensively by textbooks or practical treatment routines yet.

Methods: Case studies outline the negative consequences of TSH-oriented dosage of anti-thyroid drugs and of thyroxine in Graves' patients who display a suppressed TSH level. Deductive reasoning suggests that an incomplete model of the thyroid hormonal feedback loop, which can be seen in some textbooks, backs up this unfavourable dosage approach. Already existing empirical evidence is set forth, which completes this model: Pathological TRAb titers can suppress the TSH-level. From the completed model, the unfavourable dosage approach does not follow any more.

Results: Taking into account empirical evidence that TRAb can suppress the TSH-level, dosage of anti-thyroid drugs or of thyroxine in Graves' patients should not be oriented on the TSH-level. Instead, dosage should be aimed at normal FT3- and FT4-levels. Within the normal ranges of FT3- and FT4-levels, the patient's individual set-point should be the goal.

Conclusions: In order to reduce unnecessary suffering and treatment costs, this FT3- and FT4-oriented dosage strategy should be included into a guideline for the medicamentous treatment of Graves' disease.

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HOW WOULD YOU TREAT A PATIENT WITH SEVERE GRAVES DISEASE WHO IS RESISTANT TO ANTITHYROID DRUGS?

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Severe hyperthyroidism represents 1% or less of the cases of the disease. Treatment can be very challenging. We report a 24 yr-old lady who required multiple aggressive treatments before she could undergo surgery. She was diagnosed with severe Graves disease on Mai 2008, with all the typical, very intense symptoms, a tachycardia of >120/min, no exophtalmos and a goitre of 90g. FT4 was 72 pmol/l, FT3>30, TSH< 0.005, Anti-TPO Ab 1904:Ui/l. 131I uptake 94%, with a uniform, large goitre. Tapazole was started at 20 mg bid and Diltiazem 120 mg bid, since Beta-Blockers were contraindicated. Three months later, with no improvement, she was put on Propylthiouracil (PTU)

200 mg tid and Lithium Carbonate 300 mg tid. Her condition deteriorated and in February 2009 she consulted at our E.R for tachycardia and chest pain. ECG showed no sign of ischemia, but frequency at 140/min. An ultrasound detected a pulmonary hypertension. FT4 was 154 and FT3 41, but her clinical picture was not that of a thyroid storm. She was hospitalized and we increased PTU to 400 mg qid,Diltiazem to 420 mg die, Lithium to 450 mg tid and added Cholesteramine 4g bid, Solucortef 50 mg IV qid, Lugol 5 gts tid. 12 days later FT4 was 30.9, FT3 5.3. The following day she underwent a total thyroidectomy and she was discharged 3 days later on replacement therapy. FT4 1 day after surgery was still 29.3 and TSH did normalize 6 months later. The patient recuperated quickly and her pulmonary hypertension was no more detectable. In summary, the history of this patients indicated that cases with severe hyperthyroidism must be treated aggressively using all the medications at our disposal at the higher doses possible.

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AN UNUSUAL PRESENTATION OF TSH-SECRETING ADENOMA

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Background: Although TSHomas usually present with the signs and symptoms of hyperthyroidism caused by a macroadenoma, sometimes it is a major concern to differentiate between TSHomas and resistance to thyroid hormone action.

Aim: To present a -difficult to diagnose- case of clinically euthyroid TSHoma caused by a stable microadenoma.

Case presentation: A 64-years old male was referred to our university hospital in July, 2008. He had been in a good condition, had no chronic disease. Four months earlier, he admitted to a local state hospital for nervousness. He had elevated fT3 and fT4, while TSH was within reference ranges. Repeated measurements yielded similar results. In his first admission to our center, his blood pressure was 105/65 mmHg, pulse was rytmic and 78/minute. There was not orbitopathy. His fT3, fT4 were consistently elevated; he had normal TSH, liver enzymes, and hypolypidemia. Thyroid ultrasonography revelaed goiter (volume: 39.2 ml). The scan showed diffuse hyperplasic thyroid gland with increased uptake (69.4%). He had an increased molar ratio of α-subunit toTSH (12.2). His anti-tpo, anti-tg, TSH-receptor, and heterophyle antibodies (against to TSH, T4, T3) were all negative. Sex-hormone binding globulin was 156.2 nmol/L (14.5-48.4). Sellar MRI showed a microadenoma (5-mm). Sequencing the thyroid hormone receptor beta gene, there was no mutations. This excluded resistance to thyroid hormone as suggested by the absence of strong TSH response to TRH. In the follow-up, he complianed fatigue, nervousness and erectile dysfunction. His heart rate is 62/minute. He developed growth hormone deficiency and hypogonadotrophic hypogonadism. BMD revealed osteoporosis in both lumbar and hip regions. During the 30-months follow-up, MRIs demonstrated no change in adenoma size. Ga-68-DOTATATE scan showed a focal pathological accumulation in the pituitary region. He denied the pituitary surgery.

Conclusion: TSHoma rarely presents as microadenoma, and may be clinically euthyroid, especially in the elderly.

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A SEVERE GRAVES' DISEASE COEXISTING WITH AN UNUSUAL COURSE OF DIABETES: 30-MONTH FOLLOW-UP

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Objectives: Graves' disease (GD) and type 1 diabetes (T1D), both endocrine organ-specific autoimmune diseases, frequently coexist and in combination are classified as autoimmune polyglandular syndrome type III. GD is a risk factor for T1D.

Methods: 17-year-old boy with GD was treated with a high dose (1 mg/kg/day) of methimazole. To treat a severe thyroid orbitopathy (TO) 0.5 mg/kg/day of prednisone was added. 1 week later overt diabetes (hyperglycemia and ketosis; HbA1c 8%) was manifested and an intensive insulin treatment was initiated followed by a basal insulin glargine injection and continued with a sulfonylurea analog.

Results: 6 months later (unsuccessful monotherapy with methimazole) the patient was admitted to a pediatric endocrine department. Hormone levels (TSH 0.001 μIU/ml↓, fT4 0.41 ng/dl↓, fT3 3.01 pg/ml) and all antithyroid antibodies were positive [TRAb 111 U/l (N< 1.5), TPOAb >3000 U/ml (N< 60) and TgAb 81 U/ml (N< 60)]. All markers for autoimmunity to islet cells were also positive [GADA 113 U/mL (N < 1.0), IA2-AB 13.6 U/ml (N < 1.0) and IAA 18% (N< 5.5%)] however OGTT showed a glucose intolerance (FPG 82 mg/dl; 2 hours 152mg/dL). His insulin response to OGTT was 8.9 and 66.4 μU/ml, respectively. HbA1c was 5.5% and in relation to hypoglycemic episodes the treatment was successfully continued with metformin. Hypoglycemic episodes were no longer observed and all control HbA1c levels were < 6.1%. A combined therapy with methimazole plus L-thyroxine was started to reach euthyroidism. 8 months later the patient received total thyroidectomy followed by LT4 substitution. TRAb level significantly declined (18.9 U/l) however the levels of diabetic antibodies were still were high (GADA 141, IA2-AB 10.4 and IAA 5.7%, respectively). T1D is well-controlled with oral metformin. TO is under spontaneous regression.

Conclusions: The management of a patient with GD and T1D is challenging, and should be individualized.

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THYROID BLOOD FLOW STUDY MAY AVOID EARLY GRAVES´ DISEASE RELAPSE AFTER ANTITHYROID DRUG WITHDRAWAL

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Whereas ultrasound has become the gold-standard in the diagnostic imaging of thyroid nodules, applications in thyroid dysfunctions is less known. However, a mixed clinical-ultrasonographic approach in the diagnosis and follow-up of functional thyroid diseases has recently been shown to be effective. This field of application is known as "functional thyroid ultrasonography". Color Doppler and Color Flow Doppler (CFD) findings (peak systolic velocity PSV and arterial flow AF) are able to guide the physician in the etiological approach of hyperthyroidism, in the choice of treatment and in the decision of drug withdrawal. We studied a cohort of 31 patients with Graves´disease treated with antithyroid drugs(ATD). The ATD withdrawal was accorded to CFD findings. 3 of them relapsed rapidly. Retrospectively, we found explications of the relapse for two patients.

In Conclusion: The measurement of PSV and AF provides precious data which may avoid premature ATD withdrawal in Graves'disease.

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THYROID DYSFUNCTION AND TREATMENT STRATEGY IN PATIENTS ON AMIODARONE THERAPY

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Introduction: Amiodarone is antiarrhythmic agent that can induce mild thyroid dysfunction, but also overt hypothyroidism (AIH) and hyperthyroidism (AIT). AIT can present in two forms: type I (AITI) and II (AITII). However, mixed forms (AITx) exist.

Patients: Since 2002 a computer database with patients (pts) taking amiodarone has been constructed. A retrospective study included 665 pts on amiodarone treatment. Median age of pts was 68±10y (range 21-89y). Pts with prior thyroid dysfunction and thyroid surgery were excluded from the study. Follow-up data were present for 27% pts with median follow-up 21 months (range 1-120 months).

Methods: Serum TSH, T4, T3, FT4, FT3 concentrations were determined by chemiluminescent immunoassays (Immulite 1000/2000, Siemens, USA). Thyroid ultrasound with Color Doppler and thyroid scan were performed in AIT pts to distinguish AITI and AITII. 24-hour ^{131}I "uptake" test (^{131}Iu) was performed in AIT pts referred to ^{131}I-therapy.

Results: A total of 451/665 (68%) pts had normal thyroid function. Median T4 in euthyroid pts was 129 nmol/L, FT4 19 pmol/L, T3 1,46 nmol/L, FT3 4,0 pmol/L, TSH 1,59 mU/L. SH was recorded in 124/665 (19%) pts, AIH in 50/665 (8%) pts, AIT in 40/665 (6%) pts. AITI was recorded in 8/40 pts with median ^{131}Iu 50.1%, AIT II in 22/40 pts with median ^{131}Iu 4.7%, AITx in 5/40 pts with median ^{131}Iu 11.9%, missing data for 5 AIT pts. High dose ^{131}I-therapy was applied in 6/8 pts with AITI, and 2/5 pts with AITx (^{131}Iu≥10%). Hypothyroidism or euthyroidism was achieved in 7/8 pts after ^{131}I therapy. Three AIT pts were sent to surgery.

Conclusions: Majority of pts treated with amiodarone had normal thyroid function. SH was the most frequent thyroid dysfunction. AITII was more frequent than AITI. High-dose ^{131}I-therapy is optimal treatment for pts with AITI but can also be applied in pts with ^{131}Iu>10%.

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FEATURES OF THYROTROPINOMA IN CHILD

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Objective: Thyrotropinoma are a rare cause of hyperthyroidism, while in children this is even rarer.

Methods: In this case report we present a 7 years girl admitted with severe thyrotoxicosis, diffuse goiter and a giant pituitary adenoma of 43/37 mm.

TSH, fT4, T3, were evaluated basal, during TRH and Octreotide tests. GH was measured during OGTT and IGF1, while PRL, E2, FSH and LH as basal sampling. Pituitary tumor was evaluated by 1.5 T MRI scan. She was submitted to somatostatin analogues, then to transphenoidal neurosurgery.

Results: Basal thyroid function assays confirmed severe TSH-dependent toxicosis, measurable only after 1:50 dilution. TSH was as high as 3450 mU/L, which was not stimulated during the 400 ug i.v. TRH test but was suppressed by SMS analogues (octreotide) from 3500 to 2450 mU/L. Tumor GH cosecretion was documented basal as well as during OGTT and by increased IGF1, during 4 months case follow-up, despite lack of clinical signs. After three months when long acting SMS analogues were given, she was submitted to transsphenoidal neurosurgery. After surgery, functional tumor remnant was at 22 mm on postero-lateral extension, TSH decreased at 950 mU/L while GH was increased at an average of 60 ng/ml, not suppressible during OGTT. Pathology confirmed the highly invasive pituitary adenoma with Ki67 at 20%, and intense TSH and GH immunoreactivity. Genetic analysis is ongoing. Further SMSa were given, until the decision of other surgery or radiotherapy. Thyrotoxicosis was managed by metimazole using a normal fT4 as target.

Conclusions: thyrotropinoma in children are very aggressive tumors, requiring a multiple approach, susceptible to harbor aggressive mutations.

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P253

OSTEOPROTEGERIN AND RANKL SERUM LEVELS IN YOUNG PATIENTS WITH GRAVE'S DISEASE

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Aims: Alterations of the nuclear factor-kB ligand (RANKL)/osteoprotegerin (OPG) system have been implicated in several metabolic bone diseases characterized by increased osteoclasts differentiation and activation and enhanced bone resorption. Also it has been recognized that the balance between the levels of OPG and RANKL (ratio RANKL/OPG) may have an important role in bone metabolism. At the same time it is well known that patients with hyperthyroidism show impairment of bone metabolism. Therefore the aim of our study was to assess the levels of OPG, RANKL, ratio RANKL/OPG in young patients with Grave's disease.

Methods: We have examined 36 patients with Grave's disease (age 34,5 [27-44,5] yrs; body mass index (BMI) 24,65+3,67 kg/m2; TSH 0,065+0,07 mIU/l; FT_4 37,56+13,67 pmol/l; GFR 90,27+62,25 ml/min; cholesterol 5,2 [4,5-5,8] mmol/l; triglyceride 1,00 [0,81-1,52] mmol/l). The control group consisted of 22 normal age-, sex- and BMI-matched subjects. There have been measured levels of osteoprotegerin (OPG), RANKL, ratio RANKL/OPG in serum in both groups (before treatment). There has been assessed bone mineral density (BMD) at spine (L2-L4) and at femoral neck using DEXA.

Results: OPG level was higher in patients with Grave's disease in comparison with controls (8,08 [4,67-11,30] vs. 3,1[2,39-3,75] pmol/l, p< 0,001). RANKL level was statistically higher in patients with hyperthyroidism (0,46[0,29-0,62] vs. 0,12[0,10-0,20] pmol/l, p< 0,001). Ratio RANKL/OPG was higher in hyperthyroid patients than in control group (0,08 [0,04-0,11] vs. 0,04 [0,03-0,07], p=0,009). The OPG level positively correlated with BMD at spine (r=0,31, p=0,048), age of patients (r=0,4, p=0,002), BMI (r=0,46, p=0,005), waist (r=0,36, p=0,029), in plasma.

Conclusions: Grave's disease patients have increase of OPG, RANKL levels and ratio RANKL/OPG that may be promising strategy in understanding of accelerate bone loss. Age of patients, anthropometric data may affect OPG level in Grave's disease patients.

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BONE MINERAL DENSITY, BONE MARKERS IN PATIENTS WITH HYPERTHYROIDISM

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Background and Aims: The effect of hyperthyroidism on osteoporosis risk and its reversal remains somewhat controversial especially in young population. The aim of the retrospective cross-sectional study was to assess the bone mineral density and bone markers in premenopausal women and men younger 50 years.

Materials and Methods: 133 patients (mean age 42,6±13,3 years;105 women and 28 men) with new diagnosed hyperthyroidism and 38 controls matched with respect to gender, age and BMI were observed. The bone mineral density (BMD) at lumbar spine (L2-L4) and femoral neck was evaluated with Sophos L-XRA (DEXA). Z-score less -2,0 was used for low bone mass diagnostic according to WHO criteria. Blood was obtained to measure the levels of free T4, TSH and makers of bone turnover (N-MID osteocalcin, CTX, alkaline phosphatase).

Results: BMD (g/sm^2) was statistically lower in patients with hyperthyroidism both at spine (1, 022±0,163 vs. 1,114±0,122, p< 0,05) and at femoral neck (0,743±0,144 vs. 0,831±0,152, p< 0,05) in comparison with controls. In women, according Z-score, low bone mass was revealed in 7,62% predominantly at hip; in men low bone mass detected in 7,14%. CTX levels were abnormally high (0,678[0,415-0,975] vs. 0,287[0,125-0,335],p< 0,001), also alkaline phosphatase (180[94-250] vs. 93[71-119], p< 0,001) and N-MID osteocalcin (46,24±12,79 vs. 28,24±10,79, p< 0,001) levels were increased.

Conclusions: The data confirmed the high prevalence of bone loss in premenopausal women (7,62%) and men younger 50 years (7,14%) with new diagnosed hyperthyroidism. Low BMD revealed predominantly at femoral neck in women and at lumbar spine in men with hyperthyroidism. Biochemical markers of bone turnover are increased in patients with new diagnosed hyperthyroidism suggesting an increase in osteoclastic and osteoblastic activity as the main mechanism of bone loss.

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THYROID DYSFUNCTION AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

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Diagnostic work-up of osteoporosis comprises assessment of thyroid function. The aim of the study was to investigate the prevalence of thyroid dysfunction in asymptomatic postmenopausal women referred to bone mineral density (BMD) measurement due to suspected osteoporosis and to compare BMD in euthyroid postmenopausal women and postmenopausal women in subclinical hypothyroidism (SH).

Patients: 170 postmenopausal women referred to BMD measurement due to suspected osteoporosis. Women with prior thyroid dysfunction were excluded from the study. BMD was compared between euthyroid women (n=83) aged 55-70 years (median age 63 years) and age-matched women in subclinical hypothyroidism (n=16).

Methods: DEXA Hologic QDR4500, assessment of T3, T4, TSH with chemiluminescent immunoassays (Immulite 1000/2000, Siemens, USA). Osteoporosis was defined as total T-score for lumbar spine/hip or femoral neck T-score < -2.5. Normal BMD was defined as value >-1.0. Mann-Whitney and chi-square test were used in statistical analysis.

Results: The prevalence of hypothyroidism in postmenopausal women suspected on osteoporosis was 0,6%, SH 14,1%, hyperthyroidism 0,6% and subclinical hyperthyroidism 4,1%. Median TSH in postmenopausal women in SH was significantly higher in comparison with median TSH in euthyroid postmenopausal women (7,75 mU/L vs. 1,80 mU/L, p=0,000), while median T4 and T3 were lower. Euthyroid postmenopausal women had lower median total T-score for lumbar spine (-2,60) and left hip (-1,35) in comparison with postmenopausal women in SH (lumbar spine -2,45, left hip -1,1). However, the difference was not statistically significant. Osteoporosis was detected in 56 (67%) euthyroid postmenopausal women and 8 (50%) postmenopausal women in SH (p=0,181).

Conclusions: Thyroid dysfunction was detected in 19,4% of postmenopausal women referred to BMD measurement. SH was the most prevalent dysfunction, as expected in this group of patients. Euthyroid postmenopausal women had lower BMD in lumbar spine and left hip region and higher prevalence of osteoporosis in comparison to postmenopausal women in SH.

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COULD TSH RECEPTOR ANTIBODIES BE PROTECTIVE FOR THE BONE IN PRE- AND POSTMENOPAUSAL WOMEN WITH GRAVES' DISEASE AND GRAVES' ORBITOPATHY?

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Objectives: Thyrotoxicosis is established risk factor for osteoporosis due to increased bone turnover. Glucocorticoids often administered for Graves' orbitopathy (GO) have additional negative effect on bone mineral density (BMD) by diminishing bone formation. The aim of this study was to examine the influence of thyroid hormones, thyroid antibodies and glucocorticoid treatment on bone in women with Graves' thyrotoxicosis alone or with Graves' orbitopathy (GO).

Methods: 42 females with active Graves' disease, mean age 55.8±12.8 (23 women with thyrotoxicosis and 19 thyrotoxic with concomitant GO and glucocorticoid therapy) were enrolled in the study. 40 healthy women, mean age 53.2±7.1 surved as age-matched controls. We analyzed the clinical features, duration of thyrotoxicosis, cumulative dose and duration glucocotricoid therapy, TSH, FT4, FT3, TSH receptor antibodies (TRAb), TPO antibodies. BMD of femoral neck and lumbar spine were measured by DEXA and the 10 years fracture risk was calculated with FRAX tool.

Results: The study showed significantly lower spine and femoral BMD (g/cm^2) in both subgroups of patients with and without GO compared to controls (p=0.0002; p< 0.0001), as well as significantly higher fracture risk (p< 0.0001; p< 0.0001). Comparison between patients only with thyrotoxicosis and those with additional glucocorticoids because of orbitopathy found out significantly lower spine BMD in the first group (p=0.0049). In patients' group as a whole we observed negative correlation between FT3 and BMD (p=0.038), as well as between FT4 and BMD (p=0.005) and positive association between TRAb and BMD (p=0.039). There was a negative significant correlation between TRAb and fracture risk for hip fractures (p=0.045). We found negative association of BMD to duration of thyrotoxicosis (p=0.048).

Conclusions: Our results confirm the negative effect of hyperthyroid status on BMD. TRAb, often in high titres in patients with GO, may have protective role for the bone, but further research is needed.

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BONE METABOLISM IN FEMALE PATIENTS WITH WELL-DIFFERENTIATED THYROID CARCINOMA AFTER CHERNOBYL

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Research objective of our work was the studying of the calcium-phosphorus metabolism on the basis of blood serum biochemical parameters and bone mineral density (BMD) measurement with DEXA in female patients treated for thyroid carcinoma, in dependence of the duration of L-T4 suppressive therapy and presence of hypoparathyroidism.

Methods: We have examined 120 female following complex treatment for thyroid cancer (mean age 24.3 [19.4 - 30.0] years old). After the operation, the patients constantly received suppressive therapy with levothyroxin in the dose 2.81 [1.54- 4.81] µg/kg of body weight. Age at surgery was 14.0 [3.8-34.1] yrs. Biochemical examination of the blood serum was performed using the automatic biochemical analyzer "ARCHITECT C8000", Abbott, USA. Hormone levels and bone metabolism markers were examined in blood serum with the EIA-assays of DRG (USA) and DIALAB (Austria) manufacturers. Dual X-ray absorption densitometry was done on LUNAR (GE Medical System). BMD of lumbar spine (L_1-L_4) and proximal femur (femoral neck, upper-neck, trochanter) were estimated by Z-score.

Results: In patients with hypoparathyroidism, in spite of calcium and vitamin D_3 supplementation, average serum ionized Ca level was lower (p< 0.0001) than in those without hypoparathyroidism (1.07 a 1.20 mmol/l, respectively). BMD (Z-score below - 1) was decreased in 5.0% of patients. In patients with hypoparathyroidism, BMD (L_1-L_4) was higher (p< 0.0001) as compared with those without hypoparathyroidism (1.34 g/cm^2, Z-Score=1.32 and 1.20 g/cm^2, Z-Score=0.23, respectively). Similar data were obtained for proximal femur BMD (p< 0.0001): in hypoparathyroid patients BMD=1.17 g/cm^2, Z-Score=1.42, in patients without hypoparathyroidism, BMD= 1.03, Z-Score=0.38.

Conclusions: In the group of thyroid carcinoma patients with hypoparathyroidism, BMD was significantly higher in subjects with constant calcium and vitamin D_3 intake as compared with those who did not take any additional calcium supplements and had normal levels of parathyroid hormone.

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THE BONE PARAMETERS ANALYZE IN PATIENTS WITH LONG TERM LEVOTHYROXINE THERAPY

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Objectives: The therapy with levothyroxine (LT) might represent a risk for bone loss.

Our purpose was to analyze the postmenopausal women with LT therapy who were not under anti-osteoporotic drugs, regarding serum bone markers, dual X-ray absorbtiometry (DXA), and quantitative ultrasound (QUS). The indications of LT therapy varied from autoimmune hypothyroidism to thyroidectomy. The TSH levels were within the normal limits.

S**ubjects and Methods:** 200 women in spontaneous or surgical menopause were studied. LT was from one year up to 26 yrs. The informed consent of each patient was obtained.

The body mass index (BMI), fat mass analyze, and the serum bone markers were obtained. The DXA (GE Lunar) and QUS (Achilles and SonostChrono) were performed. The student t test was used (statistically significant - SS $p< 0.5$).

Results: The patients were divided into two groups: group 1 with 79 patients with LT therapy and group 2, control group with 121 patients without LT therapy.

The analyzed parameters- age, yrs since menopause, SI (QUS), BMD (DXA), serum turn over markers as alkaline phosphatase, osteocalcin, BetaCrossLaps, 25(OH), iPTH, fat percent(body mass analyzer).

Te BMI and the postmenopausal years were not different between the two groups. The fat percent was SS lower in LT free women. The stiffness index as shown only by one of the devices (SonostChrono, not by Achilles) is lower in LT group. The bone turnover markers, as well as the serum vitamin D and iPTH were SS different. The BMD was lower in LT group.

Conclusion: It is still a matter of debate if the LT therapy increases the risk of bone loss. A multi-factorial analyze might be more relevant.

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BONE MINERAL DENSITY (BMD) IN ELDERLY EUTHYROID

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Our aim is to determine the bone mineral density in elderly euthyroid patients suffering from thyroid diseases with or without thyroxine therapy.

Materials and Methods: We have examined 170 females, 81 of them, who suffered from different thyroid diseases and did not receive any therapy, and 89 patients on thyroid hormone suppressive or substitute therapy. The control group consisted of 20 persons not suffering from thyroid diseases. All groups of patients were of similar age (73.5, 71.5 and 72.1 respectively). All patients underwent general clinical, laboratory and instrumental examinations for the determination of the thyroid status, phosphorus-calcium metabolism, bone turnover markers, as well as thyroid ultrasonography and dual X-ray absorptiometry (DPX, Lunar of the Progidy series, General Electric, USA).

Results: Euthyroidism, endogenous or medicamental, has been found in patients of all groups, none of them having any fractures before our examination. The applied average dosage of thyroxine was within 25-150 mcg (average 57.5±12.5), with average duration of treatment being 12.5±0.5 years. The levels of TSH, FT4 and the parameters of phosphorus-calcium metabolism were normal and no statistically significant difference was found between patients with or without thyroxine therapy, as well as the persons of the control group. The parameter changes in BMD have been found in 80% of patients without thyroxine (osteopenia in 58% and osteoporosis in 22%), in 76% of patients in case of thyroxine therapy (osteopenia in 50% and osteoporosis in 26%), and in 75% of persons of the control group (osteopenia in 54% and osteoporosis in 21%). The frequency of changes of BMD did not depend on the treatment duration and thyroid dosage applied.

Conclusions: According to the data received thyroid hormones used as suppressive or substitute therapy in case of supported euthyroidism do not affect negatively BMD in elderly patients.

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ADVANCED PRIMARY BONE HYPERPARATHYROIDISM AS A RESULTS OF DIAGNOSTIC MISTAKES

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Introduction: Screening of serum calcium level in Russia Population don't realize till now. That is why more then 90% of patients present for surgery with advanced primary hyperparathyroidism (PHPT).

Material and Methods: During our practice 6 patients were presented in the Center with complicated advanced bone PHPT, caused by parathyroid adenomas up to 8 cm in size. For the first time clinico-radiologic signs of PHPT have appeared 8 and 15 years before. But PHPT cysts of skeleton (mandible, metacarpal bone, hips) considered by traumatologists, maxillofacial surgeons, pediatrists as osteoblastoclastomas, metastases, osteoporosis, rachitis. Patients were initially operated in others different hospitals. Two of them have undergone resections of mandible; one - third metacarpal bone and others - osteosynthesis for femur fractures and later - femur amputation because osteoblastoclastoma were suspected after trepanobiopsy; long-time skeletal traction and unsuccessful osteosynthesis by hardware. PHPT was found by morphologically or accidentally. Further biochemical (Ca, Ph), radioimmunoassay (PTH), radioisotope-velocity (Tc99m) and ultrasonography an examination in the Center allows to specify adenomas location. Parathyroid adenomas were removed successfully in all cases. Normalization of calcium, phosphor serum levels and positive dynamic of osteal disorders, bone consolidation were noted during different time after operations (up to 8 monthes).

Conclusion: Screening of population for blood serum calcium level and regular information of different medical specialties about PHPT clinical manifestations could improve early diagnostic, surgical treatment results and prevents of patients invalidism; later revealing of PHPT could lead by incapacitating consequences.

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SERUM OSTEOPROTEGERIN LEVELS IN HYPERTHYROIDISM

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Background: An increase in bone remodeling has been reported in hyperthyroidism, characterized by an imbalance between bone resorption and formation. Osteoprotegerin (OPG) is an inhibitor of bone resorption acting through binding and neutralization of the receptor activator of nuclear factor-kB ligand.

Aim: To investigate the alteration in plasma OPG concentrations with treatment of thyrotoxicosis, and influence of OPG on calcium-phosphorus metabolism.

Subjects-Methods: Fasting serum OPG, calcium, albumin, creatinine levels were analysed during thyrotoxicosis in 40 hyperthyroid patients (50.5±15.2 years old, 22 females, 31 with Graves disease=GD, 9 with toxic nodular goiter=TNG). The same measurements were repeated an average 3 months later, when all patients achieved euthyroidism.

Results: Serum corrected calcium [9.3 (8.9-9.5) mg/dL vs 9.0 (8.7-9.3), $p=0.152$)], phosphorus [3.6 (3.3-3.9) mg/dL vs 3.5 (3.1-3.9), $p=0.232$], and calcium-phosphorus product (CaxP) were comparable [34.4 (30.3-36.8) vs 30.2 (26.1-35.0), $p=0.331$)] during thyrotoxicosis and euthyroid phases. However, serum OPG levels were significantly lower during hyperthyroidism [142 (126-159) pg/mL vs 210 (179-264), $p< 0.001$)]. The changes in serum OPG levels were irrespective of the cause of hyperthyroidism [from 142 (123-159) to 207 (180-254) pg/ml, $p< 0.001$ in GD; from 140 (124-167) to 359 (184-434) pg/ml, $p=0.042$) in TNG]. Univariate analysis demonstrated a significant correlation between serum OPG levels and freeT4 ($r=-0.356$, $p=0.002$), freeT3 ($r=-0.337$, $p=0.004$); and between CaxP and freeT3 ($r=0.376$, $p=0.010$). A regression analysis was performed including only hyperthyroidism phase (CaxP as the dependent variable; serum freeT4, freeT3, age, OPG, creatinine, ALT levels as independent variables) demonstrated an independent association between CaXP product and freeT4, freeT3 levels, but not with OPG levels ($R^2= 0.536$, $F=5.3$, $p=0.001$).

Conclusion: Although serum OPG levels are decreased during hyperthyroidism, they do not correlate with serum calcium-phosphorus product. It is probable that elevated serum thyroid hormone levels also activate pathways acting through another mechanism(s) responsible for bone resorption.

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SERUM FREE THYROXINE TO FREE TRIIODOTHYRONINE RATIO AS A USEFUL TOOL IN THE DIAGNOSTICS OF THYROID DYSFUNCTION

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Objectives: Only a few reports have demonstrated the importance of either total or free triiodothyronine to thyroxine ratio in the diagnostics of different thyroid disorders. Our aim was to evaluate the role of the serum free thyroxine to free triiodothyronine ratio (fT_4/fT_3) in the diagnostics of thyroid dysfunction.

Methods: We included 878 consecutive subjects, examined under the suspicion of thyroid dysfunction, 723 females and 155 males aged 49.6±18.6 years, 52 with Graves´ disease (GD), 33 with toxic adenomas (TA), 12 with disseminated autonomy (DA), 7 with iodine-induced hyperthyroidism (IIH), 11 with subacute thyroiditis (ST), 323 with euthyroid Hashimoto´s thyroiditis (EuHT), 250 with hypothyroid Hashimoto´s thyroiditis (HypoHT), 45 with hyperthyroid Hashimoto´s thyroiditis (HyperHT) and 145 healthy subjects (HS). Thyrotropin (TSH), free thyroxine (fT_4), free triiodothyronine (fT_3), thyroid autoantibodes and in hyperthyroid patients also TSH receptor antibodies were measured. We also calculated the fT_4/fT_3 ratio.

Results: FT_4 levels were higher in HS than in EuHT ($P< 0.001$) and the highest in GD when compared with TA, DA, ST and HyperHT ($P< 0.001$, $P=0.003$, $P=0.012$, $P< 0.001$, respectively). Similarly, levels of fT_3 were higher in HS than in EuHT ($P< 0.001$) and the highest in GD when compared with TA, ST and HyperHT ($P< 0.001$, $P=0.003$, $P< 0.001$, respectively). FT_4/fT_3 ratio did not differ between HS and EuH (2.9±0.5 and 2.8±0.5, respectively, $P=0.578$). FT_4/fT_3 ratio was lower in HypoHT (2.5±0.7) than in EH ($P< 0.001$). Even more, patients with TSH above 20 mU/L had a lower fT_4/fT_3 ratio than patients with TSH below 20 mU/L (2.1±1 and 2.6±0.5, respectively, $P< 0.001$). In hyperthyroidism, fT_4/fT_3 ratio was significantly lower in GD (2.6±0.5) than in TA, DA, IIH, ST and HyperHT ($P=0.046$, $P=0.012$, $P=0.028$, $P=0.009$, $P< 0.001$, respectively).

Conclusions: Our results confirm the useful role of fT_4/fT_3 ratio in the diagnostics of thyroid dysfunction.

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NEPHROTIC SYNDROME ASSOCIATED WITH HASHIMOTO'S THYROIDITIS

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Objective: A case with newly diagnosed overt hypothyroidism due to Hashimoto's thyroiditis associated with nephrotic syndrome has been presented.

Case report: A 21 year old female patient was referred to nephrology outpatient clinic with generalized edema and dyspnea. On chest x-ray bilateral pleural effusion was noted. Basic laboratory investigations were as follows; serum creatinine 0.8 (0.4-1) mg/dl, albumin 1.7 (3.5-5.5) g/dl, total protein 3.5 (6.4-8.3) g/dl, total cholesterol 376 (130-200) mg/dl and LDL cholesterol 252 (< 130) mg/dl. Her complete blood count, serum electrolytes and liver function tests were within the normal range. In the 24-hour urine analysis total protein excretion was 5320 mg/day and creatinine clearance was 75 (80-125) ml/min. Based on these laboratory values a diagnosis of nephrotic syndrome was made. In search of the etiology of nephrotic syndrome, viral hepatitis serology and anti-HIV, anti-ribosomal protein, anti-Sm/RNP, anti-SSA, anti-SM, anti-SSB, antihistone, anti-Scl 70, anti-JO-1 antibodies were analysed and all were found to be negative. Analyses of the thyroid hormones were compatible with overt hypothyroidism [free T3: 1.6 (2.5-3.9) pg/ml, free T4: 0.54 (0.61-1.12) ng/dl, TSH: >100 (0.34-5.6) μIU/ml]. Positive thyroid autoantibodies [anti-TPO: 100.8 (0-9) IU/ml, anti-Tg: 15.6 (0-4) IU/ml] and the heterogenous echo pattern of the gland parenchyma on thyroid ultrasonography led to the diagnosis of Hashimoto's thyroiditis. On pathological examination of the renal biopsy specimen by light microscopy nothing except minimal tubular and interstitial injury were noted. On immunohistochemical analysis, amyloidosis and immunoglobulin deposition were found negative. L-thyroxine and methylprednisone treatment were given. One month after discharge, her thyroid hormones and 24-hour urine protein analysis were within the normal range.

Conclusion: Autoimmune thyroid diseases, albeit rarely, have previously been reported to occur concurrently with nephrotic syndrome. In this respect, this case may also represent an immune-complex mediated nephrotic syndrome associated with Hashimoto's thyroiditis.

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DECREASED HUMAN ERYTHROCYTE DIPHOSPHOGLYCERATE MUTASE (DPGM) CONCENTRATIONS IN HYPOTHYROIDISM

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Decreased erythrocyte 2, 3 diphosphoglycerate (DPG) levels and oxyhemoglobin dissociation have been observed in patients with hypothyroidism. Quantification of DPGM, the enzyme which catalyzes the conversion of 1, 3 DPG to 2, 3 DPG, by enzymatic assays in samples from hypothyroid subjects has been reported, but results are conflicting. To study the mechanism of altered oxygen affinity in hypothyroidism, erythrocyte DPGM concentrations were measured in euthyroid and hypothyroid subjects by an immunodiffusion method using a specific chicken anti-human DPGM antibody. Normal adult values are 0.98 ± 0.014 (mean ± SE). We studied eight patients, ages 22-64, with primary hypothyroidism who had been clinically hypothyroid for more than 3 months. Erythrocyte DPGM levels were 0.82 ± 0.057 ($p< 0.01$). In two patients who were studied during T4 replacement therapy DPGM levels returned to normal. Erythrocytes from these two patients were separated by the centrifugation method of Murphy (J. Lab. Clin. Med, 82:334, 1973), into light (young) and dense (old) fractions. After one months of T4 therapy, DPGM levels were normal in young cells but were unchanged in old cells. This study demonstrates decreased DPGM levels in erythrocytes of hypothyroid patients which are normalized by T4 therapy. T4 does not alter DPGM levels in mature red cells. These findings suggest that thyroid hormone is an important regulator of erythrocyte DPGM synthesis in man. This may be the mechanism of altered 2, 3 DPG levels and changes in oxygen affinity observed in patients with thyroid dysfunction.

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RISK FACTORS AND CLINICAL FEATURES OF FAMILIAL AUTOIMMUNE THYROID DISEASE

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Objectives: The purpose of this study was to investigate environmental and behavioral factors, theirs links with clinical features of autoimmune thyroid diseases (AITD) (Graves` disease, Hashimoto` disease) for patients who had at least one AITD` patient within proband`s first-degree relative.

Methods: We examined 14 families (28 Caucasian patients). The estimate number of patients with familial Graves` disease (GD) and Hashimoto` disease (HD) was 7,1% (1 family) and 64,2% (9 families), respectively. 4 families (28,6%) had both disease of the proband`s first-degree relatives. Proband was defined as a patient of younger generation. Mean age of probands and their first-degree relatives was 32,2±6,8 and 55,5±8,7 years, respectively.

The diagnosis of GD was determined on the basis of clinical and biochemical evidence of past or present hyperthyroidism and one of the following: positive TSH receptor antibodies, exophthalmos, and diffuse thyroid scan. HT was diagnosed similarly by the past or present of hypothyroidism, characteristic ultrasound picture and positive thyroid peroxidase antibodies.

Results: The female/male ratio was 26:2. 4 patients (14,2%) were smokers. Other autoimmune diseases (psoriasis, vitiligo) were seen in 2 patients

(7,1%). Patients of not manual labor were the most abundant, comprising 92,9% of the total. Occupational hazard was denied by all of them. Age of diseases` onset for probands and their first-degree relatives was 25,6±6,1 and 46,8±9,7 years, respectively. Duration of thyrotoxicosis for probands and their first-degree relatives was 3,3±4,5 and 6,0±4,2 years, duration of hupothyroidism was 7,9±6,1 and 10,1±8,1, respectively. Mean volume of thyroid gland for probands and their first-degree relatives with GD was 21,1±6,1 and 33,5±9,2 cm^3, with HD was 15,0±6,7 and 17,2±8,1 cm^3, respectively.

Conclusions: Decrease of disease`s onset occurs within two generations in familial AITD, and does not link with examined factors.

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BILATERAL SPONTANEOUS ANTEROLATERAL COMPARTMENT SYNDROME IN A NEWLY DIAGNOSED HYPOTHYROID PATIENT

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Acute compartment syndrome(ACS) is a surgical emergency that occurs in any condition that results in an increase in intra-compartment pressures of typically greater than 30mmHg. Though most commonly occurring after trauma, burns and prolonged limb compression, cases of spontaneous compartment syndrome associated with severe hypothyroidism have been reported. We report a case of bilateral antero-lateral compartment syndrome in a 39 years old Chinese lady who presented with lethargy and ankle pain and was newly diagnosed with hypothyroidism. She developed bilateral compartment syndrome and subsequent rhabdomyolysis. She required extensive muscle debridement and to date has residual bilateral foot drop. To our knowledge, this is the only locally reported case thus far and the fourth internationally reported case of spontaneous compartment syndrome in a patient with hypothyroidism.

This case illustrates that compartment syndrome may present as a non-emergent, atypical fashion to the physicians.The first patient, being reported in 1993. It is possible that hypothyroidism specifically or the autoimmune syndrome in general may be an under-recognized or emerging risk factor for the development of spontaneous compartment syndrome. Our study highlights the importance of constant vigilance on the part of physicians in considering ACS as a cause for lower limb pain in a hypothyroid patient as delay in diagnosis has been shown to be the most important determinant of a poor outcome.

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QUALITY OF LIFE OF PATIENTS WITH POSTRADIATION HYPOTHYROIDISM

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Materials and Methods: 33 patients (27 females, 3 males) aged from 30 to 80 years were included to the study. They have received radioiodine treatment for GD with the period of follow- up after treatment from 2 to 10 years. The patients were divided into 2 groups depending on the initial level of TSH. The first group was consist of 14 persons with low-normal level of TSH (0,4-2,0 mU/ml), the second group (19 persons) with upper-normal level of TSH 2,1-4,0 mU/ml. Quality of life (Q&L) was assessed by SF-36 questionnaire.

Results: In the first group the median age of patients was 53 years (min 50; max 69 years), median follow- up 7 years (min 7; max 10), the median activity 9,7 mKu (min 4.0; max 18,6) the median of TSH 1,07 mU/ml, a median dose of L-T4 75 mcg (min 50; max 100), the median point of Q&L on 8 scales questionnaire ranged from 62 (vitality) up to 94 (physical functioning).

In the second group, the median age of patients was 59 year (min 52; max 64), the median follow- up of 8 years (min 7; max 10), the median activity 6,0 mKu (min 1,1; max 18,9), median TSH level 2,89 mU/ml, a median dose of L-T4 75 mcg (min50; max100), the median point of Q&L ranged from 51 points (mental health) to 85 (physical functioning).

Statistically significant differences were observed only in the two indicators: physical functioning and general health were higher in group 1 (accordingly p =0.01 and p=0.05).

Conclusions: Quality of life of patients of both groups were more than 50%, however, the patients with upper-normal TSH had statistically lower levels of physical functioning and general state of health.

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A CASE OF CONGENITAL HYPOTHYROIDISM WITH HIRSCHSPRUNG´S DISEASE: AN UNUSUAL ASSOCIATION

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Introduction: Hirschsprung's disease (HD) as well as congenital hypothyroidism can present with functional intestinal obstruction and abdominal distension in neonate. Both the diseases are considered as differential diagnosis, rather than as coexistence. We report one such interesting case with unusual coexistence between these 2 conditions.

Objectives & Hypothesis: Thyroid hormone is necessary for neuronal migration and lamination during brain development. Although hypothyroidism impairscolonic motility resulting in pseudo-obstruction the effects of hypothyroidism on neuronal migration through bowel have not been adequately studied.

Methods: A 21 days baby girl, product of consanguineous marriage presented with vomiting and abdominal distension. Weight was 2.5 kg and length 48 cm. On examination, there was facial puffiness, open posterior fontanelles, dry skin, cold peripheries and prominent abdominal veins with visible peristalsis. There was no maternal history of hypothyroidism.Patient was subjected to various investigations.

Results: Routine hemogram, liver & kidney function tests were within normal limits. Plain abdominal radiographs revealedgas filled bowel loops with barium enema showing dilated proximal colon, empty rectum, delayed emptying time with funnel like transition zone between proximal dilated& distal constricted bowel. TSH was > 150 micro IU/ml. Thyroid scintigraphy revealed athyreosis, confirming congenital hypothyroidism due to athyreosis. Biopsyfollowing colostomy revealed aganglionic segment, confirming the diagnosis of Hirschsprung´s disease. The patient's genetic analysis revealed 46XX karyotype without any chromosomal abnormality or any mutations. Baby was discharged with oral levothyroxine treatment. Five months later, the infant weighed 6.3 kg and her length was 108 cm, and underwent a transanal endorectal pull through operation followed by colostomy closure.

Conclusion: With the present case, we propose that thyroid hormones may have a role in the development of HD. Further studies are needed to establish this.

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STUDIES ON THE EFFECT OF ALPHA – LIPOIC ACID IN THE TREATMENT OF HYPOTHYROIDISM

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Objectives: To evaluate the effect of alpha-lipoic acid on parameters of the autonomic nervous system and hormonal status in treatment of hypothyroidism.

Methods: 45 patients, 25 to 63 years with hypothyroidism of different genesis. 42 women and 3 men. (men was 45.0±7.1 years, women –45.9±1.5 years.)

Laboratory methods, heart rate variability was investigated by Omega-M ".22 patients (Group 1) received the drug alpha-lipoic acid (Tiogamma production Vervag-Pharma) at a dose of 600 mcg for 10 days as in drip injections following a 3 months oral administration, in addition to standard therapy, 23 patients (Group 2) received standard therapy without alpha-lipoic acid (hormone and symptomatic).

Results: Group 1: TSH level before treatment was 25.2±9.5mIU /ml, level of free T4-7.9±1.2pg/ml. Group 2: TSH before treatment was 24.5±5.1mIU/ml and T4 free - 8.6±2.4pg/ml. After treatment, TSH levels decreased in group 1 to 3.5±1.1pg/ml (86%), in control - up to 8.2±3.2pg/ml (66%). The level of free T4 in the intervention group increased to 19.3±2.2 mIU/ml (at 56.8%), control –14.2±3.2 mIU/ml (39%).

Cardiointervalography results in 58% of patients with hypothyroidism had declined waves of high frequency HF - which shows predominant sympathetic autonomic regulation. In 94% patients with very low frequency waves, indicate changes in neuro-humoral and metabolic regulation levels. Value

power LF/HF increased to 3.0±1.3 shows increased sympathetic tone. Marked decrease in SDNN, characterizing heart rate variability in 92.8% of patients to 21.8±1.2 ms, indicating sympathetic predominance of VNS. In patients with HT decreased RMSSD - differences of successive NN intervals from 82.9% to 18.1±1.9 ms, which shows the weakening of parasympathetic activity.

Conclusion: After treatment with combination therapy improvement in balance of autonomic regulation. Thus, the inclusion of drug alpha-lipoic acid in the treatment of hypothyroidism leads to improvement of hormone dynamics and autonomic balance.

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THE TSH – THYROID ANTIBODIES ANALYSE IN 1000 PATIENTS WITH CHRONIC THYROIDITIS: A RETROSPECTIVE STUDY

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Objectives: The wide use of the ATPO (antithyroperoxydase antibodies) and ATG (antithyroglobuline antibodies) assay allows a facile diagnosis of Hashimoto thyroiditis (HT). Most of the studies reveal the fact there is no association between ATPO and TSH.

Our purpose was to analyze the TSH and serum antibodies in patients with HT.

Method: We study 1000 patients (women:men ratio of 950:50) diagnosed with HT.

This is a retrospective study. The HT was diagnosed based on either high ATPO (> 34 UI/mL) or ATG (> 50 UI/mL) or both of them. The cervical ultrasound was performed.

Results: 460 patients (46%) associated euthyroid function. 397 (39.7%) had hypothyroidism and 143 patients (14.3%) had hyperthyroidism. From these 66% (95 patients) were TRAB positive, so the diagnosis of the Basedow Graves disease was also established. From these TRAB positive patients 26 (33%) were with euthyroidism or hypothyroidism. The ATPO levels were 620±1,060UI/mL (range from 1 to 13,000UI/mL). In 7 patients (0.7%) the ATPO was increased even they suffered a thyroidectomy. 14 patients (1.4%) use amiodarone: 6 of them were euthyroid, 4 with hypothyroidism and 2 had hyperthyroidism. 15 patients (3.25%) with euthyroidism developed hypothyroidism in 2.16±1.72 yrs. All the patients with hypothyrodism remained with this status. 3 patients with hyperthyroidism become euthyroid in 3 years with no therapy and one patient developed hypothyroidism. The evolutive type of the ATPO levels was ondulatory in 118 patients (45%), decreasing in 34 patients (34%), and increasing in 23 patients (56%). There was no linear correlation between ATPO and TSH (r = 0.17, p= 0.9).

Conclusions: The HT presents euthyroidism more than hypothyroidism. 2.5 % of the patients with euthyrodism developed hypothyroidism in 5 years. We did not found any ATPO-TSH correlation in HT.

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SUNITINIB-INDUCED HYPOTHYROIDISM

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Sunitinib is an oral multi-target tyrosine-kinase inhibitor that possesses antitumor activity by blocking the kinase domain of different receptors: VEGFR, PDGFR, KIT, FLT 3, CSF-1 etc. Its targeted binding in these signal pathways leads to the inclusion of Sunitinib in the process of treatment of tumors such as renal cell carcinoma, gastrointestinal stromal tumors (GIST) and other neuroendocrine tumors, medullar carcinoma of the thyroid gland, some lymphomas and leukemias.

The principle side effects grade 3-4 of the Sunitinib treatment are fatigue, neutropenia, thrombocytopenia, head-foot syndrome and diarrhea. The hypothyroidism is also a factor, aggravating the fatigue; it appears with different frequency in the third/fourth week after the introduction of the treatment. There is a hypothesis, suggesting that the hypothyroidism is a prognostic factor for a better therapeutic response during treatment of renal cell carcinoma.

We introduce a case report of a 62-year-old female patient, diagnosed with metastatic bright-cell renal cell carcinoma and Sunitinib-induced hypothyroidism. 4 months after beginnig of threament with sunitinib TSH - 7.17 IU/l, normal range /0.55-4.78/, FT3 - 2.14 pmol/l, normal range /2.55 - 5.38/, 3 months after withdrawl of Sunitinib TSH-5.704 FT3 - 3.14. TPO-Abs and Tg-Abs negative. US of thyroid gland shows diffuse hypoechogenity. This is first case of thyroid dysfunction after sunitinib in Bulgarian oncology practice.

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EVALUATION OF THE PSYCHOEMOTIONAL STATUS OF PATIENTS AFTER RADIOIODINETHERAPY FOR GD BY CATAMNESIS DATA

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Materials and Methods: 33 patients (27 females, 3 males) aged from 30 to 80 years with the period of follow- up after treatment from 2 to 10 years were included tj the study. Hypothyroidism was confirmed in all patients as the outcome of radiotherapy. The patients were divided into 2 groups depending on the initial level of TSH. The first group was consist of 14 persons with low-normal level of TSH (0,4-2,0 mU/ml), the second group (19 persons) with upper-normal level of TSH 2,1-4,0 mU/ml. An estimation of the psychoemotional status was conducted by means of a scale of depression of Beck and Spielberg-Khanins test.

Results: The median age of patients was 53 and 59 years accordingly, the median of follow- up were 7 and 8 years, the median activity 9,7 mKu (min 4,0; max 18,6) and 6,0 mKu (min 1,1; max 18,9), the median of TSH 1,07 mU/ml and 2,89 mU/ml, a median dose of L-T4 75 mcg (min 50; max 100) in both groups, the amount of points of depression was 12 (from 10 to 19) in both groups, which corresponds to mild depression. The median amount of points of situational anxiety 33,5 in 1-st and 42 in 2-nd groups, personal alarm 37,5 and 45 accordingly, which corresponds to a moderate level of anxiety in both groups.

Statistical analysis showed no significant differences levels of anxiety and depression in both groups (p= 0,07 and p=0,06). However, patients in the older age group was statistically significant difference between the age and the level of personal anxiety (p=0,1).

Conclusions: Psycho- emotional status (presence of anxiety and depression) does not depend on whether the patient hypothyroidism, but most likely due to age.

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ELEVATED TSH IN A NEONATE; DRUG INDUCED OR DISEASE MEDIATED?

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Introduction: Dyshormonogenesis is an uncommon cause of congenital hypothyroidism. The most common abnormality is absent or insufficient thyroid peroxidase enzyme. Maternal intake of antithyroid drug can also lead to elevated TSH in a neonate, albeit the scenario is temporary. We report one such interesting case of a neonate presenting with markedly elevated TSH, causing initial confusion regarding the etiology.

Case Report: A newborn child, product of a consanguineous marriage, borne to hyperthyroid mother on propylthiouracil 50 mg BD presented on 12th day for evaluation. Baby had weight of 2.7 kg and length 50cm. Clinically baby was euthyroid without any goiter or stigma of CH. Thyroid profile revealed T_3-163.3 ng/dl, T_4- 10.1 µg/dl and TSH- 78.4 µIU/ml. Thyroid scintigraohy revealed enlarged thyroid gland in normal pretracheal location and increase tracer uptake. Further propylthiuracil intake was stopped for 4 days. After that baby’s repeat thyroid profile revealed T_3-167.15 ng/dl, T_4- 6.6 µg/dl and TSH- 131.56 µIU/ml. For elevated TSH with increased tracer uptake on thyroid scan, probability of maternal drug induced hypothyroidism or dyshormonogenesis were considered. Disproportionately high levels of baby’s TSH in comparison to small dosage of maternal antithyroid drugs and further elevation of TSH in spite of stopping mother’s antithyroid drugs made the possibility of antithyroid drug induced congenital hypothyroidism less likely. In cases

of dyshormonogenesis, Radioiodine uptake is high owing to intact sodium iodide symporter stimulated by high TSH, and the block in iodide oxidation and organification results in an increase in intracellular iodide concentration. Upon thyroid I^{131} scan, initial uptake will be normal, owing to normal iodine uptake. But the delayed uptake would be abnormal, owing to defective iodination/ organification. Considering dyshormonogenesis as the cause of baby's elevated TSH, 25 µg levothyroxine daily was prescribed.

Conclusion: Early institution of therapy can prevent mental retardation and other features of hypothyroidism.

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USE OF HPLC – MASS SPECTROMETRY FOR T4, T3 AND RT3 ANALYSIS AS COMPARED WITH IMMUNOASSAYS

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Objective: To evaluate the use of HPLC MS for measuring thyroid hormones.

Mass spectrometry is used in research and clinical practice as gold standard in endocrine clinical chemistry. However, routine thyroid chemistry does not involve rT3 measurements.

Methods: In our study we included 22 patients with thyroid disorders, in which we measured T3, T4, by both immunoassay and HPLC- tandem MS. In addition, TSH and fT4 were measured by immunoassay, for a precise functional thyroid status and rT3 by HPLC- tandem MS method. Two cases were hyperthyroid; all the others were euthyroid, either natural or as result of antithyroid drugs regimen for hyperthyroidism.

Results: Immunoassay proved to measure on average 17% more than HPLC-MS for T3 and T4 ($p< 0.05$); however, TSH and fT4 was measured only on immunoassay, while rT3 was available only on HPLC MS, which is a limitation of our study.

Conclusion: An analysis of thyroid status can be stated by combination of immunoassays, while HPLC-MS can provide data about thyroid hormones metabolism and is reserved mainly for research.

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THYROID DISORDERS IN ADULT POPULATION OF KRAKOW - THE PILOT STUDY

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Natural history of thyroid disorders has not been fully understood. In yeas 1998-1990 and 1998-1000 two large studies on thyroid diseases in adult Polish population were performed.

Aim of the study was to assess the frequency of thyroid dysfunction in previously healthy adult population of Krakow.

Material and Methods: Study included 95 subjects (56 females, 39 males) aged 60.4±15 years. None of them had the thyroid dysfunction recognized during previous exams in 1988-1990 and 1998. In each subject TSH, FT4 levels and anti-TPO titer were assessed and thyroid US was performed.

Results: Mean TSH level was 1.71 ± 0.95 mIU/l, mean FT4 level - 14.8 ± 2.7 pmol/l. During 12 years 12 (12.6%) persons developed hypothyroidism. Additional 5 subjects were diagnosed with hypothyroidism during the study. Increased anti-TPO titer was found in 15.6% of the study group. Mean thyroid volume in females was 10.4 ± 3.71 ml, and 16.39± 5 ml in males. Parenchymal goiter was noticed in 5.3% of the study group, and nodular goiter in 49.4 % of subjects: in 18.9% single nodule, in 20.5% multinodular goiter.

Conclusion: In ten years observation up to half of the adults may develop thyroid dysfunction.

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THYROID NODULES IN PATIENTS WITH MALIGNANCIES

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Objectives: To analyze thyroid function and pathology of thyroid nodules in patients with primary non thyroid malignancies referred from the oncology service.

Background: Synchronous or metachronous thyroid nodules and malignancies are not rare, especially in countries with previous iodine deficiency. Metastases in the thyroid gland were initially suspected, but various other etiologies could be encountered.

Methods: 9 patients (4M/5F), aged 60 ± 8 years, were diagnosed with thyroid nodules during follow-up for various malignancies. TSH, FT4 were measured by immunochemiluminescence, ATPO by microenzymatic immunoassay, calcitonin by chemiluminescence; thyroid ultrasonography, ^{131}I scintigraphy and fine needle aspiration (FNAB) with cytology exam were performed.

Results: Primary malignancies in our series were: invasive ductal mammary carcinoma (n=2), malignant melanoma (n=2), renal carcinoma (n=2), rectal carcinoma (n=1), pulmonary adenocarcinoma (n=1), laryngeal carcinoma (n=1). Only one patient (laryngeal carcinoma) underwent cervical irradiation. Thyroid nodules were either synchronous (n=5) or metachronous (n=4) with primary malignancy. Thyroid toxic adenomas were diagnosed in 3 patients; 2 patients showed subclinical and one overt hyperthyroidism; anti thyroid drug treatment followed by radioiodine therapy was prescribed. Follicular well-differentiated adenomas with euthyroidism were diagnosed by FNAB in 2 patients; active follow-up was indicated; Synchronous papillary thyroid carcinoma was diagnosed by FNAB in 2 patients, one with pulmonary and one with renal carcinoma. Total thyroidectomy, followed by radioiodine treatment was administered. Calcitonin was normal in all patients.

D**iscussion:** Previous iodine deficiency is related to thyroid nodule prevalence, especially in older people; repeated iodine overload via contrast agents used for imaging in patients with malignancies may be responsible or hyperthyroidism in these patients; however, coexisting thyroid carcinoma can be present in some patients, making FNAB mandatory.

Conclusion: In patients with non thyroid primary malignancies, thyroid nodules originating from follicular thyroid epithelium require specific endocrine therapy, apart from oncologic management.

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LATE FOLLOW UP RESULTS AFTER RADIOIODINE AND SURGERY TREATMENT OF TOXIC THYROID ADENOMA

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Purpose: The aim of the study was to evaluate late follow-up results in surgery and radioiodine treatment of toxic thyroid adenoma and compare incidence of hupothyroidism and recurrence hyperthyroidism in treated patients.

Material and Methods: We observed 93 treated patients(77 female,26 male,age range 18-76years) with adenoma toxicum. 29(32,2%)pts underwent surgery(adenectomia),while 64(67,8%)pts received 131-iodine therapy(555-1100 MBq). The long term results of the treatment were followed 1-15years after therapy(median 9,2years).

Results: Reccurent hyperthyroidism occurred in 4/29(13,8%) pts after surgery adenectomia in comparison to 5/64(7,8%) pts after radioiodine therapy. The patients after enucleation of autonomous nodule of the thyroid show increase incidence of late recurrent hyperthyroidism. These results are likely to be due to persistent functional autonomy in the parenchyma surrounding

the autonomous adenoma. Apparently this persistent autonomy could be seccesfully removed by radioiodine. Appear of hypothyroidism was observed in 6/64(9,3%) pts treated with J-131,while after surgery had in 3/29(10,3%) pts. Incidence of hypothyroidism between operated patients and radioiodine treated patients was approximately the same.

Conclusion: Radioiodine therapy is useful,economical and effective treatment of toxic thyroid adenoma that provides a safe protection in preventing late recurrent hyperthyroidism and is more successful therapy that surgery treatment.

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EVALUATION OF THYROID SURGERY: 10 YEARS OF EXPERIENCE IN A MILITARY HOSPITAL

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Introduction: Thyroid surgery is nowadays associated with low morbidity and extremely low mortality. A consistent association has been observed between high surgical volume and better outcomes. Patients who undergo surgery by a skilled surgeon have fewer complications. On the other hand, different surgical techniques have been associated with different outcomes. Since 1997, thyroid diseases are treated in our department by a multidisciplinary team.

Objective: To access the results of thyroid surgery in our hospital, over the last 10 years.

Methods: We studied retrospectively the patient's medical files that underwent thyroid surgery from 1999 to 2010.

Results: A total of 240 patients underwent thyroid surgery over the 10-year study period. The mean age of the patients was 54 years and 76% were females. Pre-operative diagnosis was thyroid nodular disease in 83,3% (13,9% toxic multinodular goiter and 12,5% substernal goiter), papillary carcinoma in 6,7% and follicular neoplasm in 5,8%. 4,2% of the patients had relapsed Graves Disease.

We performed lobectomy in 42,2% of cases and total thyroidectomy in 57,6%. 8% of patients had permanent complications (total thyroidectomy 6,4% and lobectomy 1,6%). Permanent laryngeal recurrent nerve lesions occurred in 3,4% of patients. Permanent hypoparathyroidism occurred in 4,2% of cases, always associated with total thyroidectomy.

Conclusions: Benign thyroid disease is the main surgical diagnostic indication in our hospital. Lobectomy is associated with better outcomes. Our complications rates are slightly higher than international reference centres.

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PRE SURGICAL THYROGLOBULIN DETERMINATION AS A MALIGNANT MARKER IN THYROID NODULES

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Thyroglobulin (Tg) is a 660 kD glycoprotein synthesized by the rugous endoplasmic reticulum The determination of serum thyroglobulin is commonly used for detecting the presence of residual thyroid tissue or cancer recurrence in patients treated for differentiated thyroid cancer (DTC).

Objective: Determine the high level of thyroglobulin as a malignant marker in thyroid nodules.

Material and Methods: These was a retrospective study.Serum thyroglobulin was assayed by an immunoradiometric method.

Results: There were included 70 patients, 62 females (88.5 %) and 8 males (11.4 %), with a mean age of 47 years,with high level of thyroglobuline which was measured in addition to the standard pre-operative tests (fine-needle aspiration biopsy, ultrasonography, 99mTc scanning and hormonal profile). 30 patients underwent surgery for total thyroidectomi The histopathological diagnostics reported were: benign thyroid nodule: 18 patients (60 %), from which 11(61.1%), presented euthyroid multinodular goitre 7 (38.9%) presented with cold nodule in pre-operative evaluation. Malignant thyroid nodule: 12 patients (40%) and all presented papillary thyroid cancer The thyroglobulin measurement reported: a mean of 479 ng/dL (± 508 ng/ dL). A minimum value of 200 ng/mL and a maximum value of 1168 ng/mL. The thyroglobulin values in patients with malignant report were: average 593.7 ng/mL (± 244 ng/dL) with range 245 - 1168.

Conclusions: These results indicate that 40 % of the patients with high level of thyroglobuline presented thyroid cancer. There is also an overlap of the values of the Tg between benign and malignant nodules, but measurements of serum Tg might be an important additional diagnostic tool in the pre-operative work-up of patients with thyroid nodules.

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RIEDEL´S THYROIDITIS – A CASE REPORT

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Riedel´s thyroiditis is very rare form of chronic thyreoiditis of unknown etiology characterized by fibrotic thyroid changes with involving of surrounding neck structures. Our intention was to report a case of 38-year old female patient with Riedel´s thyroiditis initialy presented with symptoms of subacute thyreoiditis (fever-38.5°C, elevated erythrocyte sedimentation rate (116 mm/hr), and enlarged, painfull thyroid). TSH was slightly elevated, thyroid antibodies were positive. Thyroid was almost not visible on Tc-99-m pertehnetate scan, and ultrasound revealed enlarged, hypoechogenic, inhomogeneous structure of thyroid, without nodes. Cytological finding confirmed a diagnosis of subacute thyreoiditis de Quervain. In spite of symptomatic therapy with analgetics, glucocorticoids and L-thyroxin because of hypothyreosis, the goiter rapidly increased causing dyspnea, dysphagia and weakness. Repeated fine-needle aspiration biopsy (FNAB) suggest chronic lymphocitic thyreoiditis. Because of compresive symptoms patient underwent surgery, but fibrotic changes with invading the adjacent structures permited only partial thyreoidectomy-isthmectomy with left partial lobectomy. Pathological findings confirmed fibrotic invasive thyreoiditis (Riedel). The disease progressed next few months, but after a while treatment brought a improvement of symptoms and favorable outcome. Only few cases of Riedel´s thyroiditis presented with symptoms of subacute thyreoiditis was reported in literature. The association with Hashimoto thyreoiditis was also described. Our patient introduced with symptoms of both disease, subacute thyreoiditis at the beginning, but prolongated clinical course suggest chronic thyreoiditis.

Table 1. Comparative results of surgical complications (for Abstract P278)

		Total thyroidectomy		Lobectomy	
	N	Permanent hypoparathyroidism	Permanent laryngeal recurrent nerve lesion	Permanent hypoparathyroidism	Permanent laryngeal recurrent nerve lesion
Military Hospital, 2010	240	5,1%	5,1%	0,0%	4,0%
Feldmann, 2008	231	4-8%	2,6%	1,8%	1,6%
Pieracci, 2008	372	4,1%	1,6%		
Connolly, 2010	216	2,6%	0,7%		
Sosa, 1998	846	0,4%	1,1%		0,4%

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A CASE OF THYROID LIPOMATOSIS

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Introduction: Uncommon conditions characterized by the presence of fat in the thyroid gland are thyrolipoma (adenolipoma), thyrolipomatosis (diffuse lipomatosis of the thyroid), and heterotopic nest of adipose tissue (1). Among these, thyroid lipomatosis is an extremely rare condition characterized by diffuse infiltration of an otherwise normal thyroid by mature adipose tissue and no evidence of encapsulation (1). We present here a male patient with chronic renal insufficiency and thyroid lipomatosis.

C**ase Report:** A 43 year old man presented with asymmetrical diffuse swelling on both sides of the neck over the past eight months. He had chronic renal failure due to amyloidosis and was under hemodialysis treatment. On physical examination, thyroid gland was moderately firm, grade II diffusely palpable with an asymmetrically larger right lobe. On laboratory examination, he was euthyroid [free T3: 2.66 (2.5-3.9) pg/ml, free T4: 0.96 (0.61-1.12) ng/dl, TSH: 0.52 (0.34-5.6) µIU/ml]. Thyroid autoantibodies (anti-Tg and anti-TPO) were negative. Thyroid ultrasonography revealed a heterogeneous gland parenchyma. Tc^{99m} thyroid scan showed irregular uptake and bilateral hyperplastic thyroid gland with partial suppresion. On fine needle aspiration biopsy of the thyroid normal follicular cells were detected. The patient underwent total thyroidectomy. Pathological examination of the surgical specimen was amyloid negative and compatible with thyroid lipomatosis.

Conclusion: Thyroid lipomatosis is an extremely rare condition of which the etiology and natural history are currently unknown. However, the association of thyroid lipomatosis with heterotopias of the thyroid and parathyroid glands in some previous reports suggests, the possibility of thyroid lipomatosis being a component of developmental abnormality during embryogenesis of the cervical organs (1).

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TEENAGE GIRLS ENDEMIC GOITER AND FUNCTION OF THE THYROID GLAND AGAINST THE LATENT IRON DEFICIENCY

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Research Objective: Estimation of the intensity of the endemic goiter in a group of teenage girls; analysis of the influence on the given indicators.

Methods: The object of the research was a group of girls of Tyumen region aged from14 to 16 years (n=279). Thyroid gland clinical testing and ultrasonic research was carried out, as well as TSH and fT4 research. Hematologic research was carried out; additionally, serum ferritin (SF) and soluble trasferrin receptors (TfR) measurements were explored by the ELISA method. The grant of the President of the Russian Federation «MD - 4781.2010.7».

Results: Since 1997 iodine preventive maintenance has been conducted in Tyumen region with the help of iodine-treated salt. In 2010 a group of Tyumen children aged from 6 to12 years showed the 145 µg/l mediana urinary iodine.

In a group of teenagers thyroid gland rising occurrence was 10,75% based on the results of ultrasonic research. TSH level was 1,5 ± 1,4 mU/l, fT4 16,2 ± 2,8 pmol/l. Subclinical hypothyroidism occurrence (SCH) was 2,2 %, while clinical hypothyroidism occurrence was (CH) 0,36 %. The latent iron deficiency occurence was 30,5% by the SF level < 15 µg/l. 15,5 % of girls showed the increased level of TfR> 1,7 mg/l. No significant correlation between the volume of a thyroid gland and SF was defined in the general group, while in SCH girls group correlation between the volume of a thyroid gland and SF (r = 0,65; p=0,000) was defined.

Conclusions: Teenage girls form a goiter risk group, despite the fact that the iodine consumption by the region population has improved. Also girls are vulnerable to the latent iron deficiency, that could be substantiation for the additional preventive measures.

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RETROSPECTIVE ANALYSIS OF 728 CASES OF THYROID PATHOLOGY DATA IN BAOTOU

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Objective: Summarize the experience of thyroid disease's biopsy, and re-evaluate the diagnosis of thyroid diseases. To briefly discuss the value of fine-needle aspirationcytology. Commentary the treatment principles and latest developments aboutthyroid nodules and thyroid cancer.

Methods: A retrospective statistical analysis 728 cases of thyroid pathological diagnosis to combine together the other clinical data, fine-needle aspirationcytology, ^{131}I radionuclide scan and color Doppler in the First Affiliated Hospital of Baotou Medical College of Inner Mongolia Science and Technology University in January 2000 ~ December 2007.

Results: 1. In this study, 728 cases of thyroid cases accountd for the total number of 2.28% inthe same period.Patients aged from 9 to 77 years old. 31 ~ 60- year-old accounted for 90.29%.

2. In all cases, nodular goiter is the first one (about 54.81%), followed by thyroid adenomas (about 30.36%), thyroid cancer (about 8.24%). Papillary thyroid carcinoma is the first one of all thyroid cancer (about 6.59%).

3. In the cases of thyroid cancer surgery, people under age 45 accounted for 65% Clinical stage I, II period accounted for 95.00%. Thyroid carcinoma with lymph node metastasis accounted for 38.33%.This is related to the biological characteristicsof thyroid cancer.

4. Randomly selected 58 cases which have pre-operative examination of FNAB.Analysis of the results between FNAB and histopathological examination. In the 58 FNAB cases, 49 cases are confirmed in histopathological diagnosis and the total coincidence rate is 84.48%.

Conclusions:

1. Thyroid disease is common in surgical pathology. The research results showed that the prevalence of thyroid disease in Baotou is that nodular goiter is the first one,followed by thyroid adenomas, and the third one is thyroid cancer.
2. Thyroid fine-needle aspiration biopsy is the the gold standard of thyroid nodule cytology diagnosis and differential diagnosis.

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HISTOLOGICAL AND HISTOMETRICAL CHANGES OF OSTRICH THYROID GLAND DURING SUMMER AND WINTER SEASONS IN TEHRAN-IRAN

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The seasonal changes of ostrich thyroid structure in tehran,which has a hot summer and a relatively cold winter, were studied. The study was made on thyroid glands of 20 ostriches in 2 groups(summer and winter group).The samples were collected with maximum 0.5 cm thickness by autopsy and were fixed in 10 % formalin saline.The samples were embeded in paraffin,sections at 5-6 micrometer, stained by Hematoxilin and Eosin,PAS and Reticulin.the results showed that the season had a significant effect on thyroid parenchyma-stroma ratio.This ratio was significant increased in winter.The number and diameter of thyroid follicles were increased in winter too.The histometrical results showed that the number of thyroid follicles,active follicles,follicles with vacuolated colloid were significant increased in winter. The diameter of large follicles and epithelium height of follicles were also increase in winter significantly.

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THE FREQUENCY OF MIXED PATHOLOGY IN NODULAR GOITER

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Aim of the work: Examine the frequency of comorbidity in nodular goiter.

Research Methods: The study data of 77 patients operated on for nodular goiter in 2008-2010.

Clinical Results: 77 patients (14 men, 63 women) having NG, which was diagnosed from 1 to 12 years. The patients´ age: 29-67 (47,7 ± 3,1). The number of nodes - from 1 (19 patients) to 2-6 (58 patients), duration of observation before surgery - 0,1-12 years. Patients were sent to surgery for large goiter size, rapid growth of nodes and the detection of cancer by fine-needle aspiration biopsy. A number of patients with the differentiated thyroid carcinoma (DTC) was in 2008 - 6 among 19 (31,5%, 4 - papillar cancer (PC), 1- follicular cancer (FC), 1- papillar-follicular cancer (PFC); 2009 - 12 among 35 (37,4%, 8 - PC, 3 - FC, 1 - PFC); 2010 - 13 among 23 (56,5%, 8 PC, 5- FC. In total within 3 years - 29 patients with DTC (37,7%). The follicular adenomas (FA) were amounted 18 (23,4%). The micro-macro-follicular goiter (MMFG) - 20 (25,9%), colloid goiter (CG) - 10 (12,9%), lymphoid infiltration (LI) - 24 (31,2%), toxic goiter - 4 (5,2%). 33 among 77 patients (42,8%) had mixed pathology: PC+FA+LI; PC+MMFG+LI; FC+FA+CG; PC+FA; PC+FC+MMFG.

Conclusion: Taking into account the high percentage of diagnostic DTC, FA and mixed pathology in NG should be more frequently used surgical treatment.

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TGF-β_1 IN THE EXPRESSION OF THYROID DISEASES AND ITS CLINICAL SIGNIFICANCE

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Objective: Transforming growth factor β_1 (TGF-β_1) promoting tumorigenesis, is a multifunctional cytokine which can regulate cell proliferation and differentiation. anti-TGFβ_1 monoclonal antibody is used to detect the expression of TGF-β_1 in thyroid disease in order to investigate its clinical significance.

Methods: The expression of TGF-β_1 was detected in 30 cases of thyroid carcinoma 30 cases of benign thyroid disease by SP (Streptavidin-Peroxidase) immunohistochemistry. The datas(including the first part datas)are analysised by χ^2 test and Fisher exact probabilities.

Results: The experimental results show that in 30 cases of thyroid cancer, expression of TGF-β_1-positive is 19 cases (63.3%). Comparing with benign thyroid disease, there was a significant difference ($P< 0.05$). Between the group of the benign thyroid disease (nodular goiter, thyroid adenoma, diffuse toxic goiter, Hashimoto´s thyroiditis) is no significant difference. The expression of TGF-β_1 is no significant difference between PTC and FTC.In thyroid cancer, different gender and age group is no significant difference.The lymph node metastasis was more significantly increased than that without lymph node metastasis of TGF-β_1 expression.

Conclusion:

1. Through this research, it may be speculated that TGF-β_1 have a certain role in the incidence and development of thyroid cancer. Meanwhile,it is closely related to the biological behavior of thyroid cancer.
2. TGF-β_1 has no relationship with benign thyroid disease (nodular goiter, thyroid adenoma, diffuse toxic goiter, Hashimoto´s thyroiditis). In thyroid carcinoma, TGF-β_1 has no relationship with pathological type, age, sex and has relationship with lymph node metastasis.
3. It can be used as auxiliary diagnosis of thyroid cancer indicators and provide some basis for its treatment choice.

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ROSUVASTATIN TREATMENT REDUCES THE MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS IN THYROIDS OF AGED MICE

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Formation of cold follicles and hypothyroidism are frequent disorders due to ageing.

In this study, we better characterized the follicular alterations and tested rosuvastatin having PPARg-mediated protective effects on oxidative stress.

We used three groups (n = 5 - 9) of C57bl mice 1) 2-month-old, 2) 9-month-old, 3) 9 month-old treated with rosuvastatin (20 mg/kg/day) for 12 weeks. The thyroids were processed for immunohistochemistry to detect T4, 4 hydroxynonenal (HNE, marker of oxidative stress), catalase (H202 detoxifiant), and PPARg.

In 9-month-old mice, some follicles presented an altered phenotype. T4 was absent from the colloid, but highly detected in the cytoplasm. The thyrocytes were columnar and irregularly shaped, and the high HNE cytoplasmic expression was indicative of an oxidative stress. Catalase and PPARg expression was increased inside the cytoplasm. Nuclear PPARg expression was observed only in well iodinating follicles.

The proportion of altered follicles was significantly higher in 9-month-old mice (x ± SEM : 6.2 ± 2%) than in young mice (1.6 ± 0.2%). As compared to untreated 9-month-old mice, rosuvastatin treatment significantly reduced the proportion of altered follicles to 2.9 ± 0.7%. This beneficial effect of rosuvastatin was mediated by PPARg whose expression was overexpressed in the nuclei of the thyrocytes, as well as in the adipocytes located near the thyroids.

In conclusion, during ageing, a higher proportion of thyroid cells are submitted to an oxidative stress related to abnormal intracellular iodination and H202 excess. The stress could be partly compensated by antioxidant defenses like catalase, but also PPARg. Rosuvastatin treatment prevents the follicular alterations due to ageing by increasing the nuclear expression of PPARg.

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THYROID TUBERCULOSIS: A CASE SERIES AND REVIEW OF LITERATURE

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Background: Tuberculosis of thyroid gland is extremely uncommon. The incidence is low even in countries where the prevalence of tuberculosis is high. Compared to pulmonary tuberculosis extra-pulmonary tuberculosis may have different clinical manifestations and may be difficult to diagnose. For accurate diagnosis clinical and radiological features are nonspecific and a histological examination is required.

Objective: Tuberculosis of the thyroid gland is a very rare disease. The incidence of extra pulmonary tuberculosis has been showing a progressive increase, in the recent years. We present three cases of primary thyroid tuberculosis.

Methods: Two cases were diagnosed on the basis of fine needle aspiration cytology as they presented with thyroid nodule (Figure 1 & 2). The third case was diagnosed on histopathology as the patient under went total thyroidectomy for the left side nodule which was a Follicular lesion on fine needle aspiration cytology. Tuberculosis was diagnosed on the other lobe of thyroid which was not involved. Clinically and biochemically all were euthyroid.

Result: All three patients were given anti thyroid treatment for nine months. The two who presented with nodule their nodular lesions completely resolved after treatment while, the third patient had successfully completed the nine months of anti tuberculous treatment and remained asymptomatic.

Conclusion: Although rare the thyroid tuberculosis should be kept in mind in the differential diagnosis of thyroid masses, even in patient with no history and symptom of tuberculosis disease else where and especially in countries like Pakistan where there is a high prevalence of tuberculosis. Diagnosis is made by histological examination and rarely by demonstration of the tubercle bacilli from biopsy or aspiration specimen. Administration of antituberculous drugs is considered as the treatment of choice. Rarely surgery or drainage may be required for large abscess along with anti tuberculous drug therapy.

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THYROID FOLLICLE SIZE IS DECREASED NOT ONLY IN AMES DWARF BUT ALSO IN GROWTH HORMONE RECEPTOR KNOCKOUT (GHRKO) MICE

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Altered somatotrophic signaling is among the most important potential mechanisms of extended longevity. Ames dwarf (df/df) mice are homozygous for mutation at the Prop-1 gene, leading to a lack of growth hormone (GH), prolactin and thyroid stimulating hormone (TSH). Mice homozygous for targeted disruption of the growth hormone receptor/growth hormone binding protein gene are known as GH receptor knockout (GHRKO) mice or "Laron dwarf". Both, df/df and GHRKO mice are characterized by reduced body size, low plasma insulin and insulin-like growth factor-I, and extended longevity. Recently, by crossing df/df and GHRKO mice, double-mutant Ames dwarf/GHRKO (df/KO) mice were produced. These mice are smaller than Ames dwarfs or GHRKOs, and also have reduced insulin and IGF-I levels.

Objectives: The aim of the study was to investigate if and to what extent certain thyroid morphological parameters, such as inner follicular surface area, inner follicular perimeter, as well as the follicular epithelium thickness are changed in the examined dwarf mice. This quantification was performed in thyroids collected from df/df, GHRKO and df/KO female mice, at approximately 5-6 months of age. We used a computerized plotting program that combines a live microscopic image of the slide with an operator-generated overlay.

Results: Inner follicular surface area and inner follicular perimeter were decreased in all examined kinds of dwarf mice. Moreover, decreases in these two parameters were more pronounced in df/df and df/KO than in GHRKO mice. Concerning the follicular epithelium thickness, a tendency towards decrease of this parameter was found in dwarf mice.

Conclusion: Parameters characterizing thyroid follicle size are decreased not only in Ames dwarfs but also, however to a lesser extent, in GHRKO mice, which may explain decreased thyroid hormone levels in both mutants and may suggest that beside TSH, also GH signaling constitutes a crucial element in thyroid growth and, possibly, function.

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THE GENETIC DETERMINANTS OF THYROID FUNCTION MAY BE DIFFERENT BETWEEN CHILDREN AND ADULTS

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Objective: Genome wide association and candidate gene studies have identified single nucleotide polymorpisms (SNPs) which effect thyroid hormone parameters. Common variation in rs4704397in *PDE8B* influences TSH levels by approximately 0.2 SD/allele. Common variation in rs2235544 in *DIO1* adjusts the T_3/T_4 ratio through altering T_4 levels by 0.14 SD/allele. These associations and others have all been identified in adult cohorts; however no studies have been performed to date in children.

Design: We utilized the Avon Longitudinal Study of Parents and Children birth cohort. The children in this cohort are now aged 19. Full thyroid function tests in 664 children were performed from stored frozen blood samples taken at age 7. We then studied the impact of variation in rs4704397 in *PDE8B,* and rs2235544 in *DIO1,* on thyroid hormone parameters.

Results: We identified that variation in rs2235544 in *DIO1* was associated with T_4 levels in children. As in adults, individuals with the C allele appear to have increased *DIO1* activity resulting in lower T 4 levels ($p = 7.01 \times 10^{-6}$,-0.24 SD/allele SE 0.054). However we found no evidence of association between variation in rs4704397 in *PDE8B* and TSH levels in children (p=0.49, -0.032 SD/allele SE 0.055)

Conclusion: It appears the genetic determinants of thyroid function may be different between children and adults. Although we had 90% power to see an effect size of 0.1SD/allele with *PDE8B* on TSH levels we found no evidence of its association with TSH in children. In contrast, the effect of variation in *DIO1* on T_4 levels was if anything enhanced. New markers need to be identified to allow genetic association studies of the thyroid hormone pathway to be performed in childhood epidemiological cohorts. We are also currently repeating thyroid function in the same children at age 15 to assess the effect of puberty on these relationships between SNPs and thyroid hormone parameters.

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ASSOCIATION OF THE TYPE 2 DEIODINASE GENE POLYMORPHISM AND THE RISK OF RECURRENT DEPRESSIVE DISORDER

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Background: Thyroid hormones play an important role in etiology of the recurrent depressive disorder (rDD), and thyroid dysfunction is believed to be a negative prognostic factor for rDD. Accordingly, decreased T_3 levels are characteristically found in depressive patients.

Thyroid hormones concentrations are influenced by many factors, including the activity of specific enzymes - deiodinases. Here we propose a hypothesis that genetic variants of type II deiodinase gene (DIO2), altering activity of the enzyme and - subsequently - the level of thyroid hormones, are associated with rDD.

To our knowledge, no genetic studies have been performed in which associations between DIO2 gene and depression would be examined. Thus, we tried to evaluate relationship between two single nucleotide polymorphisms (SNPs) (Thr92Ala; T/C, ORFa-Gly3Asp; C/T) and the risk of rDD.

Materials: For Thr92Ala the preliminary study was performed in 153 patients suffering from rDD and in 71 healthy subjects, while for ORFa-Gly3Asp - in 101 rDD patients and 69 controls. Evaluation of SNP occurrence was performed by the PCR technique.

Results: Statistical significance between rDD patients and the control group was observed for the allele (rDD: T-57.92%; C-42.92%; controls: T-44.17%; C-58.83%; p=0.0168; c^2 Pearson's test = 5.71) and for genotype frequencies (rDD: TT-29.70%, TC-56.43%, CC-13.86%; controls: TT-21.67%, TC-45.00%, CC-33.33%; p=0.0135; c^2 Pearson's test = 8.61) at ORFa-Gly3Asp locus. Distribution of the allele T was significantly higher in rDD patients, with odds ratio value 1.1 (95% CI = 1.1-2.75).

Conclusion: Data obtained in this study may support the hypothesis that genetic variants of the DIO2 gene are associated with rDD risk.

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EXPRESSION OF PHOSPHOINOSITIDE 3-KINASE SUBUNITS IN CHRONIC THYROIDITIS

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Objectives: Associations between thyroid cancerogenesis and a background of chronic thyroiditis remain to be determined. PI3K pathway alterations have been observed in various human tumours, including thyroid cancers (especially mutations and amplification of *PIK3CA* and amplification of *PIK3CB*). Contemporaneously, subunits p110δ and -γ are closely related to inflammatory processes in different tissues. The expression of genes *PIK3CA*, *PIK3CB*, *PIK3CD* and *PIK3CG* (coding the isoforms p110α, -β, -δ, and -γ, respectively) in Hashimoto's thyroiditis (HT), being a chronic disease associated with an assumed increased risk of the development of thyroid cancer, is still unknown. The aim of the study was assessment of *PIK3CA*, *PIK3CB*, *PIK3CD* and *PIK3CG* genes expression levels in HT.

Methods: 67 cases of chronic thyroiditis were analyzed. Following preparation of smear for cytological examination, extraction of total RNA from remnant biopsy needle material was obtained, using modified method of Chomczynski and Sacchi. Total RNA was reverse transcribed into cDNA and investigated by Real-Time Quantitative PCR. The relative expression levels of *PIK3CA*, *PIK3CB*, *PIK3CD* and *PIK3CG* genes were assessed, using ABI PRISM 7500 SDS Software.

Results: Significantly higher expression levels (RQ) for *PIK3CD* and *PIK3CG* genes have been noted, when compared with *PIK3CA* and *PIK3CB* expressions in HT group ($p< 0,05$).

Conclusion: These results may suggest an involvement of *PIK3CD* and *PIK3CG* alterations in HT pathogenesis; its role in multistep cancerogenesis process cannot be excluded.

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CONGENITAL HYPOTHYROIDISM (CH) DUE TO A NOVEL HOMOZIGOUS MUTATION IN THYROGLOBULIN (TG) GENE

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CH due to TG defect is an autosomic recessive disease, with a prevalence of 1:40000-1:100000 newborns. It is clinically characterized by goiter, low serum levels of FT4, FT3 and TG, elevated TSH values, with a negative perchlorate test.

Human TG protein is formed by 2768 aminoacids, encoded by a gene of 48 exons, located on chromosome 8.

The objective of this study was to perform genetic analysis in two sisters born by consanguineous parents, affected by CH.

Two italian sisters were detected as affected at neonatal screening for CH, and confirmed at serum TSH test, so they started levothyroxine therapy (LT4).

After the withdrawal of LT4 at seven years, in order to determine the persistence of hypothyroidism, the first sister showed hypothyroidism and undetectable serum TG. Neck 123-I scan showed a normally located thyroid gland, with an uptake of 12% after 24 hours. Neck ultrasound indicated a normal sized eutopic gland.

The other sister, although the early substitutive treatment with LT4, was also affected by mental retardation. As her sister, she presented a normal sized gland, and undetectable serum TG.

Genomic DNA was extracted by patients' and father's blood. All 48 exons in TG gene were amplified with PCR and analyzed. In sisters' samples a novel homozygous point mutation was found in exon 10 (CGA/TGA), which determined a stop codon in 768 position (R768X). The result is a prematurely truncated and non functioning protein. We also identified allelic variants already described. The father harbored the same point mutation in the heterozygous state.

In conclusion, we identified two sisters affected by CH with a normal gland and undetectable serum TG. Genetic analysis demonstrated a TG defect as cause of hypothyroidism.

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ASSOCIATION OF PAPILLARY THYROID CANCER WITH FOXE1 GENE IN POLISH POPULATION

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Papillary thyroid cancer (PTC) is usually sporadic cancer, however its family occurring its well established and is more frequent than in the other solid tumors. It is estimated, that approximately 5% of differentiated thyroid cancers (where PTC is the most frequent) are hereditary. PTC occurs as primary feature (familial nonmedullary thyroid cancer, FNMTC), where a susceptibility genes are poorly known, and also as a component of monogenetic familial cancer syndromes. Recently published data showed the association of PTC with FOXE1 gene (formerly - TTF2, Thyroid Transcription Factor 2) located on chromosome 9.

The aim of the study was to analyze the association of FOXE1 gene with PTC in Polish population.

910 DNA samples from PTC patients and 886 controls were analyzed. Both groups were matched according to gender (women: 85,6% cases and 82,60 %. controls); median age for PTC group was higher than for controls (53 versus 44,5 years). Two SNPs of FOXE1 gene (rs1867277 and rs1443434) were analyzed by allelic discrimination technique (7900HT Fast Real-Time PCR System, Applied Biosystems).

Genotype distribution of rs1867277 and rs1443434 differed significantly between PTC and controls ($p=0.000004$ and $p=0.00005$ respectively). In PTC the number of rs1867277 AA homozygotes (25.7%) and AG heterozygotes (49.0%) was higher than in controls (18.9% and 46.0% respectively). For the presence of at least one A allele the OR value was significantly increased (OR=1.6; 95%CI: 1.30-1.96) In PTC there were higher frequency of rs1443434 GG homozygotes(24.7%) and GT heterozygotes(49.6%) than in controls(18.4% and 47.0% respectively). OR value for at least one G allele was 1.5(95% CI: 1.24-1.89).

Conclusion: We confirmed the association of FOXE1 gene polymorphisms with PTC in Polish population, however the further studies are necessary to understood genetic background to PTC predisposition.

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CORRELATION BETWEEN POLYMORPHISM OF TRAIL AND TGF-β1 GENES AND NODULAR THYROID DISEASE

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Objective: TRAIL has been viewed specific anti-tumor molecules as a great potential. TGF-β1, promoting tumorigenesis, is a multifunctional cytokine which can regulate cell proliferation and differentiation.Probe in TRAIL +1525 G / A and TGF-β1 +869 T / C gene polymorphism in patients with thyroid nodular disease; Systematical research on the relation between individual gene polymorphism and thyroid nodules diseases.

Method: The TRAIL 1525A/G and TGF-β_1 +869T/C gene polymorphism was identified by Polymerase Chain Reaction Restriction fragment length polymorphism (PCR-RFLP) and Polymerase Chain Reaction-Single Strand Conformation Polymorphism (PCR -SSCP) in clinical patients,67 cases of nodular goiter, 75 cases of Graves'disease, 71 cases of Hashimoto thyroiditis, 34 cases of thyroid adenoma, who were from First Affiliated Hospital of

Baotou medical college between 2007.9 - 2009.9 and 100 healthy control subjects.The datas were analyzed by the software of SPSS 13.0.

Results: 1.The TRAIL+1525G/A genotype distributions among nodular goiter group, adenoma group and healthy control were significantly different ($P < 0.05$); But the relationship of nodule size with distribution of genotype frequencies was not statistically significant ($P > 0.05$).

2 Nodular goiter with hyperthyroidism and toxic thyroid adenoma are collectively known as nodular hyperthyroidism group, there is a significant difference about the distribution of TGF-β1 +869 T / C genotype frequency compare with simple Graves disease hyperthyroidism group ($P < 0.05$).

Conclusion: TRAIL+1525G/A and TGF-β_1+869T/C gene polymorphism may be related to the incidence of nodular thyroid diseases, G allele of TRAIL and C allele of TGF-β_1 may be predisposing genes of patients with nodular goiter. There is no significant difference among genotypes about goiter size of nodular thyroid diseases and Graves disease exophthalmos.But C allele of TGF-β_1 may be relevant to the incidence of nodular goiter, adenomas accompany hyperthyroidism.

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DETECTION OF NOVEL GENETIC CHANGES IN THE *RAS* GENES IN PAPILLARY THYROID CARCINOMA

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Objectives: Activating point mutations in the *RAS* genes (*H-RAS, K-RAS, N-RAS*) are reported in follicular thyroid adenoma (FTA), follicular thyroid carcinoma (FTC) and follicular variant of papillary thyroid carcinoma (FVPTC). The aim of this study was to determine the frequency of *RAS* mutations in thyroid tumors.

Methods: DNA was extracted from 82 samples, including 64 fresh frozen thyroid samples and 18 paraffin-embedded formalin-fixed samples. The cohort contained 67 PTCs (47 FVPTCs, 12 mixed follicular-classical types and 8 classical variants), one FTA, 7 FTCs, 4 poorly differentiated carcinomas (PDC) and 3 anaplastic carcinomas (ATC). The presence of *RAS* mutations in exon 1 and exon 2 of the *H-RAS, K-RAS, N-RAS* genes was determined by direct sequencing.

Results: In the *N-RAS* gene, the mutation in codon 61 was detected in four patients. In the *K-RAS* gene, the mutation in codon 61 simultaneously with the silent mutation in codon 60 (exon 2) in two patients, the missense mutation CAA/AAA in codon 3 (exon 1) in one patient and the missense mutation ACC/ATC in codon 50 simultaneously with the silent mutation CTC/CTT in codon 56 (exon 2) in one patient were detected. In the *H-RAS* gene, the silent mutation CCG/CCA in codon 42 (exon 1) was detected in five patients. These all mutations were found in FVPTC, except of one patient with the mutation in codon 42 that was detected in mixed follicular-classical type. The polymorphism 81T→C was present in 49% PTCs, in one ATC, one FTA and 3 PDCs. The association with phenotype was not apparent.

Conclusion: *RAS* mutations in our cohort of thyroid cancer were screened. In addition to six mutations in codon 61 (GTPase domain), we revealed other silent and missense genetic changes. However, their influence on the development of PTC needs to be confirmed.

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ADRA2B GENE INSERTION/DELETION POLYMORPHISM AND GRAVE´S DISEASE IN POPULATION OF NOVOSIBIRSK

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The purpose of this study was to examine the joint association polymorphism I/D ADRA2B gene with Grave´s disease (GD).

Materials and Methods: In this association study ADRA2B D/I polymorphism was genotyped in 244 subjects. The study population included 102 Novosibirsk patients with GD and and 142 healthy controls. The presence of biochemical hyperthyroidism together with either the presence of dysthyroid eye disease or a diffuse goiter and a significant titer of microsomal, or TSH receptor autoantibodies defined GD. The average ages (in years) of patients with GD were 42±1.2. All control subjects had normal thyroid function and were thyroid autoanti-body negative. Genotyping of I/D polymorphism was performed by conventional PCR method.

Results: The ADRA2B gene II homozygotes genotype frequency was strongly increased in patients with GD 54 % versus controls 30 %, $\chi^2 = 11,57$, p=0,0001. The DD genotype frequency was 9 % in patients with GD versus controls 20 %, $\chi^2 = 13,80$, p=0,014. The II genotype were associated with the increased risk for GD: odds ratio OR=4.12 95% CI 1.77-9.62 (the II genotype versus DD); odds ratio OR=2.69 95% CI 1.58-4.57 (the II genotype versus other two genotypes).

Conclusion: The ADRA2B D/I polymorphism is a joint susceptibility locus for GD.

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RELATIVE QUANTIFICATION OF CYCLOOXYGENASE-2 GENE EXPRESSION LEVEL IN CHRONIC AUTOIMMUNE THYROIDITIS, PAPILLARY THYROID CARCINOMA AND NON TOXIC NODULAR GOITRE

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Objectives: Chronic lymphocytic thyroiditis (Hashimoto thyroiditis - HT) is characterized by the cell-mediated immune reaction and an intense infiltration of thyroid gland by lymphocytes. Reactive changes in epithelial cells, affected by severe inflammation are frequently difficult to distinguish from neoplastic lesions. Additionally, epidemiological and histological studies reported a possible association between HT and risk of papillary thyroid carcinoma (PTC). Recent studies have shown that cyclooxygenase-2 (COX-2) is an important regulator of many cellular events. The product of COX-2 activity has been implicated in carcinogenesis by inhibiting apoptosis, promoting angiogenesis, increasing cell invasion and stimulating cell proliferation. Therefore, a role of COX-2 in regulation of cell apoptosis or in immune response linked with inflammation, appears to be an interesting subject of a research.

Methods: The patients have been selected basing on the results of routinely performed FNAB. Cytological specimens from 120 patients (105 females and 15 males) have been studied, including: patients with HT, PTC and non toxic nodular goitre (NTG). Each aspirate was used for routine cytology, and the remaining part of aspirate was immediately washed out of the needle. The obtained cells, have been used for further molecular analysis.

Results:

1. The performed analysis has revealed higher expression level of the *COX-2* gene in PTC group, in comparison to HT and NTG groups.
2. There were no correlations between *COX-2* expression, anti-TPO antibodies level (HT group), or patient's gender and age in studied groups.

Conclusions:

1. *COX-2* gene expression level is significantly higher in the PTC group, in comparison to HT and NTG groups.
2. The present results confirm the validity of genetic analysis of material collected from FNAB.
3. *COX-2* gene is not one of the possible elements of molecular association between HT and PTC. However, in PTC seems to play a role in neoplastic transformation.

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THE TRANSCRIPTION FACTOR PAX8 REGULATES SELENOPROTEIN DIO1 EXPRESSION THROUGH ITS BINDING IN THE 3'UTR REGION

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In a previous study we performed whole genome analysis of *in vivo* Pax8-binding sites using ChIP-Seq and expression arrays in order to define Pax8 transcriptional output in rat thyrocytes. Using this strategy we observed a downregulation of selenoprotein Dio1 (Deiodinase 1) mRNA ($p< 0.005$) after the abolishment of Pax8 expression by RNAi. In addition, ChIP assays confirmed that Pax8 binds efficiently to Dio1 gene and the most intriguingly, within the 3'UTR, a critical regulatory region for selenocystein insertion on selenoproteins. Thus, first we have conducted a comprehensive bioinformatics analysis by which we found that Pax8 binding site is approximately 300pb upstream of SECIS (Selenocystein Insertion Sequence). SECIS and other proteins like SBP2 allow selenocystein incorporation during selenoproteins translation, being part of a mechanism which is receiving increasing importance nowadays.

In this work we have also investigated the molecular mechanism involved in Dio1 mRNA modulation by Pax8, focusing in the role of TSH/cAMP in this regulation. In PCCl3 cells a direct effect of TSH administration on the increase of Dio1 mRNA expression was observed by RT-qPCR, which in turn was partially inhibited by IGF1. In concordance with these data, it was observed that thyroid Dio1 is downregulated in hyperthyroid rats which were treated with T_3 and T_4 and in consequence have low TSH levels. The specificity of TSH action on thyroid Dio1 expression suggests either a direct effect of cAMP responsive elements on rat Dio1 promoter or the increase of Dio1 mRNA stability for which Pax8 could be involved. As observed for NIS, the IGF1 could have an inhibitory effect on TSH-induction of Dio1 mRNA. Altogether these data open an interesting study concerning a new role for Pax8 in the control of mRNA translation of selenoproteins, particularly of Dio1.

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TRIIODOTHYRONINE CAUSES MIGRATION OF COACTIVATOR TRIP-230 FROM GOLGI APPARATUS TO NUCLEUS VIA INTRACELLULAR ACTIVATION OF PI3K KINASE

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Objectives: TRIP-230 is a coactivator involved in two important cellular pathways - Thyroid Hormone Genomic Pathway (THGP) (*via* interactions with Thyroid Hormone Receptors) and Hypoxia Induced Pathway (HIP) (*via* interactions with HIF-1β). Triiodothyronine (T3) induces TRIP-230 migration from Golgi Apparatus to Nucleus. Nuclear localization of TRIP-230 facilitates performance of its transcription coactivator activity. We hypothesized that T3-induced migration of TRIP-230 is mediated by activation of PI3K pathway. T3 activates this pathway in two different ways - *via* extracellular activation of integrin αVβ3 or intracellular interaction of thyroid hormone receptor with p85α regulatory subunit of PI3K kinase.

Methods: To verify our hypothesis we cultured Caki-2 cells on cover glasses in 24 well plates. The cells were treated with T3, T3-agarose and PI3K inhibitor (wortmannin). The cells were fixed and TRIP-230 was detected by immunofluorescence. Extranuclear or nuclear localization of TRIP-230 was determined by fluorescence microscopy.

Results: These experiments confirmed that T3 causes migration of TRIP230 to nucleus. Experiments with PI3K inhibitor - wortmannin - revealed that activation of PI3K pathway induced TRIP-230 migration. T3 coupled to agarose did not result in migration of TRIP-230. This excluded the possibility that membrane receptors (e.g. integrin αVβ3) could be involved in TRIP-230 migration.

Conclusions: We proved that T3 exerts its action on TRIP-230 by intracellular activation of PI3K kinase pathway. TRIP-230 is involved in two important pathways, THGP and HIP, which are disturbed in many cancer types. Recent studies suggest that carcinogenesis may be associated with local tissue hypothyroidism. Therefore, the role of TRIP-230 in cells with cellular hypothyroidism and disturbed THGP and HIP needs further investigation.

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MEMBRANE PERMEATION OF DUOX-GENERATED HYDROGEN PEROXIDE AND ITS BIOLOGICAL EFFECTS ON THYROID CELLS

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The organification of iodine is essential for the synthesis of thyroid hormones. This process involves the generation of hydrogen peroxide as a substrate for the oxidation of iodide thy thyroid peroxidase. Hydrogen peroxide, a strong oxidant, is thought to be causative for oxidative DNA lesions that are frequently found in healthy thyroids. It is generated in the follicular lumen by the DUOX1 and DUOX2 proteins. Therefore we evaluated the impact of the expression and activity of DUOX1/2 and their respective maturation factors, DUOXA1/2 in a comparative study between thyroidal (PCCL3, HTori) and non-thyroidal (HEK, COS) cell lines. First we examined the ability of the DUOX family proteins to generate hydrogen peroxide and the regulation of this process in all cell lines. We further examined the intracellular hydrogen peroxide levels using the novel genetically encoded sensor HyPer-1, which is more specific in the detection of hydrogen peroxide than previously available chemical radical sensors. We further examined the effects of extracellular generated hydrogen peroxide on the activation of the antioxidant response promoter element using a luciferase reporter gene assay. The expression of several antioxidant genes like glutathione peroxidases, superoxide dismutases and thioredoxin reductases was assessed using qPCR. We found that there are significant differences in the regulation of the hydrogen peroxide generation between different cell lines. We were able to reproduce earlier findings of a calcium- and PKC-mediated DUOX activation in COS7 cells, but could not demonstrate this effect in our thyroidal cell lines. We found that extracellular hydrogen peroxide easily penetrates the cell membrane. It induces a wide array of antioxidant defence genes. Some gene regulations found are specific for thyroid cells, while others are more species specific. Finally we investigated the potential of DUOX-generated hydrogen peroxide to induce oxidative DNA lesions.

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THYROID HORMONE REGULATION OF APP (β-AMYLOID PRECURSOR PROTEIN) EXPRESSION IN BRAINS AND BRAIN CULTURED CELLS

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Alzheimer´s disease, a degenerative disorder of the central nervous system which causes mental deterioration and progressive dementia, is accompanied by the presence of senile plaques of which the β-amyloid protein is

the major component. The β-amyloid protein is proteolytically derived from a set of alternatively spliced β-amyloid precursor proteins (APP). APP overexpression causes neuronal degeneration by a mechanism that likely involves an increased production of β-amyloid protein. Data from our laboratory have demonstrated that T3 represses APP gene expression in murine N2aβ neuroblastoma cells, by a mechanism that requires binding of its nuclear receptor (TR) to sequences located in the first exon of the gene. According to these results, thyroid hormones might play a role in the development of Alzheimer's disease by modulating APP content in the brain cells. Moreover, an association between hypo- or hyperthyroidism and an increased risk for developing Alzheimer's disease has been even reported.

To further analyze the effects of thyroid hormones on APP expression we have determined the levels of APP in T3-treated SH-SY5Y neuroblastoma cells, a line of human origin, and in primary cultures of brain cells obtained from rat embryos. T3 decreased APP protein levels in both, demonstrating that the repressive effect of T3 is also observed in non-transformed cells and is not species specific. Furthermore, APP mRNA was increased in the brains of hypothyroid neonatal rats and this effect was reversed by T4 treatment. In 30 days old rats, APP protein was higher in hypoccampus, a brain area implicated in Alzheimer's disease, but not in cerebellum. APP was also over-expressed in hypoccampus and cortex of adult hypothyroid mice, as well as in adult TRα1/TRβ knockout mice, which are depleted of thyroid hormone receptor. These results further confirm that thyroid hormones could play a protective role in the development of Alzheimer's disease.

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THE HINGE REGION OF THE THYROTROPIN RECEPTOR STABILIZES LIGAND BINDING AND DETERMINES DIFFERENT SIGNALING PROFILES OF HUMAN AND BOVINE THYROTROPIN

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The role of the hinge region (HinR) of the receptors for thyrotropin (TSH), follitropin (FSH), and lutropin/choriongonadotropin (LHCG) in receptor and signaling specificity is unknown. To investigate the role of the HinR for ligand binding, extracelullar signal generation and for the transmission of the signal towards the serpentine domain we replaced the HinR of the TSHR by those of LHCGR and FSHR and introduced constitutively activating mutations (CAMs) and one mutation deficient for bovine (b) TSH binding in these chimeras. Comparing the results of expression levels with bTSH binding for CAMs introduced in the chimeras we show that the HinR of the TSHR contributes to hormone binding in terms of ligand affinity and an increase in the retention time for the bound ligand as shown by dissociation experiments. Data for G_s and G_q signaling reveal that the activity of bTSH but not of recombinant human (rh) TSH depends on the HinR of the TSHR indicating that the HinR is exchangeable for rhTSH but not for bTSH signaling. For future studies regarding structure and function of the TSHR it will be necessary to characterize TSHR variants with both or more ligands.

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PROLIFERATION OF RAT THYROCYTES IS ACCOMPANIED BY INCREASED EXPRESSION OF RIBOSOMAL PROTEIN S6 KINASES S6K1 AND S6K2

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PI3K signal transduction pathway is involved in the regulation of a wide range of subcellular events. The ribosomal protein S6 kinase is an important member of this signalling cascade. It is involved in control of protein synthesis and G1/S transition of the cell cycle. There are two forms of rpS6 kinase: S6K1 and S6K2, each of which has nuclear and cytoplasm variants. Earlier we had shown that the subcellular redistribution of S6K1 and S6K2 correlated with the level of thyrocytes differentiation. The purpose of this work was to determine the status of S6K in the proliferating cells of thyroid gland. It was detected through a double immunocytochemical analysis, that in Ki-67 positive cells expression of S6K1 and S6K2 is much higher, than in other cells. A correlation analysis revealed the reliable connection between increased immunofluorescent reaction for S6K1, S6K2 and presence of Ki-67 antigen ($p< 0.01$, n=586 and $p < 0.01$, n=353, respectively). In addition, enhanceable expression of S6K1 and S6K2 was marked in Phospho-p44-42 MAPK positive cells as well. These results were tested on MCF-7 cells originated from human breast cancer which are characterized by high level of S6K1 and S6K2 expression. S6K1 and S6K2 content was analyzed at all stages of mitosis. As well as in the case of thyroid, Ki-67 and Phospho-p44-42 MAPK positive cells were characterized by increased immunochemistry reaction on S6K1 and S6K2. The effect of the increased expression of S6K1 and S6K2 was marked as for the cells growing in ordinary terms so for the insulin or FCS stimulated to proliferation. So, our data confirm engaging of S6K1 and S6K2 in the process of proliferation of the cells, in addition to more canonical role of these kinases as regulators of cell growth and maintenances of their size.

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T3-LIKE AND NON-T3-LIKE EFFECTS OF TRIAC

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Objectives: Triac is a naturally occurring T3 metabolite with low plasma levels and unknown physiological function. T3 and Triac have similar affinities for the T3 receptor TRα1 but Triac has a higher affinity than T3 for TRβ1 and TRβ2. Triac is also more potent than T3 in regulating transcription via TRβ1 and β2 but not via TRα1.

MCT8 is an important T3 transporter in particular in brain. Mutations in MCT8 are associated with severe psychomotor retardation probably through impaired T3 uptake and thus loss of T3 action in neurons. Triac is not transported by MCT8 and could be used for treatment of MCT8 patients. The aim of this study was to investigate if Triac is as potent as T3 in regulating T3-responsive genes in the SH-SY5Y neuronal cell line.

Methods: We incubated SH-SY5Y cells for 6 or 48 h with 0.01-10 μM T3 or Triac. mRNA levels were determined for hairless (HR), neurogranin (RC3), ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), Kruppel Like Factor 9 (KLF9), TRα1 and TRα2 by SYBERGreen qPCR.

Results: In general, at the different concentrations T3 and Triac showed similar potencies in stimulating the expression of the T3-responsive genes HR, ENPP2 and KLF9 after 6 and 48 h incubation, but had no effect on the expression of RC3, TRα1 and TRα2. However, incubation for 48 h with 10 μM Triac stimulated TRα1, TRα2 and RC3 expression and induced much larger stimulation of HR (36-fold) and KLF9 and lower induction of ENPP2. As these effects are not seen after 6 h incubation nor with 10 μM T3 at 6 and 48 h, they do not represent a direct genomic effect.

Conclusion: Triac is as potent as T3 in regulation of T3-responsive genes. However, high concentrations of Triac have an additional, indirect effect, the mechanism of which remains to be explored.

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IMPLICATION OF PAX8 IN THE CONTROL OF EPITHELIAL CELL POLARIZATION AND FOLLICLE FORMATION

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The mechanism that controls thyroid morphogenesis during development is being unraveled. However, epithelial cell polarization, a process required to form thyroid follicles remains unresolved. Follicles consist of a central lumen surrounded by an epithelial cell layer and are fundamental for thyroid hormone biosynthesis. In an attempt to understand better this critical process and based on the fact that Pax8-KO mice do not form follicles, we decided to study the role of this transcription factor in the establishment of cell polarity and follicle formation.

As a model system we used FRT thyroid cells that express Pax8 and have an epithelial polarized phenotype. As a control for this study, the kidney MDCKII cells that also express Pax8 were used.

First we performed three-dimensional epithelial culture systems, which allow epithelial cells to organize into structures that resemble their *in vivo* architecture. These cultures have emerged as models allowing investigations in a biologically relevant context. Thus, we cultured FRT and MDCKII cells in Matrigel Basement Membrane Matrix and we observed that both cell lines are able to form spherical epithelial monolayers enclosing a central hollow lumen. Foliculogenesis was also observed with Time-lapse movies recorded during 8 days of culture. The acquisition of apical-basolateral polarity and the formation of junctional complexes were observed by Immunofluorescence assays using β-catenin as a basolateral marker, DPPIV as an apical marker and the lateral expressed protein Cadherin-16, that interestingly in a preliminary ChIP-Seq analysis we have observed that is under Pax8 control. To study the role of Pax8, we are currently performing similar experimental approach in FRT cells in which we have abolished Pax8 expression by RNAi. Preliminary results suggest that Pax8 could play a critical role in the thyroid follicle formation by epithelial cells and future experiments will be directed to deep inside this process.

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DIFFERENCES IN TRANSPORT MECHANISMS AND CELL MEMBRANE TRAFFICKING BETWEEN PRIMARY AND SECONDARY THYROID HORMONE TRANSPORTERS

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The study of the Thyroid Hormone (TH) transporter MCT8 is one of the emerging fields in thyroid research in the last years. Recent Mct8-deficient mice data obviously make clear that additionally secondary TH transporters like from the OATP and LAT families are also very important for TH uptake and efflux in different cells types. Furthermore, MCT8, OATP1C1 and LAT1/2 play a role in TH transport at the Blood-Brain Barrier.

Here we analysed the similarities and differences between the primary TH transporter MCT8 and secondary TH transporters OATP1C1, LAT1 and LAT2 on molecular level. Based on a recent homology model and T_3 transport studies on hMCT8 we want to gain insight into the structure-function relationship of TH transport.

We found that there is very likely not a common molecular transport mechanism among the three TH transporter types. A sequence alignment revealed that known transport sensitive residues occur as conserved amino acids only within each TH transporter family but not over all considered transporters. We conclude that the molecular transport mechanism is likely organized either a) by different molecular determinants or b) the counterparts for the amino acid moiety of the substrate are at the TH transporter proton acceptors or donators.

Moreover, an identical conformation for all TH transporters is not very likely, particularly at least for the LAT family exhibiting an associated transmembrane helix that is provided by the escort protein CD98. Cell surface expression studies of secondary TH transporter domains that play a role in trafficking mechanisms confirmed that the CD98 is needed for efficiently cell surface translocation of Lat2.

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ANALYSIS OF NEW GENES DIRECTLY REGULATED BY FOXE1 IN RAT THYROID CELLS

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FOXE1 was initially identified as a thyroid-specific transcription factor that belongs to the forkhead/winged-helix family. It is unequivocally known that FOXE1 recognizes and binds to a DNA sequence present in both thyroglobulin *(Tg)* and thyroperoxidase *(Tpo)* promoters.

FOXE1 has a pioneer role during thyroid development and differentiation, due to its intrinsic capacity to initiate chromatin-opening events. Its function is essential for thyroid gland formation and migration, as well as for the maintenance of the thyroid differentiated state in adults. However, FOXE1 binding to other DNA sequences different than *Tg* and *Tpo* promoters remains almost unexplored.

In order to further investigate FOXE1 function in thyroid cells, we decided to apply a two stage high-throughput approach consisting of a transcriptional profile of FOXE1 silenced thyroid cells and a FOXE1 ChIP-Seq study.

For this purpose, we used PCCl3 cells, a continuous line of rat differentiated thyroid follicular cells. These cells express the thyroid specific genes *Tg*, *Tpo*, and *Nis* as well as the thyroid specific transcription factors TTF1, FOXE1, and PAX8.

FOXE1 was interfered in PCCl3 cells and silencing status was tested by western blotting using different time points (24, 48 and 72 hours). We have defined 48 hours condition as the best time point for FOXE1 silencing. Currently, rat whole genome arrays (60K) are being used to compare up and down regulated genes in the absence of FOXE1.

The first part of this study will allow us to generate an expression signature of genes directly regulated by FOXE1, which will be presented at the meeting.

In the future, ChIP-Seq screening for FOXE1 will be performed and results of both data sets will be combined in an integrative analysis. Finally, overlapping genes and DNA sequences will be considered as regions potentially regulated by FOXE1.

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EXPRESSION OF *THRA* GENE IN BLOOD MONONUCLEAR CELLS OF LONG-LIVED HUMANS WITH ADEQUATE THYROID STATUS IS SIGNIFICANTLY REDUCED COMPARED TO YOUNGER AGE GROUPS

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Objectives: Healthy aging is associated with normal thyroid function or with subclinical hypothyroidism. Thyroid hormones are involved in the maintenance of immune function by mediating the inflammatory response and by maintaining the number of the specific lymphocyte subpopulations. We hypothesize that immunosenescence in healthy humans is accompanied by inadequate expression of thyroid hormone nuclear receptor a in blood mononuclear cells (BMCs).

Methods: Expression of *THRA* in BMCs was measured by real-time RT-PCR. Analysis was performed in 132 individuals divided into 3 age groups: young (Y, n=43, mean age 27±3.7 years old), elderly (E, n=41, 65±3.0), and long-lived (L, n=48, 94±3.7). TSH and fT4 were measured in 108 out of 132 individuals using commercially available tests. Statistical analysis was performed using GLM procedure with SAS 9.2 package.

Results: The median expression of *THRA* in BMCs (arbitrary units, 1st, 3rd quartile) was 1.09 (1st q. 0.88, 3rd q. 1.29) in the Y, 0.96 (1st q. 0.78, 3rd q. 1.29) in the E, and 0.74 (1st q. 0.64., 3rd q. 1.02) in the L group, respectively. *THRA* expression decreased significantly with age ($p< 0.0001$, assessed on rank-transformed data). The Y *vs*. L and the E *vs*. L groups differed significantly from each other ($p=0.0001$ and $p=0.0033$, respectively), while the Y *vs*. E groups did not differ ($p=0.18$). A negative correlation between TSH and fT4 levels was observed ($p=0.0124$). There was no correlation between TSH level and *THRA* expression in BMCs when analyzed on ranks or on log-transformed data ($p=0.82$ and $p=0.80$, respectively).

Conclusions: Expression of *THRA* gene significantly decreases in age-dependent manner in BMCs of healthy humans. We suggest that this phenomenon is not related to thyroid function but, most possibly, is a result of BMC-specific phenomena, such as age-related epigenetic drift.

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