European
Thyroid Journal

42nd Annual Meeting of the European Thyroid Association

Abstracts

Budapest, Hungary
September 7–10, 2019

Guest Editors
Laszlo Hegedüs, Odense, Denmark
Endre V. Nagy, Debrecen, Hungary

KARGER

Basel · Freiburg · Paris · London · New York · Chennai · New Delhi · Bangkok · Beijing · Shanghai · Tokyo · Kuala Lumpur · Singapore · Sydney

S. Karger
Medical and Scientific Publishers
Basel · Freiburg · Paris · London ·
New York · Chennai · New Delhi ·
Bangkok · Beijing · Shanghai · Tokyo ·
Kuala Lumpur · Singapore · Sydney

Published by S. Karger AG, Basel
P.O. Box, CH–4009 Basel (Switzerland)
e-ISBN 978–3–318–06565–7

KARGER

E-Mail karger@karger.com
www.karger.com/etj

European
Thyroid Journal

Vol. 8, Suppl. 1, 2019

Contents

KARGER

E-Mail karger@karger.com
www.karger.com/etj

European Thyroid Journal

Oral Presentations

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

Published online: August 7, 2019

Presenting authors are underlined

Saturday, 7th September 2019

Oral Session 1: Topic Highlights

OP-01-01

TREATMENT OF ADVANCED TRK FUSION THYROID CANCER WITH LAROTRECTINIB

Steven Waguespack[1], Alexander Drilon[2], Anna F. Farago[3], Davendra Sohal[4], Do-Youn Oh[5], Patrick Ma[6], Ray McDermott[7], Shivani Nanda[8], Shivani Kummar[9], James Lee[10], Nora Ku[11], Michael Cox[12], Barrett Childs[13], David Hong[14], Maria E Cabanillas[15]
[1]The University of Texas MD Anderson Cancer Center, The University of Texas MD Anderson Cancer Center, Houston, Houston, USA; [2]Memorial Sloan Kettering Cancer Center, New York, USA; [3]Massachusetts General Hospital, Massachusetts General Hospital, Boston, Massachusetts, USA; [4]Cleveland Clinic, Ohio, USA; [5]Seoul National University Hospital, Seoul, Dem. People's Rep. of Korea; [6]West Virginia University Cancer Institute, West Virginia, USA; [7]St Vincent's University Hospital and Cancer Trials, Dublin, Ireland; [8]Bayer Healthcare Pharmaceuticals, Nj, USA; [9]Stanford Cancer Institute, Paolo Alto, USA; [10]University of Pittsburgh School of Medicine, Pittsburgh, USA; [11]Loxo Oncology Inc., San Fransisco, USA; [12]Loxo Oncology Inst., San Fransisco, USA; [13]Bayer Healthcare Pharmaceuticals, Whippany, Nj, USA; [14]MD Anderson Cancer Center, Houston, Texas, USA; [15]The University of Texas MD Anderson Cancer Center, MD Anderson Cancer Center, Houston, USA

Background: *NTRK* gene fusions are rare oncogenic drivers, implicated in ~1% of solid tumours across a diverse range of cancer types. Larotrectinib, an FDA-approved highly selective TRK inhibitor is efficacious and well tolerated in children and adults with TRK fusion cancer, irrespective of tumour type. We report the efficacy of larotrectinib in patients with TRK fusion thyroid cancer (TC).

Methods: Patients with measurable metastatic or locally advanced TRK fusion TC, enrolled in one of two larotrectinib clinical trials (NCT02122913 and NCT02576431), were analysed. Adult patients received larotrectinib 100 mg BID and paediatric patients received a dose of 100 mg/m^2 BID (max 100 mg BID). Response was assessed by investigator (INV) and independent review committee (IRC) per RECIST v1.1.

Results: As of 30 July 2018, 18 patients with TRK fusion TC had been treated: 14 papillary, three anaplastic and one follicular (median age, 64.5 years [range, 6–80]). Eight patients harboured *NTRK1* fusions and 10 patients harboured *NTRK3* fusions. Eighteen patients had prior therapy, including surgery (n=18), radiotherapy, including radioiodine (n=15), and at least one systemic therapy (n=12). Six patients had ≥3 prior systemic therapies. Of 16 evaluable patients per INV, overall response rate (ORR) was 81% with two CRs, six PRs, five PRs pending confirmation, one SD and two PD. Of 10 patients evaluable per IRC, ORR was 70%, with one CR, six PRs, one SD and two PD. At a median follow-up of 17.5 months, median duration of response had not been reached (range, 2.1+ to 29.6+ months). One anaplastic patient had a PR and progressed after 5.5 months of treatment. Adverse events were mostly grade 1–2.

Conclusions: Larotrectinib demonstrates high and durable responses with a favourable safety profile in adult and paediatric patients with TRK fusion TC, highlighting the benefit of *NTRK* fusion testing in advanced non-medullary TC.

OP-01-02

ZEBRAFISH SBP2-/- MUTANT DISPLAYS ABNORMAL THYROID HORMONE METABOLISM, OXIDATIVE STRESS AND AORTOPATHY, RECAPITULATING KEY FEATURES OF HUMAN SBP2 DEFICIENCY

Federica Marelli[1], Erik Schoenmakers[2], Neha Wali[3], Elisabeth Busch[3], Edward Visser[4], Carla Moran[2], Krishna Chatterjee[2], Luca Persani[5]
[1]Department of Clinical Science, University of Milan, Milan, Italy; [2]Wellcome-Mrc Institute of Metabolic Science, University of Cambridge, Cambridge, UK; [3]Wellcome-Trust Sanger Institute, Sanger Institute, Cambridge, UK; [4]Dept.of Internal Medicine, Erasmus Medical Centre, Rotterdam, Netherlands; [5]Laboratory of Endocrine and Metabolic Research, IRCCS Istituto Auxologico Italiano, Milan, Italy

Selenium is incorporated as selenocysteine (Sec) into a family of selenoproteins (SPs) with diverse, biological roles. Sec incorporation is mediated by a multiprotein-complex including SECIS-binding protein-2 (SBP2). Individuals with biallelic SBP2 mutations exhibit a multisystem disorder with growth retardation, abnormal thyroid hormone metabolism (high T4, normal or low T3, high rT3 and normal TSH) due to deficiency of Sec-containing deiodinases, phenotypes (e.g. muscular dystrophy, male infertility) mediated by lack of tissue-specific selenoproteins and tissue oxidative damage due to loss of antioxidant selenoenzymes. Most recently, a complex aortopathy consisting of dilatation of aortic root and ascending aorta has been identified in several young adult patients representing a new feature of SBP2 deficiency. Histology of aortic tissues revealed the loss of elastic and muscle fibers associated with collagen and fibrotic tissues infiltrations in the aortic wall similar to that found in Marfan, Loeys-Dietz or Ehlers-Danlos syndromes. Since murine SBP2 knockout is embryonic lethal, we used zebrafish sbp2-mutants (p.Q333X) to gain insights into human SBP2-pathology. By Western Blot (WB) we confirmed that the expression of the wild-type (WT) protein is strongly diminished in sbp2$^{-/-}$. The selenoprotein profiling assessed by qPCR and WB, showed a variable regulation of SPs expression. The mRNA expression of antioxidant enzymes (*gpx1a, gpx2, trxr1,* and *mrsb1*), and of other selenoproteins (*seph, sepsh2, sep15, sepp, selt, sepn1*) was significantly reduced in sbp2$^{-/-}$ embryos. At protein level, we confirmed diminished expression of spsh2, sep15, selh, and selt. The thyroid function test performed by IHC and ELISA assays documented a high T4/reduced T3 levels in sbp2$^{-/-}$ larvae, as a result of a reduced dio2 activity. Moreover, consistent with the low levels of antioxidant selenoenzymes, both gpx and trxr activities in sbp2$^{-/-}$ were significantly lower than both sbp2$^{+/-}$ and sbp2$^{+/+}$ adults at 2 and 3 months of age. The reduced antioxidant ability of mutants resulted in accumulation of reactive oxygen species (ROS) and lipid peroxide radicals (LPR), and tissue oxidative damage due to the activation of apoptosis. In particular, the analysis of the aortic tissue of sbp2$^{-/-}$ adults exhibited a dilatation of the outflow tract, and a reduced expression of markers of both elastic and muscular compartments.

In conclusion, zebrafish sbp2-mutants present impaired T4 to T3 conversion, antioxidant selenoenzymes deficiencies, oxidative damage and aortopathy, representing a new in vivo model that recapitulates key phenotypes of human SBP2 deficiency, enabling their pathogenesis to be further elucidated.

E-Mail karger@karger.com
www.karger.com/etj

OP-01-03

GENETIC DETERMINANTS OF THYROID FUNCTION IN PREGNANT WOMEN, NEWBORNS AND CHILDREN

Tessa Mulder[1], *Robin Peeters*[2], *Henning Tiemeier*[3], *Tim Korevaar*[4]
[1]Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Academic Center for Thyroid Diseases, Department of Endocrinology, Erasmus, Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands, Rotterdam, Netherlands; [3]Erasmus University Medical Center, Rotterdam, The Netherlands, Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands, Department of Social and Behavioral Science, Harvard Th Chan School of Public Health, Boston, USA, Rotterdam, Netherlands; [4]Erasmus MC, Rotterdam, The Netherlands, Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands, Endocrinology, Rotterdam, Netherlands

Objectives: Recent genome-wide association studies in adults have identified 20 novel genetic variants associated with serum free thyroxine (FT4) concentrations. However, the genetics of thyroid function during pregnancy and childhood are unknown. Therefore, we studied if these novel genetic variants are a determinant of FT4 in pregnant women, newborns and children.

Methods: We selected mothers and children from a population-based prospective cohort with data available on maternal gestational FT4 (n=5199), newborn FT4 (n=4549), or childhood FT4 concentrations (n=2747; median age 6y). Multivariable linear regression models were used to study the association of 16 maternal and 20 child single nucleotide polymorphisms (SNPs) with maternal and child FT4. Additionally, weighted genetic risk scores (GRSs) were constructed to assess the combined effects of these SNPs.

Results: Three SNPs were associated with maternal FT4 after correction for multiple testing. Two SNPs were associated with childhood FT4. These include variant rs11726248 at the AADAT locus, which has recently been identified as a novel thyroid hormone metabolizing enzyme. The GRS of maternal SNPs explained 1.9% of FT4 during pregnancy, whereas the child SNPs explained 3.4% of FT4 at 6 years. In addition, variant rs2235544 at the DIO1 locus was associated with both maternal and childhood FT4. There was no evidence of an association between SNPs and FT4 in newborns.

Conclusion: In this study, we validated three adult FT4-associated SNPs in pregnant women, two SNPs in children at 6 years of age, and one SNP in both pregnancy and childhood. These findings provide new knowledge about thyroid hormone physiology during pregnancy and childhood. Since major fetal development processes during pregnancy are regulated by maternal thyroid hormone, genetics of gestational thyroid function can help elucidate causality for adverse pregnancy and child developmental outcomes.

OP-01-04

PROGNOSTIC SIGNIFICANCE OF TERT PROMOTER AND BRAF MUTATIONS IN CYTOLOGICALLY SUSPICIOUS OR MALIGNANT THYROID NODULES: A MONOCENTRIC CASE SERIES AT A TERTIARY-LEVEL ENDOCRINOLOGY UNIT

Simona Censi[1], *Elisabetta Grespan*[1], *Sara Watutantrige-Fernando*[2], *Elisabetta Cavedon*[3], *Jacopo Manso*[4], *Maurizio Iacobone*[5], *Eric Casal Ide*[6], *Francesca Galuppini*[7], *Ambrogio Fassina*[8], *Gianmaria Pennelli*[7], *Federica Vianello*[9], *Loris Bertazza*[10], *Susi Barollo*[1], *Caterina Mian*[11]
[1]University of Padua, Department of Medicine (Dimed), Endocrinology Unit, Padua, Italy; [2]Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Padua, Italy; [3]University of Padua, Department of Medicine (Dimed), Endocrinology Unit, Padua, Padua, Italy; [4]Endocrinology Unit, Padua University, Padua, Italy; [5]University of Padua, Department of Surgical, Oncological and Gastroenterological Sciences (Discog), Endocrine Surgery Unit, Padua, Padua, Italy; [6]University of Padua, Department of Surgical, Oncological and Gastroenterological Sciences (Discog), Endocrine Surgery Unit, Padua, Italy; [7]University of Padua, Department of Medicine (Dimed), Surgical Pathology and Cytopathology Unit, Pathology Unit, Padua, Padua, Italy; [8]University of Padua, Department of Medicine (Dimed), Surgical Pathology and Cytopathology Unit, Pathology Unit, Padua, Italy; [9]Department of Radiotherapy, Istituto Oncologico Veneto-IRCCS, Padova, Padua, Italy; [10]Dept. Medicine (Dimed), University of Padova, Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Padova, Italy; [11]Operative Unit of Endocrinology, Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Dept. of Medicine, Padova, Italy

Purpose: Follicular-derived thyroid cancers (FDTC) generally have a good prognosis. Nonetheless, a minority of them have an aggressive behavior and develop distant metastases, with increased mortality rates. Pre-surgically available prognostic markers, able to identify this group of patients are still lacking.

Methods: The study involved 436 FNA samples of malignant or suspicious cytology obtained from thyroid nodules in 436 consecutive adult patients referred for surgical excision from April 2007 to January 2017. Molecular analysis for somatic mutations of *TERT* promoter was retrospectively performed in all patients. 434 patients also underwent *BRAF* analysis. ^{131}I remnant ablation was performed in 387 patients (median dose: 100 mCi; range: 30-200 mCi). Follow-up was available for 384 of the 423 patients carrying malignant nodes (median: 59 months, range: 7-293 months).

Results: *TERT* promoter mutations and *BRAF* mutations were detected in 20/436 (4.6%) and in 257/434 thyroid nodules (59.2%), respectively. At the end of the follow-up, 319/384 patients (83%) had an excellent outcome, 37/384 (9.7%) had an indeterminate response and 28/384 (7.3%) had biochemical or structural persistent disease or died because of thyroid tumor. Tumor size (p=0.002), presence of extrathyroidal extension (p=0.0015), vascular invasion (p=0.0024), lymph node involvement (p=0.0001), with N1b with a higher risk then N1a involvement (p<0.0001), distant metastasis (DM) (p<0.0001), advanced stage at diagnosis (p<0.0001) and *TERT* promoter mutation (p=0.0002) were all significantly correlated with the risk of persistent/recurrent disease or disease-related death. At multivariate analysis, only cancer size (OR 1.06, 95% CI 1.01 to 1.09), the presence of N1b lymph-node metastases (OR 8.09, 95% CI 2.62 to 25.04) and DM (OR 7.32, 95% CI 1.17 to 45.81) predicted the persistence or disease related death. *TERT* promoter mutations were related with older age (p<0.0001), largest tumor size (p=0.0002), higher tumor stages (p<0.0001), and DM (p<0.0001). DM was correlated with older age (p=0.0487), larger tumor size (p=0.0015), extra-thyroidal extension (p=0.0120), presence of N1b lymph-node metastasis (p=0.0001) and *TERT* promoter mutation (p<0.0001). Presence of *BRAF* mutation was less frequent in patients with DM (p=0.0201). *TERT* promoter mutations (OR 40.58; 95% CI 3.06 to 539.04) and N1b lymph-node metastases (OR 40.16, 95% CI 3.48 to 463.04) were independent predictors of the presence of DM at multivariate analysis.

Conclusions: *TERT* promoter mutation revealed an independent predictor for DM, giving the clinician the possibility to individuate, already in the pre-surgical setting, many of the patients that deserve a more aggressive initial treatment and closer follow-up.

OP-01-05

DIFFERENCES IN DIRECTIONAL TRANSPORT OF THYROID HORMONE IN THE HUMAN TERM PLACENTA

Zhongli Chen[1], *A.E. Hitzerd*[2], *R.I. Neuman*[2], *M. Broekhuizen*[3], *Rutchanna Jongejan*[4], *Yolanda de Rijke*[5], *Irwin K. Reiss*[6], *A. H. J. Danser*[2], *Marcel Meima*[7], *Robin Peeters*[8]

[1]Dept.Internal Medicine, Erasmus MC, Rotterdam, Netherlands; [2]Dept.of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands; [3]Department of Pediatrics; Division of Neonatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands, Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, Division of Experimental Cardiology, Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [4]Department Clinical Chemistry, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; [5]Erasmus Medical Center, Department of Clinical Chemistry, Dept. Clinical Chemistry, Erasmus MC, University Center Rotterdam, the Netherlands, Rotterdam, Netherlands; [6]Erasmus MC University Medical Center, Divison of Neonatology, Erasmus MC-Sophia, Rotterdam, Pediatrics, Division of Neonatology, Rotterdam, Netherlands; [7]Dept.of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus MC, Rotterdam, Rotterdam, Netherlands; [8]Academic Center for Thyroid Diseases, Department of Endocrinology, Erasmus, Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands, Rotterdam, Netherlands

Introduction: Fetal development in the first half of pregnancy is dependent on maternal thyroid hormone (TH). This underscores the importance of transplacental TH transport, which is however yet poorly understood. We therefore used an *ex vivo* perfusion system to investigate TH transport across human term placenta.

Methods: Intact cotyledons (n=3 or 4) from healthy pregnant women were cannulated and connected to a perfusion system within 30 minutes after delivery. 100 nM thyroxine (T4) was added to either the maternal or fetal circulation and samples taken from both circulations at different time points. 3, 5, 3'-triiodothyronine (T3), reverse T3 (rT3) and T4 concentrations in the perfusates were measured by radioimmunoassays.

Results: Although T4 in the maternal circulation decreased from 59.3 ± 4.0 nM to 43.9 ± 7.9 nM over 2.5 hours of perfusion, no measurable T4 (0.3 ± 0.5 nM) was present in the fetal circulation. Instead, maternal and fetal rT3 reached 3.9 ± 0.5 nM and 0.8 ± 0.1 nM respectively. Adding the deiodinase inhibitor iopanoic acid (0.5 mM) to the maternal circulation blocked rT3 production and increased T4 (2.9 nM) in the fetal circulation. In contrast, fetal to maternal transfer of T4 was rapid with fetal T4 decreasing from 49.9 ± 11.0 nM to 4.8 ± 1.7 nM within 2.5 hours and maternal T4 increasing to 24.8 ± 8.7 nM. T3 levels remained low (<0.3nM) under all conditions.

Conclusions: T4 is poorly transported from the maternal to the fetal circulation by intact placentas. T4 entering the maternal side of the placenta is not delivered to the fetal circulation but instead converted into rT3. In contrast T4 is rapidly transferred from the fetal to the maternal circulation. These results indicate that T4 transport across human placenta is an asymmetrical process, which may vary during different stages of gestation.

OP-01-06

BIRTH DEFECTS AFTER EARLY PREGNANCY EXPOSURE TO ANTITHYROID DRUGS AND ABNORMAL MATERNAL THYROID FUNCTION AMONG 1,243,353 CHILDREN BORN IN DENMARK DURING AF 20-YEAR PERIOD

Stine Linding Andersen[1], *Louise Knøsgaard*[2], *Jørn Olsen*[3], *Peter Vestergaard*[4], *Stig Andersen*[5]

[1]Aalborg University Hospital, Aalborg University, Aalborg, Denmark; [2]Department of Clinical Biochemistry, Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, Denmark; [3]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [4]Department of Endocrinology, Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [5]Department of Geriatrics, Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, Denmark

Objectives: Antithyroid drug (ATD) therapy in early pregnancy is associated with birth defects, but more data are needed to substantiate the risk associated with different types of ATD. Furthermore, the role of abnormal maternal thyroid function *per se* remains unclarified.

Methods: We included all children live-born in Denmark from 1997-2016 (n=1,243,353) via Danish nationwide registers and studied the frequency of subtypes of birth defects (diagnosed before 2 years of age) previously described and associated with the use of ATD in early pregnancy. Furthermore, the frequency of abnormal maternal thyroid function in early pregnancy according to birth defects in the child was investigated among 8,830 singleton children born from 1997-2003 as part of the Danish National Birth Cohort (DNBC) and among 14,483 children born from 2011-2015 as part of the North Denmark Region Pregnancy Cohort (NDRPC). In these cohorts, abnormal maternal thyroid function was assessed in a stored blood sample from the early pregnancy and defined as TSH and/or free T4 outside the pregnancy week specific reference ranges.

Results: The use of both Methimazole and Propylthiouracil in early pregnancy were associated with a higher frequency of birth defects in the previous and in the extended cohort compared with non-exposed children (Table). On the other hand, the overall frequency of abnormal maternal thyroid function in early pregnancy was similar among children with and without a diagnosis of birth defect in the DNBC (12.4% in both groups, p=0.9) and in the NDRPC (15.4 vs. 15.1%, p=0.8).

Conclusions: Results corroborate a risk of birth defects associated with the use of ATD in early pregnancy, and do not indicate that abnormal maternal thyroid function is a risk factor for birth defects.

	Non-exposed Birth defects	p	Methimazole Birth defects	**p**	Propylthiouracil Birth defects	p
Previous cohort, 1997-2008 n = 771,103	2.7%	ref.	6.1%	< 0.001	5.1%	0.001
Extended cohort, 1997-2016 n = 1,243,353	3.1%	ref.	6.4%	< 0.001	4.4%	0.03

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

Oral Session 2: Thyroid Nodules and Ultrasound

OP-02-07

A MULTICENTER VALIDATION STUDY FOR THE EU-TIRADS USING HISTOLOGICAL DIAGNOSIS AS GOLD STANDARD

Gilles Russ[1], *Pierpaolo Trimboli*[2], *Rose Ngu*[3]
[1]Centre de Pathologie et D'imagerie, La Pitié-Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France; [2]Thyroid Center, Oncology Institute of Southern Switzerland, Lugano, Switzerland; [3]Guy's and St Thomas' Hospital, Imaging Floor 23, London, UK

Objective: Many systems for risk stratification of thyroid nodule with ultrasound (US) have been proposed and the EU-TIRADS issued by the ETA in 2017 was the last to have been published. The present study was undertaken to evaluate if the malignancy risk of each category corresponded to the given range of the guidelines and assess the diagnostic value of EU-TIRADS in a multi-institutional trial with histology as gold standard.

Design: Three institutions in Switzerland, France, and United Kingdom shared this retrospective study. Enrollment period was 2013 to 2017. Included were patients who had undergone surgery with a detailed preoperative thyroid US.

Methods: Cancer risk was calculated for each EU-TIRADS score and compared between the three institutions. Predictivity tests were estimated. Non parametric statistical analysis was used.

Results: The final series included 1058 nodules of which 257 (24.3%) carcinomas. Nodules were classified as EU-TIRADS 2, 3, 4 and 5 in 6.7, 46.4, 26.2, and 20.7%, respectively. Cancer prevalence was 1.4%, 3.5%, 17% and 87.7% in classes 2 to 5, respectively ($p<0.0001$). EU-TIRADS 5 had a significantly higher cancer rate than the other summed categories (7.7%) ($p<0.0001$) with OR 84.7. When EU-TIRADS 4 and 5 were combined, 93% sensitivity and 97% NPV were found and findings of the three institutions were quite similar.

Conclusions: The cancer rate were within or close to the given range described in the EU-TIRADS guidelines. The diagnostic value was satisfactory. The results were similar in the three institutions participating in the study.

OP-02-08

INTER-OBSERVER VARIATION OF ULTRASOUND NODULE CHARACTERISTICS AND THE DIAGNOSTIC PERFORMANCE OF FIVE TIRADS CLASSIFICATION SYSTEMS

Tamas Solymosi[1], *Steen Joop Bonnema*[2], *Andrea Frasoldati*[3], *Laszlo Jambor*[4], *Zsolt Karanyi*[5], *Gábor László Kovács*[6], *Endre Nagy*[7], *Enrico Papini*[8], *Karoly Rucz*[9], *Gilles Russ*[10], *Laszlo Hegedüs*[11]
[1]Bugat Hospital, Dept. of Thyroidology, Gyöngyös-Mátrafüred, Hungary; [2]Department of Endocrinology and Metabolism, Odense University Hospital, Department of Endocrinology, Odense University Hospital, Denmark, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense C, Denmark; [3]Department of Endocrinology, Azienda Ospedaliera Santa Maria Nuova DI Reggio Emilia, Italy, Endocrinology Unit of Arcispedale S. Maria Nuova, Reggio Emilia, Italy, Italy; [4]Medical Imaging Clinic Radiology, University of Debrecen, Clinical Center, Debrecen, Hungary; [5]Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [6]Department of Internal Medicine, Flor Ferenc Hospital, Kistarcsa, Hungary; [7]Division of Endocrinology, Dept. of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [8]Dept. of Endocri. & Metabol. Disease, Ospedale Regina Apostolorum, Albano Roma, Italy; [9]Ist Department of Medicine, University of Pecs, Pecs, Hungary; [10]Centre de Pathologie et D'imagerie, La Pitié-Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France; [11]Dept. Endocrinol. Odense Uni. Hosp., Odense University, Odense University Hospital, Odense, Denmark

Objective: TIRADS scores are integral in thyroid ultrasound reporting and represent the main indication for thyroid nodule FNA. Until now only few studies on observer agreement are available, typically based on analysis of prerecorded and preselected static images.

Methods: After the blinded online evaluation of video-recordings of the ultrasound examinations of 123 operated thyroid lesions (41 consecutive malignant and 82 consecutive benign nodules) 7 experts from 7 thyroid centers answered 17 TIRADS-related questions resulting in 29,274 responses. Five different TIRADS scores (ATA, AACE/ACE/AME, ACR, ETA, Korean TIRADS) were generated. Inter-observer variations of each ultrasound characteristic and final TIRADS scores were compared using Gwet's AC1 values (an inter-rater coefficient, more accurate than Fleiss' kappa; higher values mean better concordance, the maximum being 1.0). We additionally made pair-wise analyses, and determined difference in the judgement of important ultrasound features among all 21 possible pairs of the seven investigators.

Results: The kappa values were 0.29, 0.18, 0.43 and 0.28, and the Gwet's AC1 values 0.53, 0.34, 0.73 and 0.79 for the most important features in decision making, i.e. microcalcifications, lobulated margins, hypoechogenicity and extrathyroidal spread, respectively. On pair-wise analysis significantly different judgements were present in 85.7%, 61.9%, 76.2% and 57.1% of cases for microcalcifications, lobulated margins, hypoechogenic nodules and extrathyroidal spread, respectively. According to Gwet's AC1, the concordance of TIRADS scores were better than the concordance of individual characteristics on which the scores were based, with inter-observer values ranging from 0.66 to 0.81.

Conclusions: Blinded examination of dynamic video recordings, a condition close to the real world situation, resulted in substantial disagreement among investigators regarding the interpretation of each of the four most important ultrasound characteristics. However, these discrepancies were less reflected in the final TIRADS scores. To which degree these findings influence our decision to recommend thyroid FNA remains to be explored.

OP-02-09

LONG-TERM OUTCOME FOLLOWING LASER THERAPY OF COMPLEX THYROID NODULES

Helle Døssing[1], *Finn Bennedbaek*[2], *Laszlo Hegedüs*[3]
[1]Odense University Hospital, Department of ORL Head & Neck Surgery, Department of ORL Head & Neck Surgery, Odense, Denmark; [2]Herlev University Hospital, Herlev Hospital, Denmark, Dept. of Endocrinology, Herlev, Denmark; [3]Dept. Endocrinol. Odense Uni. Hosp., Odense University, Odense University Hospital, Odense, Denmark

Introduction: Laser therapy (LT) is considered a safe and effective procedure for inducing thyroid nodule necrosis, fibrosis and shrinkage. Little is known about long-term efficacy of LT in benign complex thyroid nodules.

Design and methods: One hundred and ten euthyroid outpatients [28 men and 82 women; median age 48 years (range 17-82)] with a recurrent cytologically benign cystic (≥ 2 ml cyst-volume) thyroid nodule causing local discomfort were assigned to LT. Using one laser fibre, LT was performed after complete cyst aspiration and under continuous ultrasound (US)–guidance. Nineteen patients (17 within 6 months) had surgery after LT. All had benign histology. The median follow-up for the remaining 91 patients was 45 months (range; 12-134).

Results: Remission of the cystic part (volume ≤ 1 ml) was obtained in 82 of 110 (75%) patients after LT. The overall median nodule volume in the 91 patients decreased from 7.3 ml (range; 2.0–50.0) to 0.8 ml (range; 0.0-16.1) ($p<0.001$) at the final evaluation, corresponding to a median reduction of 92% (range; -10% to 100%). The median cyst volume decreased from 5.5 ml (range; 2.0-45.0) to 0.0 ml (range; 0.0-4.0) ($p<000.1$), corresponding to a median reduction of 100% (range; 43%-100%). The median volume of the solid part of the nodule was reduced from 1.7 ml (range; 0.0-17.0) to 0.6 ml (range; 0.0-15.0) ($p<0.001$). These results correlated with a significant decrease in pressure as well as cosmetic complaints. Thyroid function was unaltered throughout and side effects were restricted to mild local pain.

Conclusion: US-guided aspiration and subsequent LT of benign recurrent cystic thyroid nodules results in a satisfactory long-term clinical response in the majority of patients. It is a safe and well-tolerated procedure and significantly reduces long-term recurrence rate, and nodule related symptoms. LT constitutes a clinically relevant alternative to surgery in such patients.

OP-02-10

LONG-TERM EFFICACY OF PERCUTANEOUS LASER ABLATION TREATMENT OF LARGE BENIGN THYROID NODULES

Maria Scutari[1], *Teresa Rago*[1], *Alessandro Brancatella*[1], *Paolo Piaggi*[2], *Paolo Vitti*[1]
[1]Endocrinology Unit, Dept. Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Phoenix, AZ, USA

Introduction: Percutaneous laser ablation treatment (PLA) is a therapeutic option of the benign thyroid nodule (BTN).

Aim: Evaluate the efficacy and complications of PLA in patients with BTN.

Material and Method

Patients (Pts): 300 consecutive Pts (mean age 52.13 ± 12 aa; range 27-88; 260 F and 40 M) with single / dominant large nodules were treated with PLA. The patients had compressive symptoms and / or cosmetic problems with contraindications or refusal of surgery, and they gave informed consent. The results are reported in a subgroup of 194 Pts with a follow-up of 6-60 months.

Methods: The nodules were benign at fine needle aspiration cytology. The Pts were euthyroidism, with undectectable serum calcitonin. Thyroid ultrasonography was performed to determine nodular volume (VN) and ultrasound features. Elastosonography (USE) was performed in 41 cases. A single (n = 155) or double session (n = 39) was performed using 1 (n = 37) or 2 (n = 157) optical fibers, (1.064 nm, neodymium yttrium-aluminum garnet laser source Echolaser; Elesta). The energy delivered was 3600 Joules for the nodules <13 ml and 7200 Joules for those> 13 ml. VN and compressive symptoms were assessed at 6 and 60 months after PLA. A questionnaire was administered to evaluate compressive disorders and aesthetic problems and collected information on tolerability, side effects and complications.

Results: The basal VN was 30.7± 21.86 mL (mean ± SD; range 6.4-146 mL). A reduction of VN (RVN) >50% was observed in 83% of cases (51 ± 20 %, mean ± SD; 2.4-97%) ($p<0.001$). RVN <10% in 3% of cases; 10-30% in 11% and >30% in 87% ($p<0.001$). RVN was 45 ± 18%, 48 ± 19%, 50 ± 18%, 51 ± 22%, 48 ± 27%, and 47 ± 24%, at 6, 12, 24, 36, 48 and 60 months, respectively ($p<0.001$). RVN was greater in nodules with basal VN <24.7 ml than in those >24.7mL (51% vs 40%). The RVN correlated with the delivered energy ($r=0.57$, $p<0.001$), did not correlate with the ultrasound features (p = NS), the TSH (p = 0.86), the thyroglobulin (p = 0.77), the area of basal necrosis (p = NS). The 41 cases examined with USE showed a reduction in elasticity in the treated area. Compressive disorders decreased from 50 to 5% (p = 0.002) and aesthetic ones from 80 to 13%. No complications were observed.

Conclusions: The PLA determines a reduction of the VN and an improvement of the compressive and aesthetic disorders, with no complications.

OP-02-11

TIRADS SYSTEM SCORES VERSUS EXPERT EVALUATIONS FOR NODULE SELECTION FOR FINE NEEDLE ASPIRATION: EXPERTS ARE BETTER. A STUDY EMPLOYING ULTRASOUND VIDEOS OF 123 NODULES EVALUATED BY 7 EXPERTS FROM 7 DIFFERENT THYROID CENTERS

Karoly Rucz[1], *Steen Joop Bonnema*[2], *Andrea Frasoldati*[3], *Laszlo Hegedüs*[4], *Laszlo Jambor*[5], *Zsolt Karanyi*[6], *Gábor László Kovács*[7], *Endre Nagy*[8], *Enrico Papini*[9], *Gilles Russ*[10], *Tamas Solymosi*[11]
[1]Ist Department of Medicine, University of Pecs, Pecs, Hungary; [2]Department of Endocrinology and Metabolism, Odense University Hospital, Department of Endocrinology, Odense University Hospital, Denmark, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense C, Denmark; [3]Department of Endocrinology, Azienda Ospedaliera Santa Maria Nuova DI Reggio Emilia, Italy, Endocrinology Unit of Arcispedale S. Maria Nuova, Reggio Emilia, Italy, Italy; [4]Dept. Endocrinol. Odense Uni. Hosp., Odense University, Odense University Hospital, Odense, Denmark; [5]Medical Imaging Clinic Radiology, University of Debrecen, Clinical Center, Debrecen, Hungary; [6]Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [7]Department of Internal Medicine, Flor Ferenc Hospital, Kistarcsa, Hungary; [8]Division of Endocrinology, Dept. of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [9]Dept. of Endocri. & Metabol. Disease, Ospedale Regina Apostolorum, Albano Roma, Italy; [10]Centre de Pathologie et D'imagerie, La Pitié-Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France; [11]Bugat Hospital, Dept. of Thyroidology, Gyöngyös-Mátrafüred, Hungary

Objective: TIRADS scores are useful in patient selection for fine needle aspiration cytology (FNA). There are few studies which compare the performance of TIRADS scores against the personal judgement of the investigator.

Methods: After viewing, blindedly and without knowledge of the malignant to benign ratio, the video-recordings of ultrasound examinations of 41 consecutively operated malignant and 82 consecutively operated benign thyroid lesions, 7 expert investigators not aware of pathology results, answered 17 TIRADS-related questions, resulting in 29,274 responses. Five TIRADS scores (ATA, AACE/ACE/AME, ACR, ETA, and Korean TIRADS) were generated. Indications for FNA, based on TIRADS scores and on personal judgement of the investigators, were compared.

Results: Cytology was indicated in 74.6% and 82.1% of the nodules, based on the average of TIRADS classification-scores and personal opinion of the investigators, respectively ($p<0.001$). However, there was a less marked difference if only potentially lethal malignancies (i.e. T2-T4 by final histology of the surgical specimen) were considered: 90.2% versus 94.2% for TIRADS score systems and investigators' opinion, respectively ($p=0.03$). FNA was indicated in 76.2% and in 78.9% of benign nodules, TIRADS-system scores and the personal opinions of the investigators, respectively (p= ns). For

nodules < 1 cm, cytology was suggested in 0% (by definition) and 81.9%, based on TIRADS-system scores and the personal opinion of the investigators, respectively ($p<0.01$).

Conclusions: By using TIRADS scores instead of the individual personal judgement of the investigators, 4% of potentially lethal malignancies (T2-T4) were overlooked, while 7.5% of FNAs were spared. Investigators tended to suggest FNA in the majority of nodules < 1 cm, ignoring past and current recommendations against this practice. The complex consequences of variations in practice for cost of follow up, quality of life, and not least disease related morbidity and mortality need to be explored.

OP-02-12

NON-INVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES: AN ANALYSIS OF PROSPECTIVE DATA COLLECTED BY THE ITALIAN THYROID CANCER OBSERVATORY

Valeria Ramundo[1]
[1]Sapienza University of Rome, on Behalf of the Italian Thyroid Cancer Observatory, Italy

Objectives: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was introduced in March 2016 to replace a subset of follicular variant of papillary thyroid carcinoma (FVPTC) with the aim to promote more conservative management of these tumors. The NIFTP Nuclear Standardized Scoring System has been validated to evaluate the nuclear features of papillary thyroid carcinoma. The aim of this study was to evaluate the rate of NIFTP among FVPTC and to analyze differences in pathological reports of different Italian thyroid clinical centers.

Methods: The Italian Thyroid Cancer Observatory (ITCO) was established in 2013 to collect prospective data on thyroid cancers consecutively diagnosed in member centers (currently 48 sites across the country). We collected data of all pathologically confirmed well-differentiated thyroid cancers cases since March 2016, present in the database on 4 March 2019. Centers with at least one NIFTP were included in the study.

Results: A total of 3701 patients (72.4% females, median age 50 years, interquartile range 21 years) belonging to 17 centers were enrolled. Among these patients, the prevalence of FVPTC and NIFTP was 24.4% and 1.8%, respectively. Considering the ITCO centers included in the study, the rate of NIFTP ranged from 0.9% to 33.3%, with a higher prevalence in the northern regions. In 31 centers, no single case of NIFTP was reported.

Conclusions: This study showed a high variability of pathological reports for NIFTP in different Italian thyroid centers, probably related to an interobserver variation among pathologists in reporting nuclear features and capsular invasion of FVPTC. These preliminary data suggest that a better standardization for NIFTP diagnosis is needed, to optimize treatment and follow-up intensity of these tumors.

Oral Session 3: Thyroid Hormone, Metabolism and Action

OP-03-13

AGE-DEPENDENT RECOVERY FROM HYPERGLYCAEMIA IN HYPOTHYROID DIO2-DEFICIENT ZEBRAFISH

Anne Houbrechts[1], *Veerle Darras*[1]
[1]Laboratory of Comparative Endocrinology, Biology Department, Ku Leuven, Leuven, Belgium

Objectives: Thyroid hormones (THs) are important regulators of carbohydrate metabolism and hypothyroid patients often show disturbed glucose homeostasis. Also, activity-reducing mutation in human type 2 deiodinase (DIO2) enzyme, important for TH activation in peripheral tissues, has been associated with an increased risk for insulin resistance and type 2 diabetes mellitus. We investigated the link between Dio2 deficiency/hypothyroidism and glucose homeostasis at different levels using male Dio2-knockout (Dio2KO) zebrafish which show severely reduced T_3 levels throughout the body. We used adult fish from 6 months (M) up to 24M to find out if there were age-dependent changes in the observed glucose-related phenotype.

Methods and results: Compared to wild-type (WT) zebrafish, young adult Dio2KO zebrafish (6-9M) were hyperglycaemic. This was accompanied by increased insulin and glucagon expression in gastrointestinal tract (including pancreas). At 18-24M however blood glucose levels in mutants were normalized while insulin and glucagon expression remained upregulated. Insulin receptor expression in muscle was downregulated at all stages while glucagon receptor expression was only lowered at 18-24M. Expression of glucose transporter 2 and 12 were decreased in gastrointestinal tract at all stages except 6M, while their expression in muscle remained stable except for 9M. Investigation of hepatic gluconeogenesis showed reduced expression of glucose-6-phosphatase but not phosphoenolpyruvate carboxykinase at 9-18M while expression of hexokinase and pyruvate kinase, involved in glycolysis in muscle, were reduced at 6-9M. Finally, histological analysis showed that at 6-9M pancreatic islet size and total islet cell number were similar in WT and Dio2KO zebrafish while both parameters were almost 4-fold higher in mutants at 18M.

Conclusion: Young adult Dio2KO zebrafish are hyperglycaemic and show signs of insulin resistance. There is however a spontaneous normalization of glycaemia in older fish which may be linked to a compensatory increase in pancreatic islet size in Dio2KO zebrafish.

OP-03-14

DEIODINASES ARE DYNAMICALLY EXPRESSED IN FAPS DURING MUSCLE REGENERATION

Cristina Luongo[1], *Daniela Di Girolamo*[1], *Maria Angela De Stefano*[1], *Raffaele Ambrosio*[1], *Caterina Miro*[1], *Monica Dentice*[1], *Domenico Salvatore*[1]
[1]University of Naples Federico II, Naples, Italy

Fibro-adipogenic precursor cells (FAPs) are a heterogeneous population of intramuscular multipotent cells that give rise to fibroblasts and adipocytes. FAPs are activated in response to muscle injury, and cooperate with inflammatory and muscle stem cells to promote muscle regeneration. In pathological condition, as muscular dystrophies, this coordinated response is lost and then an accumulation of FAPs is observed that is responsible for a maladaptive fibrosis, ectopic fat deposition and impaired muscle regeneration.

We hypothesized that in adult FAPs adipocyte-fibroblast fate decisions involve a tight regulation of TH availability. To this aim, we (i) characterized D2 and D3 expression in adult FAPs, (ii) determined TH and D2 role in adipogenic FAPs differentiation (iii) analyzed how *in vivo* modulation of TH availability by D2 downregulation affect adipogenic process.

D2 and D3 were expressed in FAPs. Furthermore, THTs and TRs were also highly expressed in FAPs, thus suggesting that TH signal is active in this cell context.

Next, we determined the role of deiodinases in FAPs during in vitro adipogenic differentiation. We cultured FAPs under adipogenic condition (AIM) and measured the expression of deiodinases, THTs and TRα. D2, THTs and TRα mRNA were up-regulated while D3 was down-regulated compared to NM (normal condition). Furthermore, when FAPs were cultured in the presence of exogenous THs, we observed increased expression of relevant adipogenic genes. On the contrary, FAPs cultured in the presence of 30 nM rT3, a D2 inhibitor, had reduced in vitro adipogenic potential.

Finally, we speculated that D2 might play a critical role in muscle fatty infiltration in vivo. To test this hypothesis, we injected glycerol into gastrocnemius and tibialis anterior muscles of D2WT *vs* D2KO mice (a muscle injury model, which has been demonstrated to induce fatty infiltration). The expression of different adipogenic markers was significantly reduced in D2KO mice respect to WT mice. Oil Red O staining on WT mice *vs* D2KO mice after 7 days upon glycerol injection confirmed a decrease in the number of Red Oil + cells in D2KO mice.

Taken together, these data show that TH signalling is active in FAPs and that D2-produced T3 is required for a full adipogenic FAP differentiation.

Our work could have numerous applications in muscle regeneration research for muscle dystrophies diseases, by providing a better understanding of the mechanisms underlying TH availability in the control of FAPs adipogenic differentiation.

OP-03-15

RELEASE OF ENDOGENOUS 3-IODOTHYROACETIC ACID IN A MOUSE MODEL OF SHORT-TERM BRAIN ISCHEMIA

Francesca Tozzi[1], *Grazia Rutigliano*[2], *Marco Borsò*[3], *Grazia Chiellini*[4], *Alessandro Saba*[5], *Nicola Origlia*[6], *Riccardo Zucchi*[7]

[1]Nrc Institute of Neurosciences, San Miniato, Italy; [2]Scuola Superiore Sant'anna, National Research Council (Cnr), University of Pisa, Pisa, Italy; [3]University of Pisa; [4]Dept. of Pathology, University of Pisa, Pisa, Italy, Pisa, Italy; [5]University of Pisa, Pisa, Italy; [6]Nrc Institute of Neurosciences; [7]University of Pisa, Dept. of Pathology, University of Pisa, Pisa, Italy

Objectives: While 3-iodothyronamine (T1AM) and 3-iodothyroacetic acid (TA1) have been detected in rodent tissues and in human blood, it is still unclear under which physiological and/or pathophysiological conditions these compounds are produced or released. Since we have recently reported that exogenous T1AM reduces ischemia-induced synaptic dysfunction in mouse, we investigated whether ex vivo brain ischemia is associated with T1AM or TA1 release.

Methods: Horizontal slices including entorhinal cortex and hippocampus were obtained from C57bl mice. Slices were exposed to an oxygen-glucose deprivation protocol (OGD) for 10 min and then perfused for 50 min with standard oxygenated buffer, using a peristaltic pump at a rate of 2 ml/min. The effluent was collected 5-10 min intervals, and T1AM and TA1 were assayed by mass spectrometry coupled to liquid chromatography. To evaluate cellular necrosis, the release of lactate dehydrogenase (LDH) was measured, while functional injury was determined by the reduction of field excitatory post-synaptic potential (fEPSP).

Results: Results are mean±SEM of 6 experiments. At the baseline, a minimum release of T1AM or TA1 was detected, which did not reach the threshold of statistical significance (0.5±0,5 and 0.7±0.4 ng/ml, respectively). During OGD, T1AM and TA1 concentrations reached 2.5±1.7 and 11.8±3.4 ng/ml, ($P<0.05$ for TA1) and in the first 10 min of reoxygenation they averaged 1.6±1.1 and 6.5±2.9 ng/ml, respectively ($P<0.05$ for TA1), with progressive decrease at later times. No release of LDH was observed, while fEPSP decreased to 44±19% of the baseline.

Conclusions: In a model of functional brain injury ex vivo, significant release TA1 was observed, in the absence of biochemical evidence of necrosis. It remains to be determined whether TA1 is produced by T1AM oxidative deamination and whether this phenomenon should be considered as a deleterious effect of ischemia or rather as a protective event.

OP-03-16

T3-MEDIATED CARDIAC HYPERTROPHY IS A PHYSIOLOGICAL EFFECT OF CANONICAL THYROID HORMONE RECEPTOR ALPHA ACTION

Daniela Geist[1], *Sebastian Hönes*[1], *Dagmar Führer*[1], *Kristina Lorenz*[2], *Lars C. Möller*[1]

[1]Department of Endocrinology, Diabetes and Metabolism, University Hospital Essen, Essen, Germany; [2]Leibniz-Institut für Analytische Wissenschaften, Dortmund, Germany, Institute of Pharmacology and Toxicology, University of Wuerzburg, Würzburg, Germany

Objectives: Thyroid hormones (TH) play a major role in the cardiovascular system. Thyroid hormone receptors (TRs) α and β can either influence gene transcription (canonical action, type 1) or rapidly activate cellular signaling pathways (noncanonical action, type 3). Triiodothyronine (T_3) had been shown to cause cardiac hypertrophy (CH) in humans and mice. Aim of this study was to determine which receptor, TRα or TRβ, and which mode of action, type 1 or 3, mediates CH.

Methods: We studied wildtype (WT), TRα knockout ($TR\alpha^0$), TRβ knockout ($TR\beta^{KO}$) mice and a knock-in mouse model with a mutation in the TRα DNA-binding domain ($TR\alpha^{GS}$) which abrogates canonical TRα action while noncanonical signaling is preserved. Mice were treated with T_3 (400 ng/mL in drinking water) for 7 weeks. Hearts were studied with echocardiography at day 0 and after 3.5 and 7 weeks. We measured heart weights (HW; ventricles) after 7 weeks and compared thickness of the intraventricular septum (IVS) and the left ventricular posterior wall (LVPW).

Results: Ventricular weight did not differ between $TR\beta^{WT}$ and $TR\beta^{KO}$ mice (183mg and 167mg, n.s.) but $TR\alpha^0$ HW was significantly lower than that of $TR\alpha^{WT}$ littermates (127mg and 181mg, $p<0.0001$). Wall thickness (IVSd and LVPW) were measured over time and confirmed a lack of a T_3-mediated development of CH only in $TR\alpha^0$ mice, demonstrating that the T_3 effect on CH is mediated by TRα. Next, $TR\alpha^{GS}$ mice were compared to their WT littermates: Ventricular mass was increased by T_3 in WT (206mg) but not in $TR\alpha^{GS}$ mice (138mg, WT vs. $TR\alpha^{GS}$ $p=0.0027$). WT mice had a significantly thicker IVSd than $TR\alpha^{GS}$ mice (0.81mm and 0.67mm; $p=0.0052$). Thus, noncanonical TRα signaling is not responsible for T_3-induced and TRα-mediated CH.

Conclusion: T_3-induced cardiac hypertrophy is mediated by canonical TRα action.

OP-03-17

THE RS17606253 MCT10 POLYMORPHISM DOES NOT AFFECT THYROID HORMONE LEVELS IN ATHYREOTIC PATIENTS

Fabio Maino[1], *Silvia Cantara*[1], *Claudia Ricci*[1], *Carlotta Marzocchi*[1], *Furio Pacini*[1], *Maria Grazia Castagna*[1]

[1]Department of Medical, Surgical and Neurosciences, Uoc Endocrinology, University of Siena, Siena, Italy

Introduction: Since thyroid hormone action takes place intracellularly, transport across the plasma membrane by specific TH transporters, such as MCT8, MCT10 and OATP1C1, is necessary. Several single nucleotide polymorphisms (SNPs) in genes encoding for transporters have been associated with serum thyroid hormone concentrations with inconsistent results. hypothyroid patients' preference for L-T4 + L-T3 replacement therapy.

Aim: The aim of this study was to assess the clinical and biochemical significance of the rs17606253 in *SLC16A10* gene alone and in combination with the *DIO2* Thr92Ala variation in athyreotic patients.

Methods: Patients (n=100) already characterized for the DIO2 gene polymorphisms, were analyzed for the presence of polymorphisms/mutations in the SLC16A10 gene, which encodes for the transporter MCT10. The variants were analyzed alone or in combination through a dominant and recessive model with respect to the post-surgical serum levels of FT3.

Results: Regarding to *SLC16A10* gene polymorphism rs17606253, both wild type and heterozygous patients had a significant reduction in FT3 post-surgical levels ($p=0.01$ and $p<0.0001$; respectively). No difference was observed in the rare homozygous group (5% of the patients). According with rs225014 in *DIO2* gene, wild type patients had similar pre- and post-surgical FT3 levels ($p=0.097$) while heterozygous and rare homozygous patients displayed a significant reduction in FT3 post-surgical levels ($p<0.0001$ and $p=0.01$; respectively). When we stratified patients into two groups ("FT3 un-changed" and "FT3 reduced") using a cut-off of at least 0.5 pg/ml as a significant variation between pre- and post-surgical FT3 values, the rs17606253 was not statistically associated with reduced FT3 levels after surgery at genotype and at allele levels. On the contrary, the Thr92Ala (rs225014) in *DIO2* gene was confirmed statistically associated with reduced FT3 levels after surgery with a $p=0.035$ at genotype level and $p=0.014$ at allele level resulting in an odd ratio (OR) of 2.116 (1.157-3.870 95% CI). We, then, performed the analysis of allele distribution for rs225014 in *DIO2* gene in combination with rs17606253 in *SLC16A10* gene and we found a statistically significant difference ($p=0.017$), but this difference was only linked to allele distribution of rs225014 in *DIO2*.

Conclusion: we confirm the role of *DIO2* (rs225014) polymorphism on T3 levels. On the contrary *MCT10* (rs17606253) polymorphism seems do not impair hormone levels in athyreotic patients treated with levo-thyroxine therapy.

OP-03-18

TRANSTHYRETIN REGULATES NEURAL STEM CELL FATE IN THE ADULT MOUSE BRAIN

Pieter Vancamp[1], *Jean-David Gothié*[2], *Cristina Luongo*[3], *Anthony Sebillot*[4], *Barbara Demeneix*[5], *Sylvie Remaud*[4]
[1]Muséum National D'histoire Naturelle, Cnrs, Umr 7221, Paris, France; [2]Montreal Neurological Institute & Hospital, Mcgill University, Department of Neurology & Neurosurgery, Montreal, Canada; [3]University of Naples Federico II, Naples, Italy; [4]Muséum National D'histoire Naturelle, Centre National de la Recherche Scientifique, Umr 7221 Evolution des Régulations Endocriniennes, Paris, France; [5]Muséum National D'histoire Naturelle/Cnrs, Centre National de la Recherche Scientifique, Umr 7221 Evolution des Régulations Endocriniennes, Paris, France

Objectives: Choroid plexus epithelial cells produce and secrete cerebrospinal fluid containing proteins among which Transthyretin (TTR). TTR binds thyroid hormones (THs), facilitating their distribution to target brain cells. Adult *Ttr* knockout mice displayed increased neural stem cell (NSC) survival in the subventricular zone (SVZ). We hypothesized TTR can also affect NSC fate, since the intracellular TH status determines NSC commitment to either a neuronal or an oligodendroglial fate.

Methods: We first investigated *Ttr* mRNA and protein levels by RTqPCR and immunohistochemistry in isolated neuroblasts *versus* oligodendrocyte precursor cells (OPCs), both *in vivo* and *in vitro* using SVZ-derived neurospheres. We then studied the balance between neurogenesis and oligodendrogenesis *via* immunohistochemistry in wild-type and *Ttr* knockout mice, including males and females to assess potential gender differences.

Results: In addition to the choroid plexus, *Ttr* mRNA and protein were detected in SVZ-derived neuroblasts, but not in OPCs. Furthermore, *Ttr* mRNA levels gradually increased during neuronal determination, while remaining low in cells committed to an oligodendroglial fate. *Ttr* knockout male and female mice displayed increased oligodendrogenesis at the expense of neurogenesis in the lateroventral SVZ. However, in the dorsal SVZ, adjacent to the corpus callosum, neurogenesis was decreased only in *Ttr* knockout males. Moreover, an increased ratio of young neuronal precursors *versus* mature neuroblasts in the whole SVZ suggested hampered neuronal differentiation. Lastly, OPC numbers in the corpus callosum were increased only in *Ttr* knockout males.

Conclusions: Our data indicate that a local hypothyroid state in the adult SVZ due to a lack of TTR alters TH-dependent NSC fate. However, *Ttr* expression in SVZ-derived cells suggests an unexpected, intracellular role in addition to its TH-distribution function. Moreover, gender-specific differences imply that TH signalling differentially affects male and female SVZ microdomains (lateroventral *versus* dorsal SVZ), providing a hint on men-women dissimilarities in TH-related neurological disorders.

Oral Session 4: Thyroid Cancer Management

OP-04-19

SECOND FINE-NEEDLE ASPIRATION CYTOLOGY IN A SERIES OF BENIGN THYROID NODULES: ARE THE 2015 ATA GUIDELINES RECOMMENDATIONS HELPFUL?

Annalisa Bufano[1], *Gilda Dalmazio*[1], *Noemi Fralassi*[1], *Fabio Maino*[1], *Raffaella Forleo*[1], *Furio Pacini*[1], *Maria Grazia Castagna*[1]
[1]Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy

Introduction: Malignancy rates of only 2% have been reported in large retrospective series that analyzed the utility of systematic repeat fine needle aspiration cytology (FNAC) in nodules with prior benign cytology results. The American Thyroid Association (ATA) guidelines recommended to repeat FNAC in benign nodules within 12 months in the presence of high suspicion ultrasonography (US) pattern; instead, in nodules with low to intermediate suspicion US pattern, FNAC should be repeated in the presence of US evidence of growth or development of new suspicious US features during follow-up.

Aim: to validate the ATA recommendations in a series of benign thyroid nodules re-evaluated by a second FNAC during follow-up.

Patients: We retrospectively evaluated 532 patients (654 thyroid nodules), 81% women and 19% men with an initial cytological diagnosis of benign nodule (Thy2), who underwent at least one repeat FNAC during follow-up (median 4.5 years).

Results: Thy2 cytology was confirmed in 631/654 nodules (96.5%), while 20/654 (3.0%) were reclassified as Thy3 and 3/654 (0.5%) as suspicious/malignant nodules (Thy4/Thy5). The US features able to predict a possible worsening of the nodule cytology were a large volume at the first evaluation (p=0.008) and the maximum diameter at diagnosis (p=0.01). Indeed indeterminate/malignant nodules were found at repeat FNAC in 2/608 (0.32%) nodules with maximum diameter <40 mm and in 1/46 (2.4%) nodules with maximum diameter ≥40 mm (p=0.01). On the contrary, a volumetric increase ≥50% during the follow-up was not associated with a higher risk of suspicious/malignant cytology at the time of the second FNAC (p=0.55). In a subgroup of 321 nodules, US risk class defined according to ATA guidelines was available; 225/321 (70%) were classified at low risk, 60/321 (18.7%) at intermediate risk and 36/321 (11.3%) nodules at high risk. At the time of second FNAC, rate of malignant nodules was higher in high risk nodules (2.7% versus 0% in intermediate, 0.4% in low risk nodules). We evaluated the cancer rate at the time of second FNAC in low/intermediate risk nodules, according to changes in volume, and we didn't find any difference between stable nodules and nodules with a significant volume increase (>50%) (0.8% in stable nodules; 0% in nodules with increasing volume during follow-up).

Conclusion: We demonstrate that benign nodules (Thy2), initially classified at low risk according to ATA US stratification, can be managed only with US follow-up, also in the presence of volume increase. On the contrary, an additional FNAC can be useful in nodules classified at high risk, since cytological reassessment could reduce the rate of false negative cytological results.

OP-04-20

MOLECULAR TESTING BY THE CUSTOM PTC MASS ARRAY GENOTYPING PLATFORM IN THYROID FINE NEEDLE ASPIRATES

Gabriele Pogliaghi[1], *Carla Colombo*[2], *Marina Muzza*[3], *Sonia Palazzo*[4], *Giacomo Gazzano*[4], *Guia Vannucchi*[1], *Leonardo Vicentini*[5], *Luca Persani*[6], *Laura Fugazzola*[7]
[1]Division of Endocrine and Metabolic Diseases, Istituto Auxologico Italiano IRCCS, Milan, Italy, Italy; [2]Division of Endocrine and Metabolic Diseases, Istituto Auxologico Italiano IRCCS, Milan, Italy, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [3]Division of Endocrine Diseases, Milancusano Milanino, Italy; [4]Pathology Unit, IRCCS Istituto Auxologico Italiano, Milan, Milan, Italy; [5]Endocrine Surgery Unit, IRCCS Istituto Auxologico Italiano, Milan, Milan, Italy; [6]University of Milan, IRCCS Istituto Auxologico Italiano, Ospedale San Luca, Milan, Italy; [7]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, Endocrine Unit, Fondazione Policlinico IRCCS, Milan, Italy, Milan, Italy

Background: Molecular testing is a diagnostic tool useful to guide the clinical management of thyroid nodules with indeterminate cytology. Aim of the present study was to test the accuracy of a custom Mass Array platform (PTC-MA), recently developed by our group, which allows the simultaneous detection of the 13 hotspot mutations and 7 fusion genes more frequently found in thyroid cancer (such as BRAF, RAS, TERT, PI3K, PAX8/PPARγ, RET/PTC, etc) in a time (2 days) and cost-effective (150 euros/sample) manner. *Patients*: We submitted to cytology and molecular analysis 109 thyroid nodules, 55 of whom have undergone thyroidectomy (TX) at the time of the present abstract submission. Only cases with histological data are shown.

Results:

Cytology class (Bethesda)	Genetic analysis	Histology
I n=3	WT n=3	Nodular hyperplasia (NH) n=2
		Riedel's thyroiditis n=1
II n=3	WT n=3	NH n=3
III/IV n= 35		
	WT n=25	Follicular adenoma (FA)/NH n=20
		Follicular variant PTC n=3
		Classic variant PTC (CPTC) n=2
	$BRAF^{V600E}$ n=2	CPTC n=2
	$TERT^{c.-124C>T}$ n=2	FTC n=2
	$H\text{-}RAS^{Q61K}$ n=1	NIFTP n=1
	$HRAS^{Q61R}$ n=4	FA n=4
	$TERT^{c.-124C>T}$ and $N\text{-}RAS^{Q61R}$ n=1	Atypical FA n=1
V/VI n=14	$BRAF^{V600E}$ n=10	
	$BRAF^{V600E}$ and $TERT^{c.-124C>T}$ n=2	CPTC n=12
	RET/PTC1 n=1	CPTC n=1
	RET/PTC3 n=1	Solid variant PTC n=1

The genetic data obtained on the FNA were always confirmed on the histological sample. The analysis of these preliminary data showed a sensitivity of 76%, a specificity of 84% and an accuracy of 80%.

Conclusions: The PTC-MA panel represents a useful approach to identify malignant thyroid nodules. The benefit of this method is the low cost and the short time lapse needed. Improvement of sensitivity and specificity of the method will be obtained increasing the cytological and surgical series. The implementation of the method with the analysis of rarer genetic alterations will likely allow to reduce the number of false negative cases.

OP-04-21

RECOMMENDATIONS FOR RADIOIODINE REMNANT ABLATION IN DIFFERENTIATED THYROID CANCER PATIENTS ACCORDING TO 2018 ITALIAN CONSENSUS: DOES IT CHANGE ANYTHING?

Raffaella Forleo[1], *Fabio Maino*[2], *Noemi Fralassi*[2], *Silvia Cantara*[2], *Filomena Barbato*[2], *Lucia Brilli*[2], *Tania Pilli*[2], *Marco Capezzone*[2], *Furio Pacini*[2], *Maria Grazia Castagna*[2]

[1]Siena, Italy; [2]Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy

In October 2016 the American Joint Committee on Cancer (AJCC) published the 8th edition of the AJCC/TNM cancer staging system. The effect of most of the changes in the new edition was the downstaging of a significant number of patients into lower stages, reflecting their low risk of thyroid cancer-related death. One of the most relevant modification refers to the role of the microscopic extra-thyroidal tumor invasion (MEI), which is no longer considered as criterion for the classification of T3 tumors. In the recent 2018 Italian Consensus (ITA), the 8th edition of the AJCC/TNM is used to define the risk class of DTC patients and also the indication for radioiodine ablative therapy.

With the present study we want to assess 1) how many patients with DTC are downstaged using the 2018 ITA Consensus; 2) the rate of patients in whom ablative therapy is not routinely indicated; 3) the risk of delaying distant metastases diagnosis in patients not submitted to radioiodine ablative therapy according to the 2018 ITA Consensus.

We retrospectively evaluated 373 differentiated thyroid cancer patients (72% females) treated with total thyroidectomy and radioiodine ablative therapy. MEI was present in 177/373 (47.4%) patients and 170/177 (96%) of them were classified at intermediate risk according to ATA risk class. Seventy-one of these 170 intermediate risk patients (41.7%) had only MEI as negative prognostic factors and were re-classified at low risk using ITA risk stratification. The rate of low risk patients was 35.6% using ATA guidelines and raised to 54.8% with ITA consensus.

A significant difference in the radioiodine recommendations was observed between ATA and ITA ($p<0.0001$). Specifically, radioiodine ablation was not indicated in 239/373 (64%) patients according to the ITA consensus and in 145/373 (38.8%) patients according to the ATA guidelines. Twenty-one/373 (5.6%) patients had distant metastases at post-ablative whole body scan. The rate of metastatic disease in patients without indication for radioiodine therapy was 4/144 (2.7%) according to ATA guidelines and 9/328 (2.7%) according to ITA consensus.

In conclusion, the ITA consensus significantly decrease the number of patients treated with radioiodine ablative therapy without difference in losing patients with distant metastases, when compared to ATA guidelines.

OP-04-22

IMPACT ON QUALITY OF LIFE AND TOLERABILITY OF US-GUIDED LASER ABLATION FOR IODINE REFRACTORY LYMPH-NODE METASTASIS OF THYROID CARCINOMA

Enrico Papini[1], *Giancarlo Bizzarri*[2], *Carmela Coccaro*[1], *Agnese Persichetti*[1], *Marco Chianelli*[1], *Antonio Bianchini*[2], *Rinaldo Guglielmi*[1]

[1]Dept. of Endocri. & Metabol. Disease, Ospedale Regina Apostolorum, Albano Roma, Italy; [2]Dept. of Diagnostic Imaging, Ospedale Regina Apostolorum, Albano Roma, Italy

Background: Ultrasound (US)-guided laser ablation (PLA) is reported as an effective procedure for the control of local recurrences of thyroid carcinoma. Aim of the study was to evaluate the tolerability of the procedure and its impact on the QoL of the patients

Patients and Methods: From December 2013 to December 2018, 38 cervical recurrences were treated with PLA. All patients (24 papillary, 4 follicular and 4 medullary cancers) had radioiodine-refractory recurrences after total thyroidectomy and cervical lymph-node dissection. Patients gave their informed consent to undergo PLA as an alternative option to surgery. Treatment was performed in the outpatient clinics with a Nd:YAG laser source (Echolaser, Elesta, Italy) and an energy delivery of 500-6000 Joules on the basis of volume and structure of the lesion. After the procedure, patients

were given an analgesics injection. Intraprocedural pain was assessed with a validated questionnaire and after 6 months patients were requested about the impact of the procedure on their quality of life and the loss of working days.

Results: Intraprocedural pain was defined as well tolerated by 26 of 32 patients (81.2%). No major complication was observed and no patient required hospitalization. Mean volume of recurrences decreased from 3.1±4.9 at baseline to 0.07±0.8 ml (-80%) at 12 months. After six months 28/32 (87.5%) patients declared that PLA treatment did not adversely influence their present QoL and 4/32 (12.5%) complained of minor persistent discomfort. No loss of working days was recorded besides the two days immediately following treatment.

Conclusions: PLA is a well-tolerated minimally invasive outpatient procedure for local control of cervical radioiodine-refractory lymph-node metastasis. PLA induced a significant decrease of the burden of disease and had no relevant adverse effect on the QoL and the working activities of the vast majority of patients.

OP-04-23

PREDISPOSING FACTORS OF RESPONSE OR RESISTANCE TOTYROSINE KINASE INHIBITORS (TKIS) THERAPY IN METASTATIC MEDULLARY THYROID CARCINOMA (META-MTC) PATIENTS

Katerina Saltiki[1], *George Simeakis*[1], *Sparti Ntai*[1], *Paraskevi Konstantakou*[1], *Evanthia Kassis*[1], *Maria Alevizaki*[1]
[1]Endocrine Unit, Dept.Clinical Therapeutics, Medical School National Kapodistrian University, Athens, Greece

Objectives: Locoregional interventions and/or TKIs administration are indicated for patients with metastatic/rapidly progressive MTC. Aim of our study was to investigate possible factors predisposing to TKIs treatment response-resistance in meta-MTC patients followed-up in our Unit since 1979.

Methods: 42/297 MTCs had metastatic disease. Therapeutic interventions and clinical course were recorded.

Results: 28/42(66.7%) meta-MTCs were men, sporadicMTC=34, age at diagnosis:5-78yrs. Tumor size:3.3±1.9cm, multifocality:45.0%, lymph-node infiltration:100.0%, capsular invasion:84.6%, soft-tissue invasion:76.5%. Calcitonin-doubling-time: 2-36 months. 10/42pts (23.8%) presented with distant metastases at diagnosis located in: mediastinum (4/10), lungs (2/10), liver (1/10) and ≥2loci (3/10). Distant metastases during follow-up (0.8–25yrs) presented in 32/42pts located in: mediastinum (43.8%), liver (18.8%), lungs (9.4%), bones (9.4%) and ≥2loci (12.5%). 50.0% underwent locoregional therapies: surgery (23.7%), bone radiotherapy (21.1%), liver chemo-radioembolization (10.5%). 32/42pts (76.1%) received TKIs; 18 underwent locoregional therapies combined with TKIs. Vandetanib was the first-line TKI, administrated in 22pts while others TKIs were used in 10pts; 5/10 received Vandetanib as second-line TKI. Overall, Vandetanib was administrated in 27/42 pts (64.3%), initiation time: 0.2-26yrs from diagnosis. During a follow-up period of 0.3-7yrs response to therapy was: partial response (25.0%), structural stabilization (41.7%), progression (33.3%). Most Serious Adverse Events (SAE) concerned gastrointestinal (17/27pts), skin (13/27), hypertension (5/27), polycythemia (3/27), QT-prolongation (2/27). SAE related dose-reduction (6/27pts), discontinuation (1/27). Drug interruption due to disease progression: 11/27pts. More favourable disease course was observed in familialMTC vs sporadicMTC (partial response: 37.5%vs3.0%, stabilization: 25.5%vs36.4%, progression: 25.0%vs24.2%, death: 12.5%vs36.4%, p=0.026). Patients with SAE Grade III-IV during the first 4 months of TKI therapy showed better response (p=0.043); those under TKIs with biochemical progression showed more often structural progression at a later point(p=0.002). Failure in Vandetanib therapy was observed in 10/27pts (period:0.3-7yrs) and in Cabozantinib (second-line) in 6/10pts (period:0.2-1.5yrs).

Conclusions: TKIs administration with or without locoregional therapies results in disease stabilization in 67.0% of patients with metastatic MTC. SAEs may predict better response to therapy while biochemical escape under TKI treatment needs to be followed-up closely as it may indicate disease progression.

OP-04-24

OCCURENCE OF SECOND PRIMARY MALIGNANCY IN MEDULLARY THYROID CARCINOMA (MTC) PATIENTS

George Simeakis[1], *Katerina Saltiki*[1], *Paraskevi Konstantakou*[1], *Evangelia Zapanti*[1], *Evanthia Kassis*[1], *Maria Alevizaki*[1]
[1]Endocrine Unit, Dept.Clinical Therapeutics, Medical School National Kapodistrian University, Athens, Greece

Objectives: Coexistence of two different malignancies is frequently reported and sometimes occurs in the context of well-established syndromes. Multiple Endocrine Neoplasia 2 (MEN2) is a classical paradigm regarding MTC. Rearranged during transfection (*RET*), is an oncogenic driver activated in different kinds of neoplasias including: MTC, Differentiated Thyroid Cancer (DTC), Non-Small Cell Lung Cancer (NSCLC) and others. We have previously reported an increased prevalence of DTC in familialMTC patients carrying the *RET* (G533C) mutation. The aim of this study was to record the extrathyroidal malignancies in MTC patients of our Unit.

Methods: Of 297 MTC patients followed-up in our Unit 57 (19.2%) presented with second malignancy. They were classified in 3 groups; Group1: MTC+Extrathyroidal malignancy, Group2: MTC+DTC, Group3: MTC-alone.

Results: Patients were followed for 1-15 yrs (median: 5), age at diagnosis: 48.33 ± 15.1 yrs. 19/57 patients (Group1) were diagnosed with an extrathyroidal malignancy, 2-10 yrs after MTC, the location-type of malignancy being as follows: Breast (5/19), Kidney-Bladder (3/19), Sarcoma (2/19), Lung-NSCLC (2/19), Prostate (1/19), Colon (1/19) and Chronic Myeloid Leukemia (1/19). Prior to MTC, 3 patients were diagnosed with Head & Neck cancer (esophagus-tongue-vocal cords) and 1 patient with Melanoma. In Group 2 (38/57 patients) DTC was diagnosed concomitantly with MTC. Group1 patients vs Group2 & Group3 presented with worse disease stage at diagnosis (Stage I+II: 35.3% vs 69.2% vs 51.0%, Stage IV: 50.0% vs 7.7% vs 22.2%, p=0.006). Accordingly they had more frequently lymph node infiltration (75.0% vs 28.9% vs 47.5%, p=0.007) as well as capsular and soft tissue invasion (75.0% vs 21.6% vs 41.5% and 56.3% vs 10.5% vs 21.3%, p=0.001, respectively). Tumor size was larger in Group1 pts (2.42±2.01 vs 1.2±0.9 vs 1.73±1.5cm, p=0.003) and higher pre- and post-operative Calcitonin levels were recorded in them (p=0.028). C-cell hyperplasia was more frequent in Group2 pts (p=0.003). No differences were found regarding sex, family history, multifocality or distant metastases at diagnosis and follow-up.

Conclusions: Synchronous or asynchronous primary malignancies may occur with MTC. *RET* oncogenicity through several mechanisms (activating mutations, increased expression, risk-associated SNPs) has been proposed as a possible shared aetiopathogenic mechanism. Elucidation of the common genetic pathways possibly involved in coexistence of two phenotypically different types of malignancy could be crucial for precision medicine and tailor-made therapy.

Oral Session 5: Thyroid Signal During Development

OP-05-25

IN VIVO CHEMICAL GENETIC SCREENS IN ZEBRAFISH EMBRYOS REVEAL SIGNALING PATHWAYS REGULATING EARLY THYROID DEVELOPMENT

Robert Opitz[1], *Benoit Haerlingen*[2], *Isabelle Vandernoot*[2], *Achim Trubiroha*[3], *Pierre Gillotay*[2], *Nicoletta Giusti*[2], *Sabine Costagliola*[4]

[1]Inst. Exp. Ped. Endocrinol., Charité Universitätsmedizin Berlin (Germany), Institute of Interdisciplinary Research in Molecular Human Biology (IRIBHM), Université Libre de Bruxelles (Belgium), Berlin, Germany; [2]Institute of Interdisciplinary Research in Molecular Human Biology (IRIBHM), Université Libre de Bruxelles (Belgium), Belgium; [3]IRIBHM, Université Libre de Bruxelles, Brussels, Belgium, Institute of Interdisciplinary Research in Molecular Human Biology (IRIBHM), Université Libre de Bruxelles, Belgium; [4]ULB, IRIBHM, Brussels, Belgium

Defects in embryonic development of the thyroid gland are a major cause for congenital hypothyroidism in human newborns but the underlying molecular mechanisms remain still poorly understood. Organ development relies on a tightly regulated interplay between extrinsic signaling cues and cell intrinsic factors. At present, however, there is limited knowledge about the specific extrinsic signaling cues that regulate foregut endoderm patterning, thyroid cell specification and subsequent morphogenetic processes in thyroid development.

In this study, we used zebrafish embryos to perform a series of *in vivo* phenotype-driven chemical genetic screens to identify signaling cues regulating embryonic thyroid development. For this purpose, we treated zebrafish embryos during different developmental periods with a library of small molecule compounds known to manipulate the activity of major signaling pathways and scored phenotypic deviations in thyroid, endoderm and cardiovascular development using whole mount *in situ* hybridization and transgenic fluorescent reporter models.

Systematic assessment of drugged embryos recovered a range of thyroid phenotypes including expansion, reduction or even lack of the thyroid anlage, defective thyroid budding as well as a hypoplastic, enlarged or overtly disorganized presentation of the thyroid primordium. Our pharmacological screening identified BMP and FGF signaling as key factors for thyroid specification and early thyroid organogenesis, highlight the importance of low Wnt activities during early development for thyroid specification and implicate drug-induced cardiac and vascular anomalies as a possible mechanism causing various forms of thyroid dysgenesis.

When integrating our study results with previously available information from other model organisms including *Xenopus*, chicken and mouse, we conclude that signaling cues regulating thyroid development appear broadly conserved across vertebrates and that observations made in zebrafish can inform mammalian models of thyroid organogenesis to further our understanding of the molecular mechanisms of congenital thyroid diseases.

OP-05-26

TREATMENT WITH T3 VERSUS NATURAL PROCESS: COMPARATIVE ANALYSIS OF TRANSCRIPTOMES

Evelyne Duvernois-Berthet[1], *Nicolas Buisine*[1], *Muriel Rigolet*[1], *Laurent Sachs*[1]

[1]Muséum National D'histoire Naturelle, Centre National de la Recherche Scientifique, Paris, France

Objectives: Thyroid hormones (TH) act in part on the expression of the genome. It is accepted that differential gene expression following treatment with TH at physiological doses recapitulates the expression profiles taking place during natural processes induced by these hormones. Although both processes seem to correlate at the scale of a few target genes, this hasn't been addressed in a systematic manner. Our objectives are to compare transcriptome variations after TH treatment with transcriptome variations during a TH controlled natural process to characterize pharmacological versus physiological regulations.

Methods: The measurement of gene expression at genome scale (transcriptome) is obtained by sequencing all the messenger RNAs (RNA-seq). In summary, messenger RNAs captured from a tissue, are converted to complementary DNA which are sequenced using high throughput sequencing technology. The bioinformatic analysis makes it possible to evaluate which genes are expressed and then by comparing different tissues or physiological conditions, the variations of expression. Our model is one of the striking developmental processes orchestrated by TH: amphibian metamorphosis. Tadpole transformation is marked by changes including *de novo* morphogenesis, tissue remodelling and organ resorption. These changes involve cascades of gene regulation initiated by TH and their receptors. Thus, because all chordates have this homologous postembryonic developmental phase, metamorphosis can serve as an excellent model to analyse in a physiological context, the functions and mechanisms of action of TH. Here, to probe the effects of TH on the transcriptome, we performed RNA-seq for two *Xenopus tropicalis* organs with contrasted fate (either proliferation for the hind-limbs or cell death for the tail fin epidermis) during natural metamorphosis and 24h of T3 treatment.

Results: We observe differences between TH treatment and natural development in both tissues.

Conclusions: The comparison of transcriptomes of natural and induced metamorphosis allow us to reach a more precise understanding of TH action.

OP-05-27

ASYNCHRONOUS DIFFERENTIATION OF THYROID PROGENITORS IN VIVO

Ellen Johansson[1], *Shawn Liang*[1], *Henrik Fagman*[2], *Mikael Nilsson*[3]

[1]Sahlgrenska Cancer Center, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden; [2]Department of Clinical Pathology and Genetics, Sahlgrenska University Hospital, Göteborg, Sweden; [3]Sahlgrenska Cancer Center, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden

Growth and differentiation take place in a highly regulated manner during embryonic development. The thyroid gland develops from a midline primordium that transits through several stages of morphogenesis until the final bilobed gland is established. The current opinion is that thyroid differentiation and *de novo* folliculogenesis take place synchronously throughout the entire gland once morphogenesis is completed. However, this has not been formally proven regarding the isthmus portion that develops by bilateral elongation of the primordium before growth of the lateral lobes is initiated.

The objective of this study was to investigate whether progenitor cells forming the thyroid isthmus differentiate at the same time as cells forming other parts of the gland. Embryonic mice were morphologically examined between embryonic day (E) 12.5 and 17.5. Cryostat sections were subjected to immunofluorescent labeling of thyroglobulin, E-cadherin, Ki67, pericentrin, and Muc1, a luminal glycoprotein expressed at the apical membrane in endoderm-derived organs. Tissues were also analyzed with transmission electron microscopy (TEM).

Muc1 delineated the lumen of newly formed follicles in the orthotopic thyroid gland in late development. At E12.5-13.5 i.e. before lumen formation, Muc1 was also present as discrete patches in the thyroid primordium. Muc1+ patches coalesced to premature lumina along with apical re-localization of centrosomes and thyrogobulin synthesis. TEM confirmed lumen formation in the prospective isthmus at E13.5. Notably, Ki67+ proliferating cells participated in folliculogenesis in this location.

We conclude that onset of concomitant functional differentiation and folliculogenesis occur asynchronously in the developing mouse thyroid. This suggests that local factors prevent premature differentiation of thyroid progenitors that will participate in lobe formation, while other progenitors attaining a stationary position in the isthmus are allowed to differentiate at an earlier stage. The findings further indicate that embryonic thyroid growth is not restricted to unpolarized progenitors but also involves polarized cells participating in folliculogenesis.

OP-05-28

GLIS3 AS A CRITICAL REGULATOR OF THYROID PRIMORDIUM SPECIFICATION

Giuditta Rurale[1], *Federica Marelli*[2], *Paolo Duminuco*[3], *Luca Persani*[4]
[1]Istituto Auxologico Italiano, IRCCS, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan; [3]Laboratory of Endocrine and Metabolic Research, Istituto Auxologico Italiano, IRCCS, Milan, Italy; [4]Laboratory of Endocrine and Metabolic Research, Istituto Auxologico Italiano, IRCCS, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

The mechanisms leading to thyroid specification from the endoderm are presently unknown. In humans, *GLIS3* mutations are associated with syndromic and isolated congenital hypothyroidism (CH), but its involvement during thyroid organogenesis are still unclear.

Interestingly, *glis3* knockdown experiments in zebrafish embryos (called *glis3* morphants) show absent or reduced expression of the early transcription factors *nkx2.4* and *pax2a*. In later stages of development, *glis3* morphants also showed a reduced or absent expression of *tg* and *slc5a5*, the key genes involved in the metabolism of thyroid hormones. Interestingly, the reduced expression of early thyroid markers was not associated with changes in proliferation or apoptosis of the pharyngeal endoderm. In morphants, the differentiated thyroid tissue appeared severely reduced in size and disorganized, reproducing the manifestations of CH patients with thyroid dysgenesis. Rescue and overexpression experiments demonstrated the relevance of *glis3*-dosage directing the number of differentiated thyroid follicular cells. In order to exclude a global impairment of the pharyngeal endoderm in the *glis3* morphants, we analysed the expression of *foxa2*, an early endoderm-specific transcription factor. When thyroid bud becomes evident, the endoderm pouches appeared unaffected in *glis3* morphants, thus excluding an aberrant endoderm formation. Then, we investigated if other organs that arise from the endoderm (e.g. liver and pancreas) display developmental defects similar to thyroid bud. Our series of experiments revealed that, unlike liver, only the pancreatic development appears affected by *glis3* KD. Similarly to the thyroid phenotype, our *glis3* morphants displayed a reduced differentiation of the *ins2*-positive pancreatic β-cells that fail to migrate and aggregate in a disorganized shape.

In vitro and *in vivo* data support *glis3* as an effector of the Sonic Hedgehog (SHH) pathway. Molecular and pharmacological inhibition of SHH led to the development of thyroid defects resembling the phenotype of *glis3* morphants.

Therefore, we propose glis3 as a downstream effector of the Shh-pathway requiring an active Shh-signal for its transactivation activity. As a whole, *glis3* action within the SHH pathway appears to determine the number of endodermal cells committed to a thyroid fate, thus justifying the involvement of *GLIS3* in thyroid dysgenesis. Our data contribute to understand the molecular mechanisms underlying the onset on thyroid dysgenesis in patients with *GLIS3* mutations.

OP-05-29

CHRONIC EXPOSURE TO MICROCYSTIN-LR REDUCES THYROID HORMONE LEVELS BY ACTIVATING P38/MAPK AND MEK/ERK SIGNAL PATHWAY

Jihai Chen[1], *Xiaojun Ouyang*[1]
[1]Department of Geriatric Endocrinology, Geriatric Hospital of Nanjing Medical University, Nanjing, China

Microcystin-LR (MC-LR) is the most toxic and abundant microcystin that produced by cyanobacteria. Previous studies have shown MC-LR had acute toxic to thyroid, however, the mechanism is still unclear, and the effect of long-term, low-dose MC-LR on thyroid remains uncertain. In this study, we investigated the chronic, low-dose effect of MC-LR on mouse thyroid tissues and thyroid hormone metabolism. MC-LR was orally administered to mice at 0, 1, 10, 20 and 40 μg/L for 6 consecutive months for histopathological and immunoblot analysis. Nthy-ori 3-1 cells were cultured in various concentrations of MC-LR (0, 0.5, 5, 50, 500 nmol/L) for indicated time, meanwhile the cell viability and proteins change were tested. From our study, the levels of FT3 and FT4 were significantly down-regulated compared with control in *vivo* and in *vitro* studies. Moreover, MC-LR exposure induced the up-regulated of Dio3 and the phosphorylation of ERK, p38/MEK. To confirm the role of p38/MAPK and MEK/ERK signal pathway in the expression of Dio3, p38/MAPK was blocked by the inhibitor SB203580 and MEK/ERK signaling pathway was blocked by the inhibitor PD0325901. The results showed that the inhibition of p38/MAPK and MEK/ERK signal pathway could significantly reverse the upregulated Dio3 expression that induced by MC-LR. In conclusion, the chronic, low-dose MC-LR exposure can disturb thyroid hormone synthesis and metabolism through activating the p38/MAPK and MEK/ERK signaling pathways, then up-regulating the expression of type 3 deiodinase. These data support the potential toxic effects of MC-LR on thyroid tissue and thyroid hormone metabolism.

OP-05-30

IODINE DEFICIENCY LEADS TO DIFFERENTIAL THYROID-SPECIFIC GENE EXPRESSION AND TISSUE MICROSTRUCTURE IN DEHAL1 KNOCKOUT MICE

Jorge García Giménez[1], *Cristian González-Guerrero*[1], *Federico Salas-Lucia*[2], *Elisa Pulido*[1], *Carmen Grijota*[3], *Ana Guadaño*[3], *Maria De Miguel*[4], *Jose C. Moreno*[1]
[1]Institute for Medical and Molecular Genetics (INGEMM), la Paz University Hospital, Autonomous University of Madrid, Ciberer, Madrid, Spain; [2]Histology and Anatomy Department. Faculty of Medicine, Miguel Hernández University of Elche, Elche, Spain; [3]Instituto de Investigaciones Biomédicas, CSIC-UAM and Ciberer., Madrid, Spain; [4]Laboratorio de Ingenieria Celular. Idipaz., Madrid, Spain

Introduction: Thyroid hormone (TH) synthesis is influenced by the intracellular iodide content in the thyrocytes, which regulates key steps such as the iodination and coupling of the thyroglobulins´s tyrosines. DEHAL1 is an enzyme that recycles iodide in the thyrocytes. However, the effect of a DEHAL1 deletion on the thyroid´s regulatory mechanisms against iodine deficiency has not yet been described. We studied in the effects of iodine restriction in *Dehal1* knockout (Dehal1$^{(-/-)}$) and wildtype (WT) mice on thyroid-specific gene expression and thyroid microstructural changes.

Methods: *Dehal1*$^{(-/-)}$ and WT mice underwent normal (NID), low (LID) and very low iodine diets (VLID) containing 5.6, 1 and 0.25 μg I/day, respectively, for 90 days. T4 concentration was determined by radioimmunoassay. Urinary iodide concentration (UIC) was monitored by Sandell-Kolthoff reaction. qPCR gene expression in genes involved in iodide and TH transport (*Slc5A5, Slc16A2, Slc26A4*) *and*; hormonosynthesis (*Tshr, Tg*, *Tpo*, *Duox2, Duoxa2*) or transcription (*Pax8*, *Nkx 2-1*, *Foxe1, Glis3)* at 0, 15 and 28 days. Morphometric studies were performed at d90.

Results: At basal conditions (NID, d0), both WT and *Dehal1*$^{(-/-)}$ mice are euthyroid (T4: 58.5 ng/ml vs 59.9 ng/ml; $p>0.05$), however *Dehal*$^{(-/-)}$ mice loses significantly more iodide in the urine (12.12 μg/L vs 35.50 μg/L; $p<0.05$). This difference is sustained in time and progressive iodine deficiency (LID, VLID). *Dehal1* expression was undetectable in *Dehal1*$^{(-/-)}$ mice but increased 2.3-fold ($p < 0.05$) in WT mice under VLID at d28. In WT mice, average thyroid-specific gene expression was maximally upregulated (5-fold) at LID conditions, but it suffers downregulation under VLID (2-fold). In contrast, in KO mice, maximal gene overexpression occurs at VLID conditions (10-fold) suggesting the loss of a transcriptional counter-regulatory mechanism in *Dehal1*$^{(-/-)}$ mice under severe iodine restriction. Notably, *Slc5a5* and *Tpo* show the most prominent upregulation (40-fold and 16-fold, respectively). Regarding transcription factors, *Pax8, Nkx2.1 and Foxe1* are maximally expressed at LID but self-downregulate at VLID in WT. However, *Glis3* persists upregulated at VLID conditiins, escaping from such auto-regulatory mechanism. Morphometrically, LID induced a 3-fold increase in the thyroid area in both genotypes. However, only in *Dehal1*$^{(-/-)}$ average thyrocyte height was higher ($p<0.001$) and the follicular lumen smaller ($p<0.001$) compared to WT.

Conclusions: *Dehal1*$^{(-/-)}$ mice present a basal thyroid specific gene overexpression, even under euthyroid and iodine sufficiency conditions. Such overexpression increases along with the severity of iodine restriction, and escapes a transcriptional down-regulation probably involving a Glis3-related pathway. The specific overexpression pattern of *Dehal1*$^{(-/-)}$ mice is consistent with the large size of thyrocytes, translating an intrincic metabolically hyperactive thyroid gland.

Oral Session 6: Improving Clinical Management of Thyroid Cancer

OP-06-31

AVOIDING OVERDIAGNOSIS THROUGH CLINICAL GUIDELINE RECOMMENDATIONS: THE IMPACT ON REAL-LIFE PRACTICE ACCORDING TO THE ITALIAN THYROID CANCER OBSERVATORY (ITCO)

Giorgio Grani[1]
[1]Sapienza University of Rome, Dept. of Translational and Precision Medicine, on behalf of the Italian Thyroid Cancer Observatory, Italy

Objectives: The incidence of differentiated thyroid cancer (DTC) continues to rise worldwide, mostly because of the increasing number of small papillary thyroid cancers (PTCs). The main clinical challenge is to avoid overdiagnosis in patients with low-risk disease while promptly identifying those patients requiring aggressive treatment approaches. The American Thyroid Association (ATA) Guidelines published in January 2016 suggest more conservative strategies for the diagnosis and management of microcarcinomas: first, they recommend to avoid cytology for any nodule less than 1 cm, even if suspicious; furthermore, avoidance of immediate surgery and active sonographic surveillance is recognized among the management options for small subcentimeter PTCs. We performed an analysis of prospectively collected observational data to verify if these recommendations changed the clinical practice of referral centers in Italy.

Methods: The Italian Thyroid Cancer Observatory (ITCO) database was established in 2013 to collect prospective data on thyroid cancers consecutively diagnosed by Italian centers (currently 48 sites across the country, including secondary and tertiary referral centers). We collected data of all pathologically confirmed DTC cases submitted to surgery between 2013 and 2018 (data cut-off date for analysis: 4 March 2019). For the present analysis, cases with incidental, post-surgery, diagnosis of PTC were excluded.

Results: A total of 3285 patients, enrolled by 48 centers were included in the initial cohort. Overall, 1345 cases were cancers <1 cm in their maximum focus (40.9%). No significant difference was detected over time (2013: 40.1%; 2014: 43.5%; 2015: 40.0%; 2016: 41.1%; 2017: 41.1%; and 2018: 40.2%).

Conclusion: Despite the efforts to reduce the number of surgeries for microcarcinomas, these interventions are still very common. Furthermore, in recent years, in spite of the updated guidelines and scientific literature data, no relevant differences were measured in real-world clinical practice in Italy.

OP-06-32

THYROID CANCER INCIDENCE AND CHARACTERISTICS IN A COHORT OF PATIENTS TREATED WITH CHEMO AND RADIOTHERAPY FOR CHILDHOOD CANCER: A SINGLE CENTRE EXPERIENCE

Martina Tavarelli[1], *Emanuela Cannata* [2], *Nicolò Li Volsi*[2], *Giulia Sapuppo*[3], *Marco Russo*[4], *Francesco Frasca*[3], *Angela Spadaro*[4], *Andrea Di Cataldo*[2], *Romilda Masucci*[5], *Gabriella Pellegriti*[6]
[1]Universita' Degli Studi DI Catania, Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Center, Catania, Italy, Catania, Italy; [2]Onco-Ematology Unit, Departiment of Clinical and Experimental Medicine, University of Catania, Italy; [3]Endocrinology, Departiment of Clinical and Experimental Medicine, University of Catania, Italy; [4]Endocrinology Unit, Garibaldi Nesima Hospital, Catania, Italy; [5]Oncological Surgery Unit, Garibaldi Nesima Hospital, Catania, Italy; [6]Endocrinology Unit, Garibaldi Nesima Hospital, Catania, Garibaldi Nesima Hospital, Catania, Italy

Introduction: Thyroid gland is highly sensitive to ionizing radiation, as confirmed by the high incidence of thyroid disease in atomic bomb survivors or treated with external beam radiotherapy (RTE). The risk of developing thyroid cancer (TC) increase with dose and with young age at irradiation. It is still debated whether only chemotherapy (CHE) increase this risk.

Methods: We evaluated incidence, characteristics and outcome of TC in a series of 343 patients treated between 1976 and 2016 with CHE+RTE (n=165) and CHE (n=178) for childhood tumors. Mean age at treatment was 7.8 years, in CHE+RTE patients the radiation dose was 27 Gy at a mean age of 9.4 years. Patients underwent morpho-functional evaluation in the 2000-2016 period at our thyroid clinic.

Results: During follow-up 30 (8,7%) patients developed a TC, 9 in the CHE group vs 21 in the CHE+RTE group (p=0.01). TC raised after a follow-up of 19.1 years. Latency time from primary treatment to diagnosis of TC was lower in the CHE vs CHE+RTE group (p=0.001; 14.1 vs 21.1.years). Histotype was papillary in 29/30 and follicular in 1 patient. TNM staging showed a higher percentage of pT1 in the CHE than in CHE+RTE group (p= 0.04). Nodal metastases were found in 53% of cases with no difference in the two groups. I-131 was administered in 76.7% of patients. At the last visit 20.0% of patients, 5 in the CHE+RTE and 1 in the CHE group had persistent disease (lung metastases in 3 and detectable serum Thyreoglobulin in 1).

Conclusion: Patients treated with CHE +RTE have a higher incidence of TC. Our data confirm the role of RTE as risk factor for TC, but the high percentage of tumor observed in patients treated with CHE is not negligible and further research need to establish its role in pathogenesis of TC.

OP-06-33

NON THYROIDAL SECOND PRIMARY MALIGNANCIES IN DIFFERENTIATED THYROID CANCER (DTC) PATIENTS: IS THE INCIDENCE INCREASED COMPARING TO THE GENERAL POPULATION AND COULD IT BE A RADIOIODINE'S FAULT?

Virginia Cappagli[1], *Adele Caldarella*[2], *Valeria Bottici*[3], *Laura Agate*[3], *Eleonora Molinaro*[3], *Francesca Bianchi*[4], *Paolo Vitti*[3], *Rossella Elisei*[3]
[1]Department of Clinical and Experimental Medicine, Endocrine Unit, University of Pisa, Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy, Pisa, Italy; [2]Clinical Epidemiology, Center for Study and Prevention of Cancer, Florence, Italy; [3]Department of Clinical and Experimental Medicine, Endocrine Unit, University of Pisa, Pisa, Italy; [4]Department of Nuclear Medicine, University of Pisa, Pisa, Italy

Objective: The long-term survival of DTC led to question if it could be an increased lifetime risk of developing a non thyroidal second primary cancer (NTSPC) due to radioiodine treatment (131-I). This topic is still debated and conflicting data are available. Aims of this study were to evaluate the prevalence of NTSPC in DTC patients; to assess if the prevalence of a NTSPC

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

in the DTC group was higher than in the general population; to evaluate the correlation with clinical-pathological-epidemiological parameters, particularly with 131-I.

Methods: A retrospective single-center study was conducted on 1092 consecutive DTC patients followed at our Institution from 1964 to 1998. A NTSPC was defined as any primary malignancy occurred in an anatomical site other than thyroid. NTSPC diagnosed within 12 months from DTC and malignancies with a benign behavior were excluded.

Results: 19 patients were excluded. In the remaining 1077 patients, 77 had a NTSPC (7.1%) and 1000 (92.9%) didn't. No statistically significant differences were found regarding age at DTC diagnosis, gender, DTC histology,TNM stage and family history for malignancies. Regarding 131-I, neither having performed 131-I nor the total administered activity were associated with an increased incidence of NTSPC. The only statistically significant parameter associated with an increased incidence of NTSPC was a longer follow-up (*p 0.01*). Since we observed that patients who didn't received 131-I had a NTSCP and that a NTSPC was also diagnosed pre-DTC we considered this two groups together as non-131-I treated group (60 patients) and a total of 20 non 131-I dependent NTSPCs were found. The observed prevalence of a NTSPC was 0.07% in the 131-I treated group and 0.3% in the non treated one and it was statistically significant different. The analysis regarding the prevalence of NTSPC in DTC group comparing to general population is still in progress.

Conclusions: according to our results, the occurrence of NTSPC in DTC patients is not related to 131-I, neither having performed 131-I nor to the cumulative activity. Data regarding general population are still under analysis.

OP-06-34

ASSOCIATION OF CHEK2 VARIANTS WITH PAPILLARY THYROID CANCER RISK BUT NOT WITH DISEASE OUTCOME

Magdalena Wycislik[1], *Dorota Kula*[1], *Michal Kalemba*[1], *Malgorzata Kowalska*[1], *Michal Jarzab*[1], *Dominika Sznajder*[1], *Ewelina Piasna - Slupecka*[1], *Monika Halczok*[1], *Tomasz Tyszkiewicz*[1], *Beata Hejduk*[1], *Katarzyna Steinhof-Radwanska*[1], *Zbigniew Puch*[1], *Renata Cyplinska*[1], *Barbara Jarzab*[1], *Daria Handkiewicz-Junak*[1]
[1]Maria Sklodowska-Curie Institute – Oncology Center, Gliwice Branch, Poland

Association of CHEK2 variants with papillary thyroid cancer risk but not with the disease outcome

Predisposition to papillary thyroid cancer (PTC) is multigenic. Individual susceptibility is determined by interaction between genes and environmental factors. Many studies revealed that CHEK2 gene increases the risk of different malignances, among them is thyroid cancer. However, little is known about association of CHEK2 variants and PTC outcome.

Purpose: The association of c.1100delC, c.444+1G>A and c.470T>C CHEK2 variants with PTC risk was investigated in Polish population. In the next step we analyzed the association of these CHEK2 variants with the disease outcome (evaluated by lymph node metastases, distant metastases and disease recurrence).

Material and methods: The frequency of CHEK2 variants was analyzed in DNA derived from blood samples of 2279 PTC cases and 1218 controls. The c.1100delC and c.470T>C variants were analyzed with the allelic discrimination assay, while c.444+1G>A variant with the high-resolution melting method. Variants c.1100delC and c.444+1G>A were confirmed by Sanger sequencing. The data for lymph node metastases, distant metastases and disease recurrence were available for 2232 patients. Chi2 test was used for the statistical analysis.

Results: A significant association with PTC was observed for c.444+1G>A (OR = 4.49) and c.470T>C (OR = 1.99). For c.1100delC variant non-significant differences in genotypes frequencies between PTC cases and controls were seen. Next the association with disease outcome was analyzed. Data for lymph node metastases were available for 1661 patients, among them 555 (33.4%) had metastases. In 2154 patients PTC cases with the data for distant metastases available, 76 (3.5%) had metastases. Among 2232 PTC patients disease recurrence was observed in 188 cases (8.4%). The association of these PTC clinical features with CHEK2 variants was not observed (p>0.05).

Conclusion: The c.444+1G>A and c.470T>C CHEK2 variants showed association with increased PTC risk, however, not with the disease outcome evaluated on the basis of lymph node metastases, distant metastases and disease recurrence.

OP-06-35

CONTROVERSIAL MANAGEMENT OF DIFFERENTIATED THYROID CARCINOMA BETWEEN 1-4 CM. CHALLENGING CURRENT ATA GUIDELINES RECOMMENDATIONS

Irati Ruiz Rey[1], *Carolina Perdomo Zelaya*[1], *Javier Gargallo Vaamonde*[1], *Marta García Goñi*[1], *Juana Karina Zapata Cardenas*[1], *Ina Kollozi*[2], *Juan Carlos Galofré*[1]
[1]Clínica Universidad de Navarra, Pamplona, Spain; [2]University Medical Center "Mother Teresa", Tirana, Albania

Introduction: The incidence of differentiated thyroid carcinoma (DTC) is rising. Consequently, there has been an increase in the number of thyroid surgeries. The 2015 American Thyroid Association (ATA) Guidelines for DTC endorse thyroid lobectomy (TL) as an alternative to total thyroidectomy (TT) for initial treatment of low-risk 1-4 cm DTC. The Guidelines listed a number of preoperative (tissue invasion by imaging techniques, lymph node involvement, distant metastases, history of neck radiation or family history of DTC) and postoperative (aggressive variants, extrathyroidal extension, incomplete surgical margins, positive lymph nodes, vascular invasion or bilateral disease) exclusion criteria for this conservative approach. Obviously postoperative criteria are known only after surgery and are an indication for reintervention.

Aim and Methods: Identify the proportion of low risk 1-4 cm DTC patients treated with TT at our Center who would have had a reintervention if they have had a TL as per 2015 ATA recommendations. We retrospectively reviewed the clinical records of these cases treated between 1995 and 2018.

Results: We identified 143 patients (111 female; 77.6%). Median tumor size was 1.7 cm. A tumor size ≥2 cm was found in 60 (41.9%). Ninety-two (63.3%) were in Stage I (AJCC 8th Edition). Following ATA recommendations, 87 (60.84%) would need TT. Thus, they would have had a second surgery if they had undergone TL. The indications for reintervention would have been: lymph node involvement (22%), extrathyroidal extension (15%), bilateral disease (12%), aggressive subtype (7%), and vascular invasion (4%). Thirty-three subjects (23%) presented more than one criteria for completing the thyroidectomy.

Conclusions: Current ATA Guidelines recommendations fail to predict appropriate surgery extension in 60.8% of cases with DTC between 1 - 4 cm. Lymph node involvement is the main reason for TT. An accurate presurgical ultrasound assessment would aid in determining the appropriate degree of initial intervention warranted.

OP-06-36

LENVATINIB TREATMENT IN THE REAL CLINICAL PRACTICE OF PROGRESSIVE, RADIOIODINE-REFRACTORY DIFFERENTIATED THYROID CARCINOMA: ANALYSIS OF A BIG SERIES FOLLOWED IN A SINGLE CENTER

Carlotta Giani[1], *Laura Valerio*[2], *Laura Agate*[2], *David Viola*[2], *Valeria Bottici*[2], *Loredana Lorusso*[2], *Virginia Cappagli*[2], *Antonio Matrone*[2], *Gabriele Materazzi*[3], *Salvatore Mazzeo*[4], *Alessandro Ribechini*[5], *Paolo Vitti*[2], *Eleonora Molinaro*[2], *Rossella Elisei*[2]
[1]Department of Clinical and Experimental Medicine, Unit of Endocrinology, University of Pisa, Italy; [2]Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy; [3]Department of Surgical, Medical, Molecular Pathology and Critical Area, University Hospital of Pisa, Italy; [4]Radiodiagnostic Unit, Pisa Hospital, University of Pisa, Italy; [5]Departiment of Integrated Cardiothoracic and Vascular Activities, Thoracic Endoscopy Section, Pisa Hospital, Italy

Objectives: Endpoint of this study was to evaluate the efficacy and safety of Lenvatinib in a big series of patients (pts) followed in a single center and compare them with the SELECT-study.

Methods: Epidemiological, clinical and pathological data were collected in a prospective database.

Results: 60 pts started Lenvatinib: 27(45%) pts started Lenvatinib as compassionate use; 33(55%) pts started Lenvatinib after the commercialization in Italy. Differently to the SELECT-study our population showed a lower percentage of Hürthle-cell cancer and a higher percentage of PDTC (p=0.02). Eight (13.3%) pts never performed the first radiological control due to rapid death. The objective response rate (ORR), obtained after 3 months of therapy, was significantly lower than that of SELECT-study (31.7% *vs* 64.8%, p<0.001) but the best median tumor shrinkage of responders was similar (-43% *vs* -51.9%). The disease control and clinical benefit rates were obtained in 51/60(85%) pts *vs* 229/261(87.7%) pts (p=0.57) and 42/60 (70%) pts *vs* 209/261 (80.1%) pts (p=0.09), respectively. After a mean of 13 months of follow-up, 27/60 (45%) pts were still being treated: 4/27(15%) pts remained in partial-response; 20/27(74%) pts remained in stable-disease, 3/27(11%) had a progressive-disease. The median progression-free survival (PFS) and overall survival were 26 months and 15 months, respectively. Adverse events (AE) occurred in all pts. Our pts had a higher rate of fatigue (77% *vs* 59%), nausea and anorexia (70% *vs* 41%), weight loss (65% *vs* 46.4%), dysgeusia (44% *vs* 16.9%), and a lower rate of diarrhea (42% *vs* 59.4%) than pts of SELECT-study (P=0.01, p=0.0001, p=0.0059, p=0.001 and p=0.01, respectively). The incidence of arterial hypertension and proteinuria were similar.

Conclusions: Also in the clinical practice, Lenvatinib is effective and associated with a PFS longer than that of SELECT-study. In our group the ORR was lower but associated with a similar disease control and clinical benefit rates. All patients experienced AE but with a different prevalence respect to SELECT.

Oral Session 7: Thyroid Hormone Action in Tissue Function and Inflammation

OP-07-37

LOSS OF STEAROYL-COA DESATURASE 1 AFFECTS THYROID HORMONE ACTION AND INDUCES EPIGENETIC MODIFICATIONS IN CARDIOMYOCYTES

Adam Olichwier[1], *Paweł Dobrzyń*[1]
[1]Nencki Institute of Experimental Biology, Polish Academy of Science, Warsaw, Poland

Thyroid hormones (TH) play an important role in the regulation of heart function. Through monocarboxylate transporter 8 (MCT8), TH control activity of deiodinases (Dios) and thyroid hormone receptors (TRs) and affect expression of many genes involved in regulation of lipid metabolism or heart function and structure. Moreover, epigenetic enzymes like DNA methyltransferases (DNmts) or histone deacetylases (HDACs) are known as coactivators/corepresors of TRs action. Furthermore, one of the main enzyme that regulates lipid metabolism, stearoyl-CoA desaturase 1 (SCD1) which gene expression is under TH control, can also affect the level of DNA methylation. However, the mechanism of the TH-SCD1 cross-talk in the heart is still unknown. Therefore, the aim of presented study was to establish the role of SCD1 in TH action and epigenetic changes caused by TH in the heart. To induce hyperthyroidism wild type (WT) and SCD1-/- mice were injected with triiodothyronine (T3). Performed analyses showed, that lack of SCD1 leads to increase in T3 plasma level, whereas thyroid-stimulating hormone (TSH) level is decreased when compared to WT. We observed drop in expression of *MCT8* gene as well as in expression and protein level of Dio2 and Dio3 in SCD1 deficient heart. Interestingly, hyperthyroidism increased expression of *MCT8* and *Dio2* genes in SCD1 deficient cardiomyocytes. Moreover, TRα and TRβ protein levels were elevated in the heart of SCD1-/- mice. Furthermore, we observed decreased both global DNA methylation level and DNmt1 protein level in the heart of SCD1-/- mice. Additionally, elevated DNmt1 and DNmt3a protein levels in hyperthyroidism lead to increase of global DNA methylation in cardiomyocytes of SCD1-/- mice when compared to WT controls. What is more, in the heart of SCD1-/- mice TH administration increased protein level of DNmt1 downstream target HDAC1. Obtained results emphasize new and important role of SCD1 in regulation of intracellular TH pathway, through regulation of MCT8, Dio and TR expression. In turn it affects related to TR action epigenetics modifications, what together can affects caused by TH heart function and structure.

Acknowledgements: National Science Center (Poland) grants UMO-2014/13/B/NZ4/00199 and UMO-2017/27/N/NZ4/01995.

OP-07-38

ROLE OF THYROID HORMONE IN THE CONTROL OF NEURAL STEM CELL FATE THROUGHOUT LIFE

Lucile Butruille[1], *Anthony Sebillot*[2], *Barbara Demeneix*[3], *Sylvie Remaux*[1]
[1]Muséum National D'histoire Naturelle/Cnrs; Centre National de la Recherche Scientifique; Umr 7221 Evolution des Régulations Endocriniennes, Paris, France; [2]Muséum National D'histoire Naturelle, Centre National de la Recherche Scientifique, Umr 7221 Evolution des Régulations Endocriniennes, Paris, France; [3]Muséum National D'histoire Naturelle/Cnrs, Centre National de la Recherche Scientifique, Umr 7221 Evolution des Régulations Endocriniennes, Paris, France

In the adult mammalian brain, neural stem cells (NSCs) localized in the subventricular zone (SVZ) produce new neurons and oligodendrocytes throughout life. SVZ-NSCs generate neuroblasts that migrate through the rostral migratory stream (RMS) toward the olfactory bulbs (OB) where they differentiate into olfactory neurons. Furthermore, few NSCs give rise to oligodendroglial precursor cells (OPCs) that migrate toward the surrounding white matter where they differentiate into myelinating oligodendrocytes.

Thyroid hormones (THs) are involved in neurogenesis and gliogenesis during adulthood. The crucial question is to determine how THs regulate adult NSC fate toward a neuron or a glial fate. In the young adult, we recently demonstrated that THs are required for NSCs commitment toward a neuronal fate. In contrast, hypothyroidism is involved in the generation of new SVZ-OPCs, capable of restoring functional nerve conduction after a demyelinating insult. Therefore, our hypothesis is that low TH status associated with ageing maintained oligodendrogenesis at the expense of neurogenesis.

To analyze how TH signalling regulates NSC fate during ageing, we studied the neuron/glia balance in young *versus* ageing mice by immunohistochemistry. Surprisingly, the SVZ-OPC density is increased with ageing, whereas neuroblast density decreased. In the RMS, only the neurogenesis is downregulated in ageing mice. Moreover, the olfactory memory is affected, suggesting that SVZ-neurogenesis is functionally impaired. These results indicate that ageing alters the neurogenesis/oligodendrogenesis balance to maintain SVZ-OPC generation.

Further, we will examine whether the differentiation of OB neurons are affected with ageing. Lastly, the remyelination capacity of young *vs.* ageing SVZ-OPCs will be investigated using the cuprizone mouse model. Our work could have numerous applications in NSCs research for neurodegenerative diseases, by providing a better understanding of the mechanisms underlying TH in the regulation of glia-neuron cell-fate choice.

OP-07-39

NARINGENIN INCREASES PITUITARY SIRT1/TSH RATIO AND INDUCES ULTRASTRUCTURAL CHANGES IN THE THYROIDS OF OLD-AGED MALE WISTAR RATS

Marko Miler[1], *Jasmina Živanović*[1], *Vladimir Ajdžanović*[1], *Ivana Jarić*[1], *Branka Šošić-Jurjević*[1], *Verica Milošević*[1]
[1]University of Belgrade, Institute for Biological Research "Siniša Stanković", Belgrade, Serbia

Objectives: Fruit-derived polyphenols can affect pituitary thyroid stimulating hormone (TSH) secretion, which is mediated by Sirt1 protein. Recently, we have shown that citrus polyphenol naringenin (NAR) increases serum TSH level and modify thyroid structure in terms of increased hormone biosynthesis. Keeping in mind that higher serum TSH level and elevated Sirt1 expression are tightly connected with longevity, we wanted to test whether

NAR administration affects pituitary TSH and Sirt1 immunofluorescent expression and changes thyroid ultrastructure in 24-month-old male Wistar rats.

Methods: NAR was administrated orally (15 mg/kg b.m.) during 4 weeks, while the control group received vehicle, sunflower oil. Quantitative analysis of labeled TSH and Sirt1 proteins in TSH cells considered the relative intensity of fluorescence (RIF) measurements, while ultrastructural analysis was performed in the thyroids.

Results: Increased ($p<0.05$) Sirt1 RIF as well as Sirt1/TSH ratio were observed, while TSH content-reflecting RIF decreased ($p<0.05$), all after NAR treatment. In line with this effect of NAR, thyroids of the same group responded to direct TSH stimulation in comparison with the controls. Namely, ultrastructural analysis showed higher thyroid epithelium, well developed rough endoplasmic reticulum and polymorphic lysosomes which were more abundant than in the control group. Some lysosomes were attached to colloid droplets, unequivocally indicating the gland secretory activity.

Conclusion: Citrus flavanone NAR increases pituitary Sirt1/TSH expression ratio in old rats. This corresponds with decreased thyrotrope TSH content/increased secretion, while ultrastructure of the thyroids follows direct TSH stimulation. These results, for the first time, show potency of NAR to positively interfere with TSH secretion in old-aged rats, which may contribute to the healthy aging and longevity.

OP-07-40

EVALUATION OF THE EFFECTS OF TRIIODOTHYRONINE TREATMENT IN ZSF1 RATS, AN ANIMAL MODEL OF METABOLIC SYNDROME

Marta Borges-Canha[1], João Sérgio Neves[2], Cláudia Sousa Mendes[3], Glória Conceição[3], Madalena von-Haffe[3], Catarina Vale[3], Ana Rita Leite[3], Dulce Fontoura[3], Daniela Miranda-Silva[3], Sara Leite[3], Alexandre Gonçalves[3], João Almeida-Coelho[3], Inês Falcão-Pires[3], André Lourenço[3], Davide Carvalho[4], Adelino Leite-Moreira[3]

[1]Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal, Departamento de Cirurgia e Fisiologia, Faculdade de Medicina Da Universidade Do Porto., Portugal; [2]Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal, Departamento de Cirurgia e Fisiologia, Faculdade de Medicina Da Universidade Do Porto; [3]Departamento de Cirurgia e Fisiologia, Faculdade de Medicina Da Universidade Do Porto; [4]Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal, Instituto de Investigação e Inovação Em Saúde (I3s), Faculdade de Medicina Da Universidade Do Porto, Porto, Portugal

Objectives: This work aimed to evaluate the effects of triiodothyronine treatment on the liver of an animal model with metabolic syndrome.

Material and methods: Three groups of animals were evaluated- ZSF1 obese rats (animal model of metabolic syndrome) divided in non-treated (n=16; Ob) and treated (n=16, with T3 supplementation; Ob-T3) groups, and ZSF1 lean rats (control group, n=16; Ln)- with serial serum thyroid hormone testing, metabolic cage studies, insulin resistance and oral glucose tolerance testing (OGTT). By the twenty-fourth week of age, animals went through tissue collection for evaluation of hepatic histology and levels of thyroid hormones.

Results and conclusions: ZSF1-Ob rats presented significantly higher body weight (595±21g vs 451±12g, $p<0.05$), glucose area under the curve (AUC) after OGTT (12009±219mg/min/dL vs 36949±2067mg/min/dL, $p<0.05$) and hepatic lipid content (1.05±0.20 vs 0.16±0.09, $p<0.01$), than ZSF1-Ln rats. ZSF1-Ob rats also presented lower plasmatic T3 and T4 levels (T3: 0.24±0.12ng/mL vs 0.73±0.12ng/mL, $p<0.01$; T4: 42.10±3.34ng/mL vs 69.27±14.10ng/mL, $p<0.01$), without significant differences in TSH or hepatic TH levels.

About the treatment with T3, ZSF1-Ob+T3 presented significant lower body weight (595±21, $p<0.05$) and glucose AUC after OGTT (24056±1561mg/min/dL, $p<0.05$) comparing with ZSF1-Ob. Regarding the histological lipid quantification, there was a statistically significant decrease in lipid hepatic burden with T3 treatment: the ratio between the area occupied by the lipids and the surrounding tissue was 1.05±0.20 in the ZSF1-Ob group and 0.36±0.13 in ZSF1-Ob+T3 group ($p<0.01$). This treatment was associated with an increase in hepatic T3 levels (3.66±2.23ng/mL in ZSF1-Ob vs 4.43±1,43ng/mL in ZSF1-Ob+T3, $p<0.05$) and with a decrease in hepatic T4 levels (18.91±10.10ng/mL in ZSF1-Ob vs 4.86±3.37ng/mL in ZSF1-Ob+T3, $p<0.05$), without significant effects on serum T3 or TSH levels.

Concluding, the treatment with triiodothyronine increased T3 levels in the liver and strongly ameliorated hepatic histology. Therefore, in the future, new therapeutic strategies may arise from the modulation of TH effects at hepatic level.

OP-07-41

COMPARISON OF THE EFFECTS OF SHORT AND LONG TSHR-DERIVED CYCLIC PEPTIDES TO INDUCE TOLERANCE IN GRAVES´ DISEASE AND ORBITOPATHY

Martin Ungerer[1], Julia Fassbender[1], Holthoff Hans-Peter[1]

[1]Procorde - Advancecor, Martinsried, Germany

Long and short cyclic peptides derived from the first and eighth cylindrical loops of the leucin-rich repeat domain (LRD) of the thyroid-stimulating hormone receptor (TSHR) were compared for their efficacy to induce tolerance and treat symptoms in a model of Graves´ disease in mice during a long-term protocol of 4-weekly immunisations with adenovirus coding for the TSHR A subunit (Ad-TSHR289).

The long therapeutic peptides have been described before (Holthoff et al., Endocrinology 2017; 158: 2376-2390). The novel short cyclic peptides are faster to synthesize by FMOC-resin-based technology. Monthly intravenous administration of a short cyclic peptide, which was derived from the sequence of the first LRD loop, markedly reduced thyroid sizes, serum thyroxin levels, retro-orbital fibrosis and tachycardia in Ad-TSHR289-immunized mice. This 11-meric peptide was more effective than a longer, 24-meric peptide derived from the same LRD loop. In immunologically naïve mice, administration of the peptides did not induce any immune response.

In summary, optimized cyclic peptides mitigate many clinical findings in a mouse model of established Graves´ disease and orbitopathy, and may therefore provide an additional therapeutic option compared to existing drugs or interventions.

OP-07-42

HYALURONAN OLIGOSACCHARIDES PROMOTE INFLAMMATION AND DOWNREGULATE THE EXPRESSION OF THYROID-SPECIFIC GENES VIA TOLL-LIKE RECEPTORS 2 AND 4 (TLR-2 AND TLR-4) AND CD44

Rosaria Ruggeri[1], Angela D'Ascola[2], Alfredo Campennì[3], Angela Avenoso[4], Salvatore Campo[5], Teresa Manuela Vicchio[6], Salvo Cannavò[7], Francesco Trimarchi[8]

[1]Department of Clinical-Experimental Medicine and Pharmacology, Division of Endocrinology, University of Messina, Unit of Endocrinology, University Hospital of Messina, Messina, Italy, Messina, Italy; [2]Dep. of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [3]Dep. of Biomedical and Dental Sciences, and Morfo-Functional Images, Nuclear Medicine Unit, University of Messina, Messina, Italy; [4]Departmet of Biomedical and Dental Sciences, and Morfo-Functional Images, University of Messina, Messina, Italy; [5]Dep. of Biomedical and Dental Sciences, and Morfo-Functional Images, University of Messina, Messina, Italy; [6]Endocrine Unit at University Hospital of Messina., Aou Policlinico DI Messina, Messina, Italy; [7]Department of Human Pathology, Endocrine Unit, University Hospital, Dep. of Human Pathology of Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy; [8]Accademia Peloritana Dei Pericolanti at University of Messina, Messina, Italy

Objective: Lymphocytic infiltration and inflammation in Hashimoto's thyroiditis (HT) results in intra-thyroidal accumulation of hyaluronan (HA). During inflammation, HA can be degraded into small fragments, that are able to up-regulate pro-inflammatory genes, by stimulating TLR-2, TLR-4 and CD44. Also, down-regulation of thyroid-specific genes [thyroglobulin (Tg) and sodium iodide symporter (NIS)] expression has been reported during

inflammation. The present study aimed at evaluating the effect of small HA fragments, O-6-mer HA oligosaccharides, on the expression of Tg and NIS, as well as of pro-inflammatory cytokines IL-1 and IL-6, in human thyrocytes.

Methods: Primary thyrocytes were obtained from patients undergone surgery for benign thyroid nodules. Cultured cells were treated for 24 h with increasing concentrations of O-6-mer HA (12.5, 25, 50 μg/ml), with and without CD44, TLR-2 and TLR-4 blocking antibodies. mRNA and proteins expression for TLR-2, TLR-4, CD44, IL-1β IL-6, NIS and Tg were evaluated by real-time PCR, Western Blot and ELISA, respectively. Protein quantification was assessed by densitometry analysis.

Results: In cultured thyrocytes, O-6-mer HA induced the increase in both mRNA and protein of TLR-2, TLR-4, CD44 and, in turn, the increase in IL-1beta and IL-6 levels, at 25 and 50 μg/ml concentrations ($p<0.05$ and $p<0.01$, respectively). On the contrary, Tg and NIS mRNA expression and related protein levels decreased after HA treatment at 25 and 50 μg/ml concentrations ($p<0.05$ and $p<0.001$, respectively). Incubation with CD44 and/or TLR-2 and TLR-4 specific blocking antibodies significantly reduced pro-inflammatory cytokine production and prevented the down-regulation of Tg and NIS ($p<0.05$ anti-CD44; $p<0.01$ anti-TLR-2 + anti-TLR-4; $p<0.001$ anti-CD44+ anti-TLR-2 + anti-TLR-4).

Conclusions: HA fragments induce an inflammatory response, via CD44, TLR-2 and TLR-4 activation, and down-regulate thyroid-specific genes expression in human thyrocytes. A decreased Tg and NIS expression after HA fragments accumulation may result in reduced iodide active transport and thyroid hormone biosynthesis.

Oral Session 8: Thyroid Cancer: From Bench to Bed Side

OP-08-43

MOLECULAR PROFILE AND RADIOIODINE RESISTANCE IN PAPILLARY THYROID CARCINOMA

Carla Colombo[1], *Emanuela Minna*[2], *Marina Muzza*[3], *Stefano Ferrero*[4], *Delfina Tosi*[5], *Gaetano Bulfamante*[6], *Leonardo Vicentini*[7], *Maria Grazia Borrello*[2], *Laura Fugazzola*[8]

[1]Division of Endocrine and Metabolic Diseases, Istituto Auxologico Italiano IRCCS, Milan, Italy, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [2]Molecular Mechanisms Unit, Research Department, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy; [3]Division of Endocrine Diseases, Milancusano Milanino, Italy; [4]Division of Pathology, Fondazione Policlinico IRCCS, Milan, Italy, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Medical School, Milan, Italy; [5]Unit of Pathology, Asst Santi Paolo e Carlo, Milan; Department of Health Sciences, Università Degli Studi DI Milano, Milan, Italy; [6]Unit of Pathology, Asst Santi Paolo e Carlo, Milan; [7]Endocrine Surgery Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy; [8]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, Endocrine Unit, Fondazione Policlinico IRCCS, Milan, Italy

Background: A fraction of metastatic papillary thyroid cancers (PTC) are radioiodine-resistant (RAI-R), and $BRAF^{V600E}$, the most common driver mutation in PTC, has been associated with this condition.

Methods: We analyzed the molecular profile of 64 PTC tissues by a customized Mass Array platform (PTC-MA), recently developed by our group, which allows the simultaneous detection of 13 hotspot mutations and 7 recurrent fusion genes. Patients were divided into three groups: Group 1 (21 PTCs: initial RAI uptake but disease persistence), Group 2 (28 PTCs: no RAI uptake and disease persistence) and Group 3 (15 PTCs: RAI uptake and disease remission).

Results: The 64 patients (41 Females, median age at diagnosis 45 yrs) were followed at a single Center (average follow-up 86.5 months).

The analyses revealed the tendency towards a different molecular profile between the three groups, though not statistically significant likely due to the relatively low number of cases: BRAF was more frequent in Group 2 (76%) compared to Group 1 (29%) and Group 3 (33%). On the other hand, fusion genes (ret/PTC and N-TRK) were more frequent in Group 1 (33%) compared to Group 2 (18%) and Group 3 (7%).

Concerning the remaining genetic alterations, no different prevalence was found among the 3 groups. In particular: TERTp mutations were present in 19% (Group 1), 28% (Group 2) and 13% (Group 3), and RAS mutations were present in 10% (Group 1), 0% (Group 2) and 7% (Group 3).

Conclusions: Our data indicate a potential different molecular profile in RAI avid and RAI resistant PTCs: BRAF appears to be more frequent in PTCs without RAI uptake, while fusions show a higher prevalence in cases PTCs with initial RAI uptake but without therapeutic efficacy. These preliminary data need to be confirmed in larger series, in order to allow early stratification of RAI-R tumors.

OP-08-44

WHOLE EXOME SEQUENCING (WES) IDENTIFIES POTENTIALLY ACTIONABLE MOLECULAR VARIANTS IN THE PRIMARY TUMOR AND METASTASIS OF RADIOIODINE (RAI) RESISTANT ADVANCED THYROID CANCER

Helen Huang[1], *Moosa Khalil*[2], *Ralf Paschke*[3], *Markus Eszlinger*[4]

[1]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Cumming School of Medicine, Calgary, Canada; [2]Department of Pathology and Laboratory Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [3]Dept. of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Canada; [4]Departments of Oncology, Pathology and Laboratory Medicine, Biochemistry and Molecular Biology, and Arnie Charbonneau Cancer Centre, Cumming School of Medicine, University of Calgary, Cumming School of Medicine, Calgary, AB, Canada

Current resensitization strategies for patients with RAI resistant thyroid cancers use the mutation profile of the primary tumor to guide tyrosine kinase inhibitor selection for resensitization. Since the current success rate based on BRAF or RAS mutation detection is only approximately 60%, this study aims at identifying additional actionable variants in tumors and metastases.

WES was applied to 17 samples from 3 RAI resistant patients with advanced thyroid cancer. After preprocessing, read pairs were aligned (BWA) and PCR duplicates were removed (Picard tools). Filtered reads were further processed for variant calling using GATK. Somatic variants were identified and annotated using MuTect2 and Oncotator, respectively.

In patient 1 BRAF p.V600E and further variants were identified in all regions of the tall cell papillary carcinoma and in the lung metastasis. In the latter, two private variants were identified: serotonin receptor 2A p.K323L and methyltransferase like 17 p.V61M. In patient 2 NRAS p.Q61R and EIF1AX p.A113_splice were identified in two histologically different regions of the primary tumor, a poorly differentiated and a follicular variant papillary/follicular carcinoma area. AKT1 p.E17K was found to be private to the poorly differentiated part, while CDK6 p.T320S was found solely in the fvPTC/FTC part. In patient 3 E2F1 p.Q272H and RAPH1 p.T963K were identified in a Hurthle cell part and in a poorly differentiated (insular) component of the same tumor. TP53 p.R337C, TERT p.L786P and KEAP1 p.E149* were identified in the Hurthle cell part only.

In conclusion, WES identified potentially actionable variants for existing drugs in serotonin receptor 2A in the lung metastasis of patient 1, and in AKT1 and CDK6 in patient 2. This remains to be identified for RAPH1 p.T963K. Also, the implication of variants like EIF1AX and TERT detected in patients 2 and 3 for the response to RAI resensitization strategies remains to be determined.

OP-08-45

FUSION GENES IN PAPILLARY THYROID CANCER IN PEDIATRIC PATIENTS

Barbora Pekova[1], *Vlasta Sykorova*[1], *Sarka Dvorakova*[1], *Eliska Vaclavikova*[1], *Jitka Moravcová*[1], *Rami Katra*[2], *Petr Vlcek*[3], *Pavla Sykorova*[4], *Daniela Kodetova*[5], *Josef Vcelak*[1], *Bela Bendlova*[1]

[1]Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic; [2]Dept. of Etn, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Department of Ear, Nose and Throat, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [3]2nd Faculty of Medicine, Charles University, Department of Nuclear Medicine and Endocrinology, Department of Nuclear Medicine and Endocrinology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [4]Department of Nuclear Medicine and Endocrinology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [5]Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic

Objectives: Papillary thyroid cancer (PTC) is the most common endocrine malignancy in pediatric patients and its incidence is increasing. Point mutations in *BRAF*, *RAS*, *PTEN* and *PIK3CA* genes, as well as *CCDC6/RET* and *NCOA4/RET* fusions have been previously described, but other fusion genes have not been investigated in a large cohort of pediatric patients with PTC. The aim of this study was to detect known and novel fusion genes and correlate found mutations with clinical and pathological data.

Methods: The cohort consisted of 87 pediatric PTC patients (6-20 years old). RNA was extracted from fresh frozen tissues and analyzed by QIAseq Targeted RNAscan panel (Qiagen) or FusionPlex panel (Archer) and sequenced using HiSeq 2500 and MiSeq (Illumina). Bioinformatic analyzes were performed by GeneGlobe Data Analysis Center or Archer Analysis. Fusion gene positive samples were confirmed by Real-Time PCR (LC480, Roche).

Results: Fusion genes in 50 (57.5%) patients were found. The most common fusion genes were *CCDC6/RET* (24%), *ETV6/NTRK3* (20%) and *NCOA4/RET* (12%). All fusions involved known oncogenes - *RET*, *NTRK1*, *NTRK3*, *ALK*, *BRAF* and *MET*. The most often were fusions with the *RET* gene and 5' fusion partners were *CCDC6*, *NCOA4*, *BBIP1*, *IKBKG*, *ACBD5*, *PRKAR1A*, *RUFY2, TPR* or *SQSTM1*. Fusion gene positive patients had significantly more frequent lymph node metastases (80% vs. 38%, $p<0.001$) and distant metastases (18% vs. 3%, $p=0.028$) than fusion gene negative patients.

Conclusion: In summary, fusion events were found in most of pediatric PTC. Five fusion genes were novel and one fusion gene has not yet been described in thyroid cancer. Fusion gene positive patients had more extensive disease than patients without this type of mutation. The genetic molecular testing of fusion events is the benefit for pediatric patients for their diagnosis, prognosis and targeted treatment.

Supported by AZV 16-32665A and MH CR-RVO (EÚ, 00023761) grants.

OP-08-46

SIGNATURES OF MUTATIONAL PROCESSES IN NONINVASIVE FOLLICULAR THYROID NEOPLASMS WITH PAPILLARY-LIKE NUCLEAR FEATURES (NIFTPS)

Ewa Chmielik[1], *Michał Jarzab*[2], *Aleksandra Pfeifer*[3], *Marta Cieslicka*[3], *Dagmara Rusinek*[4], *Piotr Paul*[5], *Jakub Simek*[1], *Malgorzata Rydzanicz*[6], *Dominik Glodzik*[7], *Pawel Zawadzki*[8], *Tomasz Stokowy*[9], *Jolanta Krajewska*[3], *Rafal Ploski*[10], *Barbara Jarzab*[11], *Malgorzata Oczko-Wojciechowska*[12]

[1]Tumor Pathology Department, Maria Sklodowska-Curie Institute - Oncology Center Gliwice Branch, Gliwice, Poland; [2]3rd Department of Radiotherapy and Chemotherapy, Breast Unit, Maria Sklodowska-Curie Institute - Oncology Center, Gliwice Branch, Gliwice, Poland; [3]Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Institute - Oncology Center Gliwice Branch, Gliwice, Poland; [4]Maria Sklodowska-Curie Institute - Oncology Center, Gliwice Branch, Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Institute - Oncology Center Gliwice Branch, Gliwice, Gliwice, Poland; [5]Maria Sklodowska-Curie, Institute – Oncology Center, Gliwice Branch, Gliwice, Poland, Poland; [6]Department of Medical Genetics, Medical University of Warsaw, Warsaw, Poland, Poland; [7]Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK; [8]Nanobiomedical Centre, Faculty of Physics, Adam Mickiewicz University, Poznan, Poland; [9]Department of Clinical Science, University of Bergen, Norway; [10]Department of Medical Genetics, Medical University of Warsaw, Warsaw, Poland; [11]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland; [12]Maria Sklodowska-Curie Institute - Oncology Center, Gliwice Branch, Giwice, Poland

Objectives: The aim of the study was to analyze thyroid cancer mutational signatures with special focus on NIFTP and papillary thyroid cancer (PTC).

Material and methods: Seven NIFTP-like tumors were found among 1474 PTCs. Each patient, diagnosed with NIFTP-like tumor, also presented PTC foci in histopathological examination. Another 5 PTC samples from patients with lymph node metastases constituted a control group. In total, 25 tumors (7 NIFTPs and 18 PTCs) and 12 normal thyroid samples, obtained from 12 patients, were subjected to whole exome sequencing, performed with the use of Illumina HiSeq 4000 aiming at 30× coverage.

Results: Our analysis detected *HRAS* and *BRAF* mutations in PTC cases. *BRAF* mutation was found in one NIFTP-like case, whereas *NRAS* mutations were observed in additional 2 NIFTP-like cases. These results prompted us to reevaluate all histopathological NIFTP samples. After in-depth analysis of paraffin block, vascular invasion in the tumor capsule of NIFTP sample with *BRAF* mutation was noticed. In other two NIFTP-like cases, true papillary structures were found and in one NIFTP-like case thyroid parenchymal invasion was observed. Finally, only 3 cases were identified as NIFTP (updated criteria 2018). COSMIC mutation signatures SBS 30 and SBS 6 were detected in PTC and NIFTP. The analysis of pathways that are enriched in somatically mutated genes we found that integrin and collagen pathways were significant in NIFTP and PTC tumors.

Conclusions: Evaluation of *BRAF* mutation may support histopathological diagnosis, particularly when is not possible to exam the entire tumor. The analysis of pathways, significantly affected in tumors, did not show significant differences between PTC and NIFTP in exome sequencing data. Our results highlight collagen importance in the tumor microenvironment and further decipher thyroid tumor heterogeneity.

The study was supported by the National Center of Research and Development MILESTONE project STRATEGMED 2/267398/4/NCBR/2015.

OP-08-47

PRESURGICAL CIRCULATING TUMORAL DNA ANALYSIS BY NGS IN PATIENTS AFFECTED BY MEDULLARY THYROID CARCINOMA: FEASIBILITY AND PROGNOSTIC ROLE

Raffaele Ciampi[1], *Cristina Romei*[1], *Alessia Tacito*[1], *Teresa Ramone*[1], *Alessandro Prete*[1], *David Viola*[1], *Valeria Bottici*[1], *Laura Agate*[1], *Eleonora Molinaro*[1], *Liborio Torregrossa*[2], *Clara Ugolini*[2], *Fulvio Basolo*[2], *Elisabetta Ferretti*[3], *Rossella Elisei*[1]

[1]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [3]Department of Experimental Medicine, University of Rome 'La Sapienza', Rome, Italy

Background: Sixty% of sporadic Medullary Thyroid Carcinomas (sMTC) harbour mutually exclusive somatic mutations in RET and RAS. Aim of this study was to evaluate the clinical relevance of ctDNA measurement in sMTC patients undergoing surgery.

Methods: We studied 17 sMTC patients with plasma collected before surgery; ctDNA was analyzed by NGS-targeted sequencing using a custom panel analyzing 15 genes including the whole RET and RAS genes. Mutation allele frequency (AF) of the driver mutation in tissue and ctDNA were compared to the tissue mutational status, tumor size and serum calcitonin and CEA values at the time of liquid biopsy collection. Positivity for the driver mutation in ctDNA was considered for AF≥0.4%

Results: 15/17(88.2%) tumoral tissues harbored mutations in RET (n=13) and HRAS (n=2) genes with a mean AF of 31.5%. The other 2/17(11.8%) cases were negative and excluded from the ctDNA analysis. Among the mutated cases, 3/15(20%) showed the presence of the driver mutation in their ctDNA with a mean AF value of 2.4%. All the 3 ctDNA positive cases were mutated for RET M918T: the presence of a positive ctDNA was significantly correlated with the M918T mutation (*P=0.0009*).

When considering the size of the primary MTC, we found a correlation between the positivity of ctDNA and the bigger dimensions (3.9cm in ctDNA positive *vs* 2.1cm in negative; *P=0.026*). Moreover, ctDNA positive cases showed higher values of Calcitonin [17200.7ng/L] than negatives [861.3ng/L] (*P=0.0098*); the same was observed for CEA [677.5ng/mL *vs* 94.7ng/mL] (*P=0.0032*).

Conclusions: Detection of driver mutations by NGS is successful in liquid biopsies from sMTC patients. Mutations in ctDNA are more frequently detected in more aggressive tumors harboring a RET M918T mutation and larger tumors with higher calcitonin and CEA values. The diagnostic and prognostic role of ctDNA may be relevant in these cases.

OP-08-48

TREATMENT OF PRIMARY ANAPLASTIC THYROID CANCER CELLS, (OBTAINED FROM BIOPSY, OR FINE NEEDLE ASPIRATION) WITH TWO TYROSINE KINASE INHIBITORS: CLM29 AND CLM3

Giusy Elia[1], *Silvia Martina Ferrari*[1], *Concettina La Motta*[2], *Francesca Ragusa*[1], *Ilaria Ruffilli*[1], *Sabrina Rosaria Paparo*[1], *Armando Patrizio*[1], *Gabriele Materazzi*[3], *Poupak Fallahi*[4], *Alessandro Antonelli*[1]

[1]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy; [2]University of Pisa, Department of Pharmaceutical Science, Pisa, Italy; [3]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, Pisa, Italy; [4]University of Pisa, Department of Translational Research of New Technologies in Medicine and Surgery, Pisa, Italy

Nowadays, the treatment of anaplastic thyroid carcinoma (ATC) consists of a multimodal protocol of surgery, chemotherapy and hyperfractionated accelerated external beam radiotherapy, leading to a median patient survival of 6-10 months. A major advance in the management of this fatal disease would be the identification of an effective systemic treatment.

Testing the sensitivity to different drugs in primary cell cultures from ATC (pATC), obtained from each patient, could improve the treatment efficacy avoiding the administration of inactive therapeutics.

Our purpose was to evaluate the antineoplastic effect of two new "pyrazolo[3,4-*d*]pyrimidine" compounds (CLM3, CLM29) in pATC obtained both from biopsy (biop-pATC) and fine needle aspiration citology (FNA-pATC).

We tested the antiproliferative effect of these drugs on pATC from 6 patients. The concentrations of the compounds used in the *in vitro* experiments were 1, 5, 10, 30, 50, 100 mcM for CLM3 and 5, 10, 30, 50 mcM for CLM29.

In both FNA-pATC and biop-pATC, we observed a significant reduction of proliferation with respect to the control with CLM29, and a slight but significant reduction with CLM3.

The tested compounds led, in a dose-dependent manner, to an increased percentage of apoptosis either in FNA-pATC or biop-pATC.

No significant differences were reported about sensitivity to CLM29 or CLM3 between the tested ATC cells from FNA, or biopsy.

Our findings showed a similar sensitivity to tyrosine kinase inhibitors (TKIs) for both primary cells obtained by FNA and from biopsy and the efficacy of CLM29 and CLM3 in reducing cell growth as well as in increasing apoptosis in ATC.

Therefore, the administration of ineffective, and potentially dangerous drugs, could be avoided by testing the sensitivity to different TKIs in each patient opening the way to personalized treatments.

Oral Session 9: Hyperthyroidism

OP-09-49

MENTAL HEALTH IS NEGATIVELY IMPACTED BY HYPERTHYROIDISM AND DIFFERS BETWEEN GRAVES' DISEASE AND TOXIC NODULAR GOITER. A NATIONWIDE REGISTER-BASED STUDY

Thomas Brix[1], *Frans Brandt*[2], *Lars Folkestad*[3], *Laszlo Hegedüs*[4]

[1]Department of Endocrinology, Odense University Hospital, Odense University Hospital, Odense, Denmark; [2]Department of Medicine, Hospital of Southern Jutland, Sønderborg, Denmark; [3]Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark; [4]Dept. Endocrinol. Odense Uni. Hosp., Odense University, Odense University Hospital, Odense, Denmark

Introduction: Thyroid hormones are essential for the distribution and function of neurotransmitters such as serotonin and noradrenaline within the brain. Accordingly, hyperthyroidism is associated with mood symptoms and reduced quality of life. However, to which degree mental health (MH) is influenced by the cause of hyperthyroidism is unknown.

Aims: To investigate the association and temporal relation between two causes of hyperthyroidism, Graves' disease (GD) and toxic nodular goiter (TNG), and MH.

Method: From nationwide Danish health registers 56.128 hyperthyroid individuals (GD=35.838 and TNG=20.290) and 224.512 age and sex matched controls were identified and followed over a mean period of 7.6 years. Data on hospitalization and pharmacological treatment for psychosis, affective disorders, and anxiety disorders were obtained. Logistic and Cox regression models adjusted for pre-existing somatic morbidity were used to assess the risk of hospitalization and/or pharmacological treatment for psychosis, affective disorders, and anxiety disorders before (odds ratio, OR) and after (Hazard ratio, HR) the diagnosis of hyperthyroidism, respectively.

Results: Both GD and TNG cases had reduced MH before debut of hyperthyrodism as mirrored by an increased prevalence of hospitalization and/or pharmacological treatment for psychosis [OR_{GD}=1.28 (95% CI: 1.21-1.35), OR_{TNG}=1.05 (0.99-1-18)], affective disorders [OR_{GD}=1.32 (1.28-1.37), OR_{TNG}=1.14 (1.09-1.18)], and anxiety disorders [OR_{GD}=1.41 (1.37-1.45), OR_{TNG}=1.24 (1.19-1.28)]. MH was also negatively affected after being diagnosed with hyperthyroidism: psychosis; HR_{GD}= 1.17 (1.09-1.24), HR_{TNG}=1.10

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

(1.02-1.19), affective disorders; HR_{GD}=1.24 (1.20-1.28), HR_{TNG}=1.22 (1.17-1.27), and anxiety disorders; HR_{GD}=1.13 (1.07-1.19), HR_{TNG}=1.07 (1.01-1.14). When analyzing level of MH in GD using TNG individuals as controls, subjects with GD had a higher risk of hospitalization and/or pharmacological treatment for psychosis [HR=1.19 (1.09-1.30)], affective disorders [HR=1.05 (1.00-1.10)], and anxiety disorders [HR=1.07 (1.00-1.15)].

Conclusions: Hyperthyroidism negatively impacts mental health, most significantly in GD. Whether autoimmunity, beyond the role of hyperthyroidism, has an aggravating role in the pathophysiological mechanisms of mental health, should be explored.

OP-09-50

THE CONSEQUENCES OF HYPERTHYROIDISM FOR BONE MICROSTRUCTURE BEFORE AND AFTER TREATMENT - A LONGITUDINAL CLINICAL STUDY USING HR-PQCT

Pia Nicolaisen[1], *Maria Lohman Pedersen*[1], *Stinus Gadegaard Hansen*[2], *Kristian Hillert Winter*[1], *Anne Pernille Hermann*[1], *Niklas Rye Jørgensen*[3], *Laszlo Hegedüs*[1], *Steen Joop Bonnema*[1], *Thomas Brix*[1]

[1]The Department of Endocrinology, Odense University Hospital, Denmark; [2]The Department of Endocrinology, Esbjerg, Denmark; [3]The Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark

Objective: Hyperthyroidism is associated with bone mass reduction and increased fracture risk, while effects on other determinants of bone strength are sparse. We therefore investigated bone microarchitecture and estimated bone strength by High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) in hyperthyroid patients.

Methods: Two approaches were used: A) a cross-sectional case-control study comparing 61 women diagnosed with hyperthyroidism with 61 healthy women matched for age and menopause; B) a prospective follow-up study where 46 of the 61 women were re-examined one year after euthyroidism was achieved. HR-pQCT of the distal radius and tibia, and Dual energy X-ray Absorptiometry (DXA) of the lumbar spine (L1-L4) and total hip region were performed.

Results: Study A: In the radius, compared to controls, hyperthyroid patients had higher total area (13.2%), trabecular area (20.2%) and lower cortical area (-14.5%; all $p<0.001$), assessed by HR-pQCT. Total (-17%) and cortical (-6%) volumetric bone mineral density (vBMD), cortical thickness (-20.5%; all $p<0.001$), and estimated bone strength (-8.6%; $p<0.01$) were lower. No significant differences were found in tibia or DXA parameters at either site.

Study B: in the radius, significant improvements were observed in cortical area (2.1%; $p<0.01$), thickness (2.7%; $p<0.001$), and total vBMD (1.0%; $p=0.04$). Trabecular spacing increased (2.1%, $p<0.05$) and trabecular area decreased (-0.5%, $p=0.001$), while other parameters were unchanged. In the tibia, cortical area (3.0%) and thickness (3.2%) increased, and trabecular area decreased (-0.4%; all $p<0.01$), while the remaining parameters were unchanged. Areal BMD, measured by DXA, increased at the spine (0.9%, $p<0.05$) and hip (1.0%; $p<0.01$).

Conclusion: Hyperthyroid women had lower vBMD, compromised cortical microarchitecture and lower estimated bone strength in the radius. After restoration of euthyroidism significant improvements in vBMD and cortical microarchitecture were observed. Thus, hyperthyroidism seems to affect bone microarchitecture and vBMD, which are features indeterminable by DXA.

OP-09-51

EARLY INTENSIVE CONTROL OF HYPERTHYROIDISM IN GRAVES' DISEASE IS ASSOCIATED WITH IMPROVED SURVIVAL REGARDLESS OF TREATMENT MODALITY

Onyebuchi Okosieme[1], *Peter Taylor*[2], *Ishrat Khan*[3], *Mohd Shazli Draman*[4], *John Lazarus*[5], *Lakdasa Premawardhana*[6], *Colin Dayan*[7]

[1]Cardiff University, Prince Charles Hospital, Cardiff, UK; [2]Cardiff University, School of Medicine, Cardiff University School of Medicine, Cardiff, UK; [3]Cardiff University School of Medicine, UK; [4]Universiti Sultan Zainal Abidin, Cardiff University School of Medicine, Kuala Terengganu, Malaysia; [5]Cardiff University, Cardiff University School of Medicine, Cardiff School of Medicine, Cardiff, UK; [6]Yyf Hospital, University Hospital of Wales, Aneurin Bevan University Health Board, Cardiff, UK; [7]Thyroid Research Group, School of Medicine, Cardiff University, Cardiff, UK

Background: Uncontrolled hyperthyroidism carries an increased risk of mortality and cardiovascular disease. Patients with Graves' disease are routinely treated with a choice of antithyroid drugs (ATD), radioactive-iodine (RAI), or surgery but it is uncertain whether the choice of primary therapy affects long-term outcomes. We evaluated cardiovascular morbidity and mortality according to the modality and effectiveness of primary therapy in Graves' disease.

Methods: The study was conducted through linked datasets within the All-Wales Secure Anonymised Information Linkage (SAIL) Databank. We identified patients with Graves' disease using a regional laboratory TSH-receptor-antibody (TRAb) test register, (n=4,189, female 82%, 1998–2013). Patients with Graves' disease were defined by positive TRAb tests and were matched by age and sex to a control population in SAIL (n=16,756). Patients were grouped by primary treatment received within one-year of diagnosis into the following groups: (1) ATD (n=3587), (2) RAI with resolved hyperthyroidism (RAI-Group-A, n=250), and (3) RAI with unresolved hyperthyroidism (RAI-Group-B, n=182). One-year landmark Kaplan-Meier and Cox regression models were used to analyse the association of treatment with all-cause mortality and major adverse cardiovascular events (MACE, myocardial infarction, heart failure, ischaemic stroke, or death). We also analysed the relationship between one-year FT4 concentrations and outcomes using restricted cubic-spline regression models while a Cox regression model was used to analyse the relationship between one-year TSH and outcomes.

Results: Overall, patients had increased mortality compared to controls (HR 1·23, 95%CI 1·06, 1·42). Compared to ATD-treated patients, mortality was reduced in RAI-Group-A (HR 0·50, 95%CI 0·29, 0·85) but not RAI-Group-B (HR 1·51, 95%CI 0·96, 2·37). Persistently low-TSH at 1-year was associated with increased mortality independent of treatment modality (HR 1·55, 95%CI 1·08-2·24). Spline-regressions demonstrated a positive non-linear relationship between 1-year-FT4 and outcomes.

Conclusions: Regardless of therapy modality, early and effective control of Graves' hyperthyroidism is associated with improved survival and reduced cardiovascular events compared to less effective control. Our findings emphasise the importance of prompt control of hyperthyroidism in patients with Graves' disease. The choice of therapy should be driven by the prospects of successful resolution of hyperthyroidism and early definitive therapy should be offered to patients who are unlikely to achieve remission with antithyroid drugs alone.

OP-09-52

CHARACTERIZATION OF FUSION PROTEINS WITH EITHER ONE OR TWO THYROID STIMULATING HORMONE RECEPTOR (TSHR) A DOMAINS IN GRAVES´ DISEASE PATIENT SERUM SAMPLES

Martin Ungerer[1], *Gabor Laszlo Kovacs*[2], *Kerstin Uhland*[1], *Hans-Peter Holthoff*[1]

[1]Procorde - Advancecor, Martinsried, Germany; [2]1st Department of Internal Medicine, Flor Ferenc Hospital, Kistarcsa, Hungary

Objectives and Design: Graves´ disease is an autoimmune disorder, which is characterized by stimulatory antibodies targeting the human thyrotropin receptor (TSHR), resulting in hyperthyroidism and multiple organ damage. Based on previous studies on temperature-sensitive vs. –insensitive forms of the A subunit of TSHR, we combined a temperature-sensitive His-tagged TSHR A subunit protein with the Graves´ patient-derived monoclonal antibody M22 as binding partner in a novel assay format.

Methods: This assay can be used as a diagnostic method for the identification of Graves' disease patients and furthermore represents a suitable tool to identify potential therapeutic agents which may be used to induce tolerance in anti-TSHR antibody positive patients with Graves´ disease.

Results: Using this binding assay, as well as functional measurements of TSHR-dependent cAMP formation, we show a full binding characterization of the His-tagged TSHR A domain protein, which contains one A domain per molecule, and of a TSHR-Fc fusion protein, which contains two TSHR A domains per molecule. Temperature-sensitive forms of His-tagged TSHR A and TSHRFc fusion protein bind to the anti-TSHR antibody M22 at low effective concentrations (EC_{50} of 5.7 nmol/L and 8.6 nmol/L) and inhibit the effects of this antibody at high efficiencies (IC_{50}-values of 16 – 20 nmol/L). Both proteins also block the effects of polyclonal anti-TSHR antibodies occurring in Graves´ patient sera with somewhat lower average efficiencies (mean IC_{50} values of 68 nmol/L and 29 nmol/L).

Conclusion: Further *in vivo* characterization of both, his-tagged TSHR A and TSHR-Fc at low doses in a murine Graves' disease model is warranted.

OP-09-53

ANALYSIS OF CLINICAL ACTIVITY SCORE (CAS) AT BASELINE IN A LARGE COHORT OF PATIENTS WITH MODERATE TO SEVERE GRAVES ORBITOPATHY (GO)

Giulia Lanzolla[1], *Roberto Rocchi*[2], *Gabriele Coraggio*[3], *Martina Cantarella*[4], *Aldo Sainato*[5], *Paola Lepri*[6], *Maria Sole Sartini*[6], *Angela Sframeli*[7], *Francesco Latrofa*[8], *Paolo Vitti*[9], *Claudio Marcocci*[10], *Michele Marino*[1]

[1]University of Pisa, Pisa, Italy; [2]Department of Clinical and Experimental Medicine, Endocrinology Units, Pisa, Italy; [3]Department of Surgical, Medical and Molecular Pathology, Ophthalmopathy Unit I, University of Pisa and University Hospital of Pisa; [4]Department of Surgical, Medical and Molecular Pathology, Ophtalmopathy Unit I, University of Pisa and University Hospital of Pisa; [5]Division of Radiation Oncology, Azienda Ospedaliero-Universitaria Pisana; [6]Unit of Ophthalmology, Azienda Ospedaliero-Universitaria Pisana, University of Pisa; [7]Univesrity of Pisa, Department of Surgical, Medical and Molecular Pathology, Ophthalmopathy Unit 1, University of Pisa, Pisa, Italy; [8]Univesrity of Pisa, Department of Clinical and Experimental Medicine, Endocrinology Unit, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Pisa, Italy; [9]Endocrinology, Department of Clinical and Experimental Medicine, Endocrinology Unit, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy; [10]Department of Clinical and Experimental Medicine, Endocrinolgy Unit, Azienda Ospedaliero-Universitaria Pisana, University of Pisa

Objectives: Treatment of Graves' Orbitopathy (GO) with anti-inflammatory and immunosuppressive procedures is generally given to patients with an "active" disease, but not to those who have an inactive GO. GO activity, namely the extent of inflammation, is assessed by a standardized clinical activity score (CAS), including seven ocular signs and symptoms, two of which self-assessed. Being mostly a subjective assessment, CAS carries several limitations, as some of the items can be present also in normal subjects. In this regard, to our knowledge, the relative weight and importance of each of the seven items, namely their sensitivity and specificity, has not been established. Therefore, in the present cross-sectional study, we analyzed the frequency of each CAS item in a large population of GO patients, in order to establish their sensitivity and specificity.

Methods: We studied 538 consecutive, untreated GO patients (146 men and 393 women, age: 51.06±10.3 yr, range 25-80 yr) scheduled to undergo orbital radiotherapy and/or glucocorticoid treatment. We evaluated the sensitivity and specificity of the 5 non-self-assessed CAS items based on their frequency in inactive (CAS <3) or active (CAS ³3) GO, as determined by an atlas-based ophthalmological evaluation.

Results: The frequency of each of the 5 items is reported in the Table below. Eyelid swelling and conjunctival redness were the most sensitive, but less specific, items, whereas the remaining items appeared to be less sensitive, but more specific for GO activity.

Conclusions: Eyelid swelling and conjunctival redness are the most sensitive, but less specific, items within CAS. Chemosis, eyelid erythema and caruncle swelling are more specific, but less sensitive. Development of a semi-quantitative sub-scoring of each CAS item may help increasing the specificity and sensitivity of the various CAS items.

CAS	No.	Conjunctival redness	Eyelid swelling	Chemosis	Eyelid erythema	Caruncle swelling
1-2	108	50 (46.2%)	81 (75%)	28 (25,9%)	6 (5.5%)	6 (5.5%)
3-7	430	408 (94.8%)	370 (86%)	244 (56.7%)	266 (61.8%)	170 (39.5%)
Sensitivity		94.8	86.0	56.7	61.8	39.5
Specificity		53.8	25	74.1	94.5	94.5
Specificity/Sensitivity ratio		0.56	0.29	1.30	1.52	2.39

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

OP-09-54

EFFICACY OF RITUXIMAB IN PATIENTS WITH ACTIVE MODERATE-SEVERE GRAVE'S ORBITOPATHY: OUTCOMES OF DIFFERENT DOSE REGIMENS

Elisa Lazzaroni[1], *Danila Covelli*[2], *Irene Campi*[3], *Guia Vannucchi*[3], *Nicola Currò*[1], *Giacinta Pirola*[1], *Claudio Guastella*[4], *Ilaria Muller*[5], *Alessia Dolci*[1], *Maura Arosio*[1], *Mario Salvi*[1]

[1]Graves' Orbitopathy Centre, Endocrinology Department, Fondazione IRCCS Ca' Granda, University of Milan, Milan, Italy; [2]Graves' Orbitopathy Centre, Endocrine Unit, Fondazione IRCCS Cà Granda, Milano, Italy; [3]Endocrinology Department, IRCCS Istituto Auxologico Italiano; University of Milan, Milan, Italy; [4]5 Graves' Orbitopathy Centre, Otolaryngology Department, Fondazione IRCCS Ca' Granda, University of Milan, Policlinico Hospital, Milan, Italy; [5]Thyroid Research Group, Division of Infection and Immunity, Cardiff, UK, Policlinico Hospital, Milan, Italy

Aim: We assessed the efficacy of different doses of rituximab (RTX) in patients with active, moderate-severe Graves' Orbitopathy (GO).

Methods: 40 patients, 5 M/35 F; mean age (± SD) 58 ± 11 years treated with RTX were studied; 21(53%) were smokers. All patients received RTX: 14 patients (group 1) a single 100 mg dose; 15 patients (group 2) a single 500 mg dose and 11 Patients (Group 3) 2 doses of 1000 mg.

Results (1):

Results (2):

- Serum TRAb levels were significantly reduced in the in the three groups at 24 weeks (p-value Group 1 0.002, p-value Group 2 0.001, p-value Group 3 0.05).At 12 weeks serum TRAb levels decreased significantly only in group 2 (p-value 0.002)
- -13/40 patients at baseline and 14/40 at 24 weeks were persistently hyperthyroid, despite the change in serum TRAb title throughout RTX therapy.
- 7/14 patients of group 1, 2/15 of group 2 and 2/11 of group 3 had been treated before with steroid therapy
- 2 patients of group 1 (100 mg dose) developed optic neuropathy.
- 3 patients presented major adverse reaction after only 25-75 mg of RTX: acute cytokine release syndrome, clinically manifesting with marked soft tissue edema associated with pain and transient decrease of vision.

Conclusions:

1. RTX inactivated GO in all patients, independently of the doses used.
2. Serum TRAb decreased at 24 weeks in all three groups of patients. This may depend on the ongoing anti-thyroid therapy rather than to an effect of RTX.
3. The analysis of the quality of life questionnaire shows only a minimal improvement of the appearance but not of ocular function score.
4. The use of low dose RTX does not seem to prevent the development of adverse effects and the progression to optic neuropathy. We suggest that RTX should not be used in patients with subclinical optic neuropathy.

	Nr	GO duration (months)	Patients' age (years)	Baseline Proptosis OD*	24 wk Proptosis OD*	Baseline Proptosis OS *	24 wk Proptosis OS*	Baseline CAS*	24 weeks CAS*
Group 1	14	20	56	24±3	23±4	24±3	23±3	4.5 ±1	1.1 ±−0.8
Group 2	15	18	57	23±2	23±3	23±3	23±2	4.3±1	0.1±1.1
Group 3	11	18	63	21±3	22±3	21±5	22±4	4.4 ±1	0.8±1.1
ANOVA		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.04

*values are expressed as mean ±SD

Oral Session 10: Young Investigators / Clinical and Translational

OP-10-55

DURATION OF OVER- AND UNDERTREATMENT OF HYPOTHYROIDISM IS ASSOCIATED WITH INCREASED CARDIOVASCULAR RISK

Mads Lillevang-Johansen[1], *Bo Abrahamsen*[2], *Henrik Løvendahl Jørgensen*[3], *Thomas Brix*[4], *Laszlo Hegedüs*[5]
[1]Department of Endocrinology, Odense University Hospital, University of Southern Denmark, Odense, Denmark; [2]Holbæk Hospital, Department of Medicine, Open, University of Southern Denmark, Odense, Holbæk, Denmark; [3]Department of Clinical Biochemistry, Hvidovre Hospital, Copenhagen, Denmark; [4]Department of Endocrinology, Odense University Hospital, Odense University Hospital, Odense, Denmark; [5]Dept. Endocrinol. Odense Uni. Hosp., Odense University, Odense University Hospital, Odense, Denmark

Background and objective: The association between various morbidities and hypothyroidism seems to be directional. Little is known regarding specific morbidities and the effect of therapy for hypothyroidism. Here we investigate the association between hypothyroidism and cardiovascular disease (CVD) in both treated and untreated hypothyroid patients, as well as the consequences of over- and under-treatment of hypothyroidism with respect to cardiovascular risk.

Design: A case-control study nested within a cohort of 275 467 individuals with at least one serum thyroid stimulating hormone (TSH)-measurement in the period of 1995-2011.

Methods: Incident cases of CVD were matched with controls according to gender and age. Conditional logistic regression analyses were performed to calculate CVD risks associated with exposure to hypothyroidism, with adjustment for preexisting morbidities using the Charlson Comorbidity Index.

Results: Over a median of 7.0 years (interquartile range 4.1-10.4), 20 487 individuals experienced CVD [9.4%, incidence rate 13.1 per 1000 person-years, 95% confidence interval (CI), 13.0 to 13.3]. Risk of CVD was increased in untreated hypothyroid compared to euthyroid individuals [Odds ratio, OR 1.83 (95% CI, 1.43 to 2.35; p<.001)]. Cardiovascular risk was increased in both treated and untreated hypothyroid individuals per half year of elevated TSH [OR 1.11 (95% CI, 1.06 to 1.16; p<0.001) and OR 1.15 (95% CI, 1.09 to 1.23; p=0.001), respectively]. In patients treated with levothyroxine, OR for cardiovascular disease was 1.12 (95% CI, 1.06 to 1.18; p<0.001) for each six months of decreased TSH, an indicator of overtreatment.

Conclusion: Cardiovascular risk is increased in untreated, but not in treated hypothyroid patients. Among those with treated hypothyroidism, duration of decreased TSH (overtreatment) had a similar impact on cardiovascular risk as duration of elevated TSH (undertreatment), highlighting the importance of initiating treatment and maintaining biochemical euthyroidism in hypothyroid patients in order to reduce the risk of cardiovascular disease and death.

OP-10-56

MICROPAPILLARY THYROID CANCER (MPTC): RESULTS OF THE FIRST EUROPEAN, PROSPECTIVE, SINGLE-CENTER OBSERVATIONAL TRIAL

Maria Cristina Campopiano[1], *Letizia Pieruzzi*[2], *Antonio Matrone*[2], *Laura Agate*[2], *Valeria Bottici*[2], *Claudio Marcocci*[2], *Paolo Vitti*[2], *Rossella Elisei*[2], *Eleonora Molinaro*[2]
[1]Unit of Endocrinology, Pisa, Italy; [2]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Objective: Almost 40% of new thyroid cancer diagnosis are due to mPTC, probably undiagnosed before ultrasound introduction. Nowadays, the active surveillance can be considered an alternative to immediate surgery in mPTC.

Patients and methods: On November 2014 we started an active surveillance program in mPTC. The inclusion criteria were a single thyroid nodule <1.3 cm at neck ultrasound (nUS) with a Thy4/Thy5 cytology and no evidence of metastatic lymphnodes. Patients were followed-up every 6 months in the first 2 years and then annually.

Results: Over 4 years, 93/185 (50%) mPTC patients were enrolled. They were 72/93 (77%) females. The mean age was 44±15 yrs (18-82). Cytology was Thy4 and Thy5 in 55% and 45% of nodules, respectively. To date 19/93 (20%) patients withdrew the observation for personal reasons and opted for surgery without evidence of progression (median follow-up of 8 months). Three/93 (3%) patients showed a clinical progression and went to surgery with a successful cure. Seventy-1/93 (76%) are still in follow-up (median 25 (6-54) months). No differences in clinical and epidemiological features were found between stable and progressive disease, except for nodule's volume at baseline.

Conclusion: The active surveillance for mPTC is feasible also in Europe, with a rate of acceptance of the surveillance program of about 50% among screened patients. However, 20% of mPTC patients dropped out, usually in the first year of follow-up, for personal reasons. Only 3% of patients showed a clinical progression but delayed surgery did not affect their outcome. The nodule's volume at the enrolment is likely relevant in predicting the progression.

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

OP-10-57

THYROID FUNCTION AND TRADITIONAL RISK FACTORS FOR CARDIOVASCULAR DISEASE: A MENDELIAN RANDOMIZATION STUDY

Aleksander Kuś[1], *Eirini Marouli*[2], *Fabiola Del Greco M.*[3], *Layal Chaker*[4], *Robin Peeters*[5], *Alexander Teumer*[6], *Marco Medici*[7], *Panos Deloukas*[8]

[1]Academic Center for Thyroid Diseases, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands, Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands, Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland, Warsaw, Poland; [2]SMD, London, UK; [3]Institute for Biomedicine, Eurac Research, Affiliated Institute of the University of Lubeck, Bolzano, Italy; [4]Erasmus Medical Center, Rotterdam, Netherlands; [5]Academic Center for Thyroid Diseases, Department of Endocrinology, Erasmus, Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands, Rotterdam, Netherlands; [6]Institute for Community Medicine, University Medicine Greifswald, Germany, DZHK (German Center for Cardiovascular Research), Partner Site Greifswald, Greifswald, Germany, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany; [7]Radboud University Medical Center, Nijmegen, Erasmus Medical Center, Rotterdam, Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands; [8]William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK, Centre for Genomic Health, Life Sciences, Queen Mary University of London, London, UK, Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (Pacer-Hd), King Abdulaziz University, Jeddah, Saudi Arabia

Objectives: Observational studies demonstrated that even minor variation in thyroid function is associated with traditional risk factors for cardiovascular disease (CVD), including type 2 diabetes (T2D), hypertension, dyslipidaemia, and obesity. This poses the question as to whether it should be treated to prevent CVD. As observational studies could be prone to residual confounding and reverse causality, we performed Mendelian Randomization (MR) analyses to investigate whether these associations are causal.

Methods: MR using data from the largest available genome-wide association studies on TSH and FT4 levels, T2D, blood pressure, serum cholesterol levels, and body mass index (BMI). Causal estimates were assessed using the inverse variance weighted method and a P-value threshold of 0.01, after multiple testing correction. Next to normal range thyroid function, secondary analyses evaluated the causal effects of thyroid dysfunction, including (subclinical) hypo- and hyperthyroidism, on the tested outcomes.

Results: A one standard deviation (SD) increase in TSH levels is causally associated with a 0.04 SD increase in total cholesterol serum levels ($p=1.1x10^{-3}$) and a 0.31 mmHg decrease in pulse pressure (PP, $p=7.8x10^{-3}$). In line with these findings, secondary analyses suggest that (subclinical) hyperthyroidism is causally associated with increased PP ($\beta=0.15$, $p=2.2x10^{-4}$). In contrast, we found no evidence of a causal association between minor variation in thyroid function and BMI or T2D.

Conclusions: Variation in normal range thyroid function can affect the cardiovascular risk *via* its effects on cholesterol levels and blood pressure. Although the estimated effects are relatively small, they might be clinically relevant as they reflect a lifelong exposure. The fact that we found no evidence of a causal relationship between normal range TSH or FT4 levels and BMI or T2D suggests that the causal effects of minor variation in thyroid function on these outcomes are at most limited.

OP-10-58

ASSOCIATION OF MATERNAL THYROID FUNCTION WITH BIRTH WEIGHT: AN INDIVIDUAL-PARTICIPANT DATA META-ANALYSIS

Arash Derakhshan[1], *Peter Taylor*[2], *Sofie Bliddal*[3], *David Carty*[4], *Margreet Meems*[5], *Bijay Vaidya*[6], *Liangmiao Chen*[7], *Beverley Shields*[8], *Farkhanda Ghafoor*[9], *Polina V. Popova*[10], *Aya Hisada*[11], *Judith Bassols*[12], *Abel López-Bermejo*[13], *Colin Dayan*[14], *Laura Boucai*[15], *Marina Vafeiadi*[16], *Mònica Guxens*[17], *Victor J.M. Pop*[5], *Tanja G. Vrijkotte*[18], *Ulla Feldt-Rasmussen*[19], *Scott Nelson*[20], *Erik K. Alexander* [21], *Layal Chaker*[22], *Tuija Männistö*[23], *John P. Walsh*[24], *Elizabeth N. Pearce*[25], *Eric A. P. Steegers*[26], *Robin P. Peeters*[27], *Tim I. M. Korevaar*[27] *on behalf of the Consortium on Thyroid and Pregnancy*

[1]Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Cardiff University, School of Medicine, Cardiff University School of Medicine, Cardiff, UK; [3]Copenhagen University Hospital, Copenhagen, Denmark; [4]Department of Diabetes, Endocrinology & Clinical Pharmacology, Glasgow Royal Infirmary, Glasgow, UK; Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [5]Departments of Medical and Clinical Psychology, Tilburg University, Tilburg, The Netherlands; [6]Department of Endocrinology, Royal Devon and Exeter Hospital NHS Foundation Trust, University of Exeter Medical School, Exeter, UK; [7]Department of Endocrinology and Rui'an Center of the Chinese-American Research Institute for Diabetic Complications, Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [8]Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK; [9]National Health Research Complex, Shaikh Zayed Medical Complex, Lahore, Pakistan; [10]Almazov National Medical Research Centre, Saint Petersburg, Russian Federation, Department of Internal Diseases and Endocrinology, St. Petersburg Pavlov State Medical University, Saint Petersburg, Russian Federation; [11]Center for Preventive Medical Science, Chiba University, Chiba, Japan; [12]Maternal-Fetal Metabolic Research Group, Girona Biomedical Research Institute (Idibgi), Dr. Josep Trueta Hospital, Girona, Spain; [13]Pediatric Endocrinology Research Group, Girona Biomedical Research Institute (Idibgi), Dr. Josep Trueta Hospital, Girona, Spain; [14]Thyroid Research Group, School of Medicine, Cardiff University, Cardiff, UK; [15]Department of Medicine, Division of Endocrinology, Memorial Sloan-Kettering Cancer Center, Weill Cornell University, New York, NY, USA; [16]Department of Social Medicine, University of Crete, Heraklion, Greece; [17]Barcelona Institute for Global Health (Isglobal), Barcelona, Spain; [18]Department of Public Health, Amsterdam Umc, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands; [19]Department of Medical Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [20]University of Glasgow, Glasgow, UK; [21]Division of Endocrinology, Hypertension and Diabetes, Brigham and Women's Hospital, Harvard Medical School, Boston, USA; [22]Academic Center for Thyroid Diseases, Department of Epidemiology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; [23]Northern Finland Laboratory Center Nordlab and Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland; [24]Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia, Medical School, University of Western Australia, Crawley, Western Australia, Australia; [25]Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, Massachusetts, USA; [26]Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [27]Department of Internal Medicine, Erasmus University Medical Center, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands

Objective: To investigate the association of maternal thyroid function during pregnancy with birth weight.

Methods: We performed a systematic literature search and collected individual-participant data of eligible prospective cohort studies with data available on maternal thyroid function during pregnancy and birth weight. Main outcomes were birth weight (grams) and small or large for gestational age (SGA or LGA). Mixed-effects models were used to study predefined associations to account for between-study heterogeneity.

Results: A total of 46,135 participants from 19 studies were included (TSH N=46,135, FT4 N=46,003 and/or T3 N=14,692). A 1 SD higher FT4 was associated with a 21.1 gram lower mean birth weight (95% CI: -25.0 to -17.2), a 10% higher risk of SGA [OR (95% CI): 1.10 (1.06 to 1.14)] but a 10% lower risk of LGA [OR (95% CI): 0.90 (0.87 to 0.93)]. A 1 SD higher T3 was associated with 12.5 grams higher mean birth weight (95% CI: 5.83 to 19.2) and a 5% higher risk for LGA [OR (95% CI): 1.05 (1.00 to 1.10)] but not with SGA. Subclinical hypothyroidism was associated with a 34.5 grams lower mean birth weight (95% CI: -58.6 to -10.4) and a 20% higher risk of SGA [OR (95% CI): 1.20 (1.00 to 1.43)] while isolated hypothyroxinemia was associated with a 44.5 grams higher mean birth weight and a 28% lower risk of SGA [OR (95% CI): 0.72 (0.56 to 0.92)]. Similar effects were identified within the normal range, TSH was not associated with birth weight continuously.

Conclusions: High maternal FT4 and a low T3 as well as subclinical hypothyroidism are risk factors for SGA while low FT4 and isolated hypothyroxinemia are a risk factor for LGA. These results quantify the effects of maternal thyroid function on pregnancy metabolism and fetal growth and development.

OP-10-59

COMPARATIVE CLINICAL, GENETIC AND TRANSCRIPTOMIC CHARACTERIZATION OF RAI-SENSITIVE AND RAI-REFRACTORY THYROID CANCER IDENTIFIES IGF2 AS POTENTIAL DRIVER OF RAI RESISTANCE

Thomas Crezee[1], *Marika H. Tesselaar*[1], *Wim E. Corver*[2], *Hans Morreau*[2], *Ilse van Engen - van Grunsven*[1], *Johannes W.A. Smit*[3], *Romana T. Netea-Maier*[3], *Theo S. Plantinga*[1]
[1]Radboud University Medical Center, Department of Pathology, Nijmegen, Netherlands; [2]Leiden University Medical Center, Department of Pathology, Leiden, Netherlands; [3]Radboud University Medical Center, Department of Internal Medicine, Nijmegen, Netherlands

Objectives: Non-medullary thyroid cancer (NMTC) is the most frequent endocrine tumor with in most cases a good prognosis after thyroidectomy and 131-I radioactive iodide (RAI) ablation. In contrast, 30-40% of patients with metastatic NMTC are unresponsive to ^{131}I RAI treatment as a result of tumor dedifferentiation. Currently, underlying molecular mechanisms of NMTC dedifferentiation still remain elusive and predictive biomarkers are lacking. In the present study we therefore aim to discover molecular biomarkers in primary tumors that predict RAI sensitivity and to elucidate underlying intracellular processes involved.

Methods: A retrospective cohort of 63 NMTC patients, including all histological subtypes, was gathered for this study consisting of proven RAI-sensitive differentiated NMTC patients (N=35) and proven RAI-refractory (poorly) differentiated NMTC patients (N=28). Total DNA and RNA was extracted from archived FFPE tumor tissues. Extensive intratumoral mutation profiling, gene fusions analysis, TERT promoter mutation analysis and FFPE-compatible RNA sequencing was performed in all patients.

Results: RAI-refractory NMTC patients were diagnosed at older age and displayed less favorable TNM staging as compared to RAI-sensitive NMTC patients. Genetic analyses revealed an increased mutational load in RAI-refractory NMTC, including mutations in AKT1, PTEN, TP53 and TERT promoter. Furthermore, transcriptomic analyses revealed profound differential expression of insulin-like growth factor 2 (IGF2) with up to 100-fold higher expression in RAI-refractory NMTC as compared to RAI-sensitive NMTC cases.

Conclusions: Important clinical, genetic and transcriptomic differences are identified between patients with RAI-sensitive NMTC and RAI-refractory NMTC, providing molecular insights into the dedifferentiation process. Interestingly, the tumor-promoting growth factor IGF2 is identified as potential factor driving the development of RAI resistance. Genetic and functional studies are ongoing to elucidate mechanisms of IGF2 overexpression and IGF2-mediated pathways driving NMTC dedifferentiation and RAI resistance.

OP-10-60

IODINE FORTIFICATION DRAMATICALLY CHANGES THE SPECTRUM IN BOTH THYROTOXICOSIS AND HYPOTHYROIDISM SUBTYPES

Mads Petersen[1], *Inge Bülow Pedersen*[2], *Nils Knudsen*[3], *Stig Andersen*[4], *Torben Jørgensen*[5], *Hans Perrild*[3], *Lars Ovesen*[6], *Lone Banke Rasmussen*[3], *Betina Heinsbæk Thuesen*[7], *Allan Carle*[8]
[1]Aalborg University Hospital, Aalborg, Denmark; [2]Department of Endocrinology, Aalborg University Hospital; [3]Department of Endocrinology, Bispebjerg Hospital, University of Copenhagen; [4]Department of Geriatrics, Aalborg University Hospital; [5]Centre for Clinical Research and Prevention, Bispebjerg/Frederiksberg Hospital., Department of Public Health, Faculty of Health Sciences, University of Copenhagen; [6]Department of Gastroenterology, Slagelse Hospital; [7]Centre for Clinical Research and Prevention, Bispebjerg/Frederiksberg Hospital; [8]Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark

Objective: To investigate the impact of mandatory iodine fortification (IF) on the incidence of different nosological subtypes of overt thyrotoxicosis and hypothyroidism.

Methods: All possible new cases of overt thyrotoxicosis and hypothyroidism, identified in an open cohort in Northern Jutland (n=309,434 January 1st, 1997) during the years 2014-16, were individually scrutinized for all aspects of their medical history, to verify the incidence of overt thyroid dysfunction and to classify each case according to their nosological subtype. Mandatory IF of salt (13 ppm) was in effect by year 2001. A similar examination of all cases before mandatory IF was performed in 1997-00. During final verification a number of cases were excluded due to spontaneous normalization of thyroid function without treatment, with no medical history suggesting a known condition, which could cause transient thyroid dysfunction (subacute/silent thyroiditis, PPTD and iatrogenic thyroid dysfunction).

Results: The standardized incidence rate (SIR) of verified overt thyrotoxicosis decreased markedly from 97.5/100,000 person years in 1997-00 to 48.8 in 2014-16 (SIRR: 0.50 (95% CI: 0.45-0.56)). This was the result of a substantial decrease in the SIR of MNTG (SIRR: 0.18 (0.15-0.23)), STA (SIRR: 0.26 (0.16-0.43)) and to a lesser degree GD (SIRR: 0.67 (0.56-0.79)). No significant change in SIR of verified overt hypothyroidism was observed in 2014-16 (SIRR: 1.03 (0.87-1.22)), though an altered age distribution was evident with more young and fewer elderly cases.

Conclusion: Mandatory IF caused a substantial reduction in SIR of overt verified thyrotoxicosis (GD, STA and MNTG subtypes especially) while avoiding any increase in SIR of overt verified hypothyroidism.

Oral Session 11: Young Investigators / Basic

OP-11-61

FUNCTIONAL CHARACTERIZATION OF SLC17A4, A NOVEL PLAYER IN THE THYROID HORMONE TRANSPORT FIELD

Stefan Groeneweg[1], *Ferdy van Geest*[2], *Alexander Teumer*[3], *Marcel Meima*[4], *Heuer Heike*[5], *Robin Peeters*[6], *Marco Medici*[7], *W. Edward Visser*[8]

[1]Erasmus Medical Center; Academic Center for Thyroid Diseases, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands; [2]Erasmus MC, Rotterdam, Netherlands; [3]Institute for Community Medicine, University Medicine Greifswald, Germany, dzhk (German Center for Cardiovascular Research), Partner Site Greifswald, Greifswald, Germany, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany; [4]Dept.of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus MC, Rotterdam, Rotterdam, Netherlands; [5]Universitätsklinikum Essen, Klinik für Endokrinologie und Stoffwechselerkrankungen, Essen, Germany; [6]Academic Center for Thyroid Diseases, Department of Endocrinology, Erasmus, Department of Internal Medicine, Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands, Rotterdam, Netherlands; [7]Radboud University Medical Center, Nijmegen, Erasmus Medical Center, Rotterdam, Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands; [8]Erasmus Medical Center, Academic Center for Thyroid Diseases, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands

Introduction: A recent genome-wide association study identified the *SLC17A4* locus associated with circulating free T4 concentrations. Subsequently, SLC17A4, being widely expressed in the gastro-intestinal tract, was characterized as an efficient T3 and T4 transporter. Here, we further characterized the functional properties of SLC17A4 and explored the impact of several genetic variants on SLC17A4 function.

Methods: We transiently transfected COS-1 cells with an SLC17A4 expression construct, and studied the uptake and efflux of different iodothyronines in the presence and absence of the intracellular thyroid hormone binding protein CRYM, transporter saturation and cis-inhibition by different thyroid hormone metabolites. Seven different exonic single nucleotide polymorphisms (minor allele frequency > 0.1%) within *SLC17A4* were introduced by site-directed mutagenesis and their impact on SLC17A4-mediated transport was functionally evaluated.

Results: In the absence of CRYM, SLC17A4 induced the cellular uptake of T3 and T4 by 2-times, and of 3,3'-T2 and reverse (r)T3 by 1.5-times over control cells. The uptake of all substrates was 2-times higher in the presence of CRYM. SLC17A4 also induced the cellular efflux of T3 and T4, and to a lesser extent rT3 and 3,3'-T2. Apparent IC_{50} values for T3 and T4 were 0.35±0.13 µM and 0.06±0.01 µM, respectively. SLC17A4-mediated uptake of T3 and T4 was Na^+-independent and was reduced by increasing concentrations of 3,3'-T2, 3,5-T2, rT3, and different iodothyronine metabolites, including iodothyroacetic acid and proprionic acid derivatives. Thyroid hormone transport by SLC17A4 was largely diminished by the c.1040T>G (p.L347R) and c.1297C>T (p.Q433X) variants.

Discussion: Our studies show that SLC17A4 efficiently facilitates the uptake and efflux of T3, T4 > rT3 > 3,3'-T2, and identified two single nucleotide polymorphisms that reduce SLC17A4-mediated thyroid hormone transport. Future studies should elucidate if and how SLC17A4 is involved in handling of thyroid hormone in the gastro-intestinal tract.

OP-11-62

ALTERED THYROID FUNCTION REGULATES ADRENAL CORTEX DEVELOPMENT AND FUNCTION IN MICE

Konrad Patyra[1], *Holger Jäschke*[2], *Christoffer Löf*[1], *Marcin Chrusciel*[3], *Milena Doroszko*[3], *Julian Undeutsch*[1], *Fuping Zhang*[1], *Andreina Kero*[4], *Matti Poutanen*[1], *Jorma Toppari*[3], *Ralf Paschke*[5], *Nafis Rahman*[3], *Ilpo Huhtaniemi*[3], *Jukka Kero*[1]

[1]Research Centre for Integrative Physiology and Pharmacology, Tcdm, Institute of Biomedicine, University of Turku, Turku, Finland; [2]Universitätsklinikum Essen (Aör), Klinik für Endokrinologie, Diabetologie und Stoffwechsel, Department of Endocrinology, Diabetes and Metabolism, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, Essen, Germany; [3]Research Centre for Integrative Physiology and Pharmacology, Institute of Biomedicine, University of Turku, Turku, Finland; [4]Department of Pediatrics, Turku University Hospital, Turku, Finland; [5]Cumming School of Medicine, University of Calgary, Calgary, Canada

Thyroid hormones (TH) play a crucial role in the development and physiology of various organs such as brain, bones and lungs. Recently, TH have also been demonstrated to regulate adrenal development and function both in humans and mice. In hypothyroid neonates TH can regulate adrenal steroid production and affect fetal zone remodeling. Analogously, the TH can regulate the inner layer of the mouse adrenal cortex, so-called X-zone, via the thyroid hormone receptor beta. However, the physiological impact of this regulation remains unraveled. In order to further investigate the role of TH on adrenal physiology, we evaluated the adrenal development and function in both hyper- and hypothyroid mouse models. Our hyperthyroid model carries a patient-derived constitutively active thyrotropin receptor mutation D633H in the murine *Tshr* locus leading to transient hyperthyroidism at an early age between 2-4 months in both genders. In contrast, the hypothyroid model carries an inactivating mutation in the TSHR and develops congenital hypothyroidism. Surprisingly, the hyperthyroid female mice showed enlarged adrenals at 4 months of age, whereas no difference was observed in hyperthyroid males. Further histological analysis of the enlarged adrenals revealed a thick layer of vacuolated cells between the adrenal cortex and medulla. Interestingly, adrenal weight in hyperthyroid females was significantly elevated in 2- to 9-month old animals compared to wild type controls, but at 12 months of age no weight differences were observed. The enlarged adrenal phenotype was associated with elevated serum sodium levels, a thinner cortex, increased gene expression of thyroid hormone receptor beta and cytochrome P450, family 51 (*Cyp51*) and downregulated expression of proliferation marker *Ki67,* medulla marker chromogranin A, and steroidogenesis enzyme *Hsd3b1*. In contrast to the hyperthyroid model, a thinner X-zone and altered cortex histology were detected in our hypothyroid model. In summary, findings in our hyper- and hypothyroid models suggest a sex-dependent role of TH in mouse X-zone development, adrenal gene expression and function.

OP-11-63

THE INTRACELLULAR METABOLISM OF THYROID HORMONE REGULATES THE TUMOR PROGRESSION OF SKIN CANCER

Annunziata Gaetana Cicatiello[1], *Caterina Miro*[1], *Emery Di Cicco*[1], *Giuseppina Mancino*[1], *Serena Sagliocchi*[1], *Annarita Nappi*[1], *Daniela Di Girolamo*[1], *Raffaele Ambrosio*[2], *Maria Angela De Stefano*[1], *Cristina Luongo*[1], *Anita Boelen*[3], *Domenico Salvatore*[1], *Monica Dentice*[1]

[1]Department of Clinical Medicine and Surgery, University of Naples "Federico II"; [2]IRCCS SDN, Naples; [3]Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Thyroid hormone (TH) signaling regulates growth and differentiation in all cell types and tissues and, accordingly has strong impacts on cancer. Non-melanoma skin cancers (NMSCs), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most frequent cancers worldwide. While BCCs are rarely aggressive, SCCs can progress and associate with a substantial risk of metastasis. We demonstrated that, during SCC tumor progression, a switch in intra-tumoral TH is obtained by the time-specific action

of the TH-inactivating (D3) and TH-activating (D2) enzymes. Notably, TH attenuation initially promotes tumor formation, but as tumors develop and progress, a positive switch in TH signal enhances cancer invasion. These effects are mediated by a cell-autonomous mechanism of TH activation/inactivation catalyzed by the TH-modulating enzymes, D2 and D3, in cancer cells. Consequently, TH attenuation in D2KO epidermis confers growth advantage to cancer cells but reduces invasive capacity. Accordingly, in human clinical specimens, high D2 expression correlated with reduced survival and increased risk of tumor relapse. Thus, inhibiting D2 might be explored as a therapeutic approach for patients with advanced tumors.

OP-11-64

THE THYROID HORMONE TRANSPORTER MCT8 IS INDISPENSABLE FOR ADULT HIPPOCAMPAL NEUROGENESIS

Steffen Mayerl[1], *Heike Heuer*[2], *Charles Ffrench-Constant*[1]
[1]Mrc Centre for Regenerative Medicine, Edinburgh, UK; [2]University Hospital Essen, University of Duisburg-Essen, Germany

Adult hippocampal neurogenesis is a highly orchestrated process critically important for learning and memory function. Thyroid hormone (TH) is known to regulate later stages of the neurogenic program with TH deficiency compromising the birth of new granule cell neurons. However, information about TH signalling components implicated in this process is sparse. Here, we employed a combination of flow cytometry, qPCR and immunohistochemistry to decipher the spatiotemporal expression of TH signalling regulators in the hippocampal neurogenic lineage in adult mice. Not only could we detect prominent alterations in TH signalling regulators at the neuroblast stage and in mature neurons, but also revealed monocarboxylate transporter (Mct) 8 as the sole TH transporter expressed in neuroblasts. To elucidate consequences of Mct8 deficiency in vivo we performed immunostainings and lineage tracing studies in mice. Thereby, we found an insufficient differentiation of neuroblasts together with impaired generation of new hippocampal granule cell neurons in the absence of Mct8. Moreover, Mct8 knockout mice exhibited decreased levels of cell cycle inhibitor p27KIP1 in neuroblasts and immature neurons. Importantly, the same changes were also observed in conditional knockout animals lacking Mct8 expression in the adult neurogenic lineage only. We thus hypothesize that Mct8 expression in neuroblasts is essential for a timed increase in intracellular TH content which in turn stimulates p27KIP1, induces cell cycle withdrawal and allows for differentiation programs to be initiated. Together, this study improves our understanding of the role of TH for learning and memory function as well as of the impact of altered TH availability such as in Allan-Herndon-Dudley Syndrome on both functions.

OP-11-65

DIFFERENTIAL EXPRESSION PRO-INFLAMMATORY CYTOKINES DURING BRAFV600E-INDUCED THYROID TUMOR DEVELOPMENT

Carmen Moccia[1], *Elin Schoultz*[2], *Mikael Nilsson*[3]
[1]Sahlgrenska Cancer Centre, Gothenburg, Sweden; [2]Sahlgrenska Cancer Center, Institute of Biomedicine, University of Gothenburg, University of Gothenburg, Sahlgrenska Cancer Center, Gothenburg, Sweden; [3]Sahlgrenska Cancer Center, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden

A current problem in transgenic cancer models is that conditionally expressed oncogenes are synchronously activated in all target cells and this ubiquitous activation seriously constrains analysis of tumor features in the natural microenvironment. For papillary thyroid carcinoma (PTC), this problem is overcome by a novel approach In which spontaneous Cre activation in a limited number of cells enables development of multicentric tumors within a preserved normal thyroid tissue in $TgCreER^{T2};Braf^{CA/fl}$ mice. Here, we further characterized this model by investigating cancer-related inflammation as previously reported for human thyroid carcinomas.

Objectives: Characterize the spatiotemporal expression pattern of pro-inflammatory cytokines during sporadic PTC tumor development in a murine model of $Braf^{v600e}$-induced PTC.

Methods: Sampling of thyroid tissues for quantitative RT-PCR (qPCR) analysis of *TNFa*, *IL-1*, *IL-6*, *CXCR4*, *TSP1* and *MMP2* in wildtype (wt) and $TgCreER^{T2};Braf^{CA/fl}$ mice at age of 3-6-12 months, and after oral treatment with vemurafenib.

Results: Only minute cytokine mRNAs were detected in the absence of $Braf^{CA}$ activation. *IL-1* was consistently highly expressed (x5-30) at all time points. *IL-6* was expressed up to 60-fold at 6 mo but hardly detectable at 3 and 12 mo. *TNFa* was low at 3 mo but increased (x7-12) at 6 and 12 mo. C*XCR4* increased 10-20 times at 6 mo but was mostly not different from wt at 3 and 12 mo. *TSP1* was overexpressed at 3mo (x3) and 6 mo (x4-8) but undetectable at 12 mo. *MMP2* was stably overexpressed (x5) at all time points. Differential cytokine expression was evident between left and right lobes at 3 and 6 mo, and among dissected macrotumor foci at 12 mo. Vemurafenib administered at 6+1 mo nearly abolished expression of all cytokine mRNAs.

Conclusions: Sporadic PTC tumorigenesis is accompanied by multiple cytokine overexpression that follows distinct long-term kinetics for individual cytokines. Cytokine overproduction is a direct consequence of mutant Braf activation.

OP-11-66

SIX1 IS OVEREXPRESSED IN ANAPLASTIC THYROID CANCER AND PROMOTES EPITHELIAL-TO-MESENCHYMAL TRANSITION

Adrían Acuña-Ruiz[1], *Garcilaso Riesco-Eizaguirre*[2], *Pilar Santisteban*[3]
[1]Instituto de Investigaciones Biomédicas “Alberto Sols”, Madrid, Spain; [2]Hospital Universitario de Móstoles, Iib “Alberto Sols”, Universidad Francisco de Vitoria, Móstoles, Spain; [3]Instituto de Investigaciones Biomédicas, Universidad Autónoma de Madrid, Ciberonc, Instituto de Salud Carlos III, Madrid, Spain

The SIX1 homeoprotein is a developmental transcription factor that has been identified as an important player during tumour initiation and progression. Higher levels of SIX1 expression has been described in many different epithelial cancer types such as breast, prostate and endometrial carcinoma. This overexpression also correlates with poor prognosis. SIX1 participates in the regulation of the epithelial to mesenchymal transition (EMT) by the regulation of different target proteins of TGFβ signalling.

Our aim was to study the role of SIX1 in thyroid cancer, as a potential marker associated with malignancy, and its connection with the TGFβ pathway as an EMT regulator.

Our results show that SIX1 expression correlated inversely with the differentiation status according to histological sub-type. Thus, its expression was low in control Nthy-ori 3-1 and in papillary thyroid cancer cells being higher in anaplastic thyroid cancer (ATC) cell lines. These results were also validated by using public functional genomics data from the Gene Expression Omnibus (GEO) repository. Downregulation of SIX1 by shRNA reduced cell proliferation, assayed by BrdU, migration by means of wound healing and invasion by matrigel assay. The decrease of SIX1 expression was also associated with the loss of EMT markers. Opposite results were found by gain-of-function experiments. Recombinant TGFβ1 treatment increased the levels of SIX1 and the inhibition of the PI3K pathway, mediated by the overexpression of PTEN or by using the AKTi inhibitor, reduced SIX1 expression significantly in ATC cell lines.

SIX1 participates in the latest stage of thyroid dedifferentiation, promoting malignant behaviour in thyroid cancer cells by the overexpression of EMT markers and the regulation of cell cycle progression. TGFβ and PI3K pathway are involved in the regulation of SIX1 expression. We described SIX1 as a potential therapeutic marker in ATC.

Oral Session 12: Pregnancy, Hypothyroidism and Aging

OP-12-67

FREQUENCY OF MATERNAL THYROID FUNCTION ABNORMALITIES AND THYROID AUTOIMMUNITY AMONG 14,323 PREGNANT WOMEN IN THE NORTH DENMARK REGION

Louise Knøsgaard[1], *Stig Andersen*[2], *Annebirthe Bo Hansen*[3], *Peter Vestergaard*[4], *Stine Linding Andersen*[5]
[1]Aalborg, Denmark; [2]Department of Geriatrics, Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, Denmark; [3]Department of Clinical Biochemistry, Aalborg University Hospital, Denmark; [4]Department of Endocrinology Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, Denmark; [5]Department of Clinical Biochemistry, Aalborg University Hospital, Department of Clinical Medicine, Aalborg University, Denmark

Introduction: Thyroid diseases are common in women of reproductive age and mainly of autoimmune origin. Mandatory iodine fortification was implemented in Denmark in the year 2000, and the frequency of thyroid function abnormalities and thyroid autoimmunity among pregnant women in West Denmark remains to be clarified.

Methods: We consecutively collected serum residues from blood samples drawn as part of prenatal screening in the North Denmark Region from 2011-2015. The first blood sample (median pregnancy week 10) drawn in the woman's first pregnancy in the study period was included (n=14,323). TSH, free T4, thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab) were measured using an ADVIA Centaur (Siemens Haelthineers) immunoassay. Method- and week-specific reference ranges were used for classification of maternal thyroid function, and cut-off values were given by the manufacturer for TPO-Ab and Tg-Ab evaluation. Information in Danish nationwide registers was used for classification of known or later diagnosed maternal thyroid disease.

Results: Overall, 15.2% of the pregnant women had abnormal thyroid function in early pregnancy, and hypothyroidism was the most frequent thyroid function abnormality observed (Table). Altogether 14.9% were positive for TPO-Ab and/or Tg-Ab (10.9% TPO-Ab ± Tg-Ab; 10.4% Tg-Ab ± TPO-Ab). Among women with known thyroid disease (n=365), the frequency of abnormal thyroid function was 30.6% when maternal thyroid disease was previously treated and 62.8% in women receiving current treatment. Among the 313 women first diagnosed with thyroid disease after the blood sampling, 46.7% had abnormal thyroid function in early pregnancy and 54.3% were TPO-Ab and/or Tg-Ab positive.

Conclusion: The frequency of thyroid function abnormalities and thyroid autoimmunity was high, especially among women with known thyroid disease, but also among women diagnosed with thyroid disease in the years following pregnancy.

	n	%
No thyroid dysfunction	**12145**	**84.8**
Thyroid dysfunction	**2178**	**15.2**
Hyperthyroidism	**557**	**3.9**
Overt	230	1.6
Subclinical	327	2.3
Hypothyroidism	**905**	**6.3**
Overt	140	1.0
Subclinical	765	5.3
Abnormal free T4, normal TSH	**716**	**5.0**

OP-12-68

THYROID FUNCTION AND CIRCULATING METABOLITES: EVIDENCE FROM OBSERVATIONAL AND MENDELIAN RANDOMIZATION STUDIES

Nicolien van Vliet[1], *Raymond Noordam*[1], *Maxime M. Bos*[1], *Naveed Sattar*[2], *J. Wouter Jukema*[3], *Diana van Heemst*[1]
[1]Section of Gerontology and Geriatrics, Department of Internal Medicine, Leiden University Medical Center, Leiden, Netherlands; [2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [3]Department of Cardiology, Leiden University Medical Center, Leiden, Netherlands

The link between thyroid hormones and lipid metabolism is well-established, but it is unknown whether specific lipid subclasses are involved. To address this question, we conducted both an observational study in a subsample of the PROSPER trial as well as a two-sample Mendelian randomization (MR) study using published summary-level data from a genome-wide association study (N=24,925) to assess the associations of thyrotropin (TSH) and free thyroxine (fT4) levels within the reference range with metabolites from a targeted metabolomics platform.

In the PROSPER study, we used linear regression adjusted for age and sex in trial participants assigned to the placebo arm who did not use thyroid medication (N=2,293). As genetic instruments for the MR studies we used 57 genetic variants for TSH and 30 genetic variants for fT4. Associations between the genetic instruments for TSH and for fT4 and the metabolites were modeled using Inverse Variance Weighted (IVW), and MR Egger and Weighted Median were used for sensitivity analyses. All analyses took multiple testing for 37 independent metabolites into account (P<1.34x10-3).

Observationally, TSH was associated with 25% of the metabolites (mainly VLDL), and fT4 was associated with 60% of the metabolites across all lipoprotein subclasses, ketone bodies and branched-chain amino acids. Out of 123 metabolites, genetically determined higher TSH levels were associated with lower concentration of very large HDL only (IVW -0.09 SD, 95% C.I. -0.14;-0.05, P=1.66x10-4), while genetically determined higher fT4 levels were associated with higher glycoprotein acetyls only (IVW 0.12 SD, 95% C.I. 0.05;0.19, P=7.88x10-4). We found no evidence for directional pleiotropy, as results for MR Egger and Weighted Median were similar.

Possible explanations for the observed discrepancy in the results between the observational and MR analyses include differences in power, residual confounding or different biological mechanisms for the observed compared to the genetically determined thyroid status.

OP-12-69

LEVELS OF THYROID STIMULATIONG HORMONE AND THE RISK OF CARDIOVASCULAR MORBIDITY: META-ANALYSIS OF 5 COHORT STUDIES

Line Tang Moellehave[1], *Allan Linneberg*[2], *Tea Skaaby*[3], *Nils Knudsen*[4], *Torben Jørgensen*[5], *Inge Bulow Pedersen*[6], *Betina Thuesen*[7]

[1]Center for Clinical Research and Prevention, Frederiksberg and Bispebjerg Hospital, Frederiksberg, Denmark; [2]Research Centre for Prevention and Health, Centre for Health, The Capital Region of Denmark, Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark, Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark, Glostrup, Denmark; [3]Research Centre for Prevention and Health, Centre for Health, The Capital Region of Denmark, Glostrup; [4]Bispebjerg University Hospital, Copenhagen, Denmark; [5]Research Centre for Prevention and Health, The Capital Region of Denmark, Glostrup, Denmark, Faculty of Medicine, Aalborg University, Aalborg, Denmark, Faculty of Health Sciences, Copenhagen, Denmark, Glostrup, Denmark; [6]Dept. Of Medicine and Endocrinology, Medicinerhuset, Mølleparkvej Aalborg, Aalborg, Denmark; [7]Research Centre for Prevention and Health, Centre for Health, The Capital Region of Denmark, Glostrup, Denmark

Objectives: Thyroid dysfunction may affect cardiovascular morbidity through effects on myocardial and vascular tissue and metabolism. Levels of thyroid stimulating hormone (TSH) is an indicator of thyroid function. We aimed to examine the association between TSH-levels in the general adult population and incident ischemic heart disease and stroke in five Danish cohorts.

Methods: 13,865 participants (age range 18–71 years, 51.6% women) were included. TSH was measured at the baseline examination and divided into quintiles in each cohort. Incident cases of ischemic heart disease (IHD) and stroke were derived from the Danish National Patient Register. Data were analyzed by multivariate Cox regression with age as underlying time axis and adjusted for sex. The individual study results were pooled by random-effects meta-analysis.

Preliminary results: Median TSH was 1.35 mU/l (inter quartile range: 0.90–1.95 mU/l). 1305 incident cases of IHD and 986 incident cases of stroke were identified through 189,454 person years and 194,014 person years, respectively (mean follow-up: 14.1 years). Analyses showed no association between high TSH and IHD (HR 1.045 (95%CI 0.867-1.259) for TSH in the 5th vs. 3rd quintile) or stroke (HR 1.061 (95%CI 0.862-1.306) for TSH in the 5th vs. 3rd quintile). Nor did we find an association between low TSH and IHD (HR 1.067 (95%CI 0.884-1.287) for TSH in the 1st vs. 3rd quintile) or stroke (HR 0.945 (95%CI 0.647-1.380) for TSH in the 1st vs. 3rd quintile). However, analyses suggested an increased risk of IHD with TSH in the 4th vs. 3rd quintile (HR 1.208 (CI95% 1.013-1.442)).

Conclusions: Our results did not consistently support an association between elevated or depressed levels of TSH and an increased risk of IHD or stroke. However, a small-moderate effect or effect in sub-groups cannot be ruled out.

OP-12-70

INCREASED RISK OF DEMENTIA IN AUTOIMMUNE HYPOTHYROIDISM. A DANISH NATIONWIDE REGISTER-BASED STUDY

Marianne Thvilum[1], *Frans Brandt Kristensen*[2], *Lars Folkestad*[3], *Thomas Brix*[4], *Laszlo Hegedüs*[5]

[1]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark; [2]Hospital of Southern Jutland, Hospital of Southern Denmark, Department of Internal Medicine, Sønderborg, Denmark; [3]Department of Endocrinology and Metabolism, Ibsa Nordic, Odense University Hospital, Odense, Denmark; [4]Department of Endocirnology, Odense University Hospital, Odense University Hospital, Odense, Denmark; [5]Dept. Endocrinol. Odense Uni. Hosp., Odense University, Odense University Hospital, Odense, Denmark

Background: Autoimmune hypothyroidism (AIH) has been linked with an increased risk of both somatic and psychiatric morbidity as well as persistent cognitive deficiency and decreased quality of life. Whether AIH is associated with increased risk of dementia remains unknown. Therefore, we evaluated, at a nationwide level, the risk of dementia in patients with AIH.

Methods: Register-based study of the entire Danish population from 1995-2012. Based on record-linkage of Danish health registers, 111,565 subjects with AIH were identified and each matched for age and sex with 4 randomly selected euthyroid controls and followed over a median period of 6 years (range 0-17). Presence of dementia, in cases as well as controls, was recorded. The risk of dementia following the diagnosis of AIH was estimated using Cox proportional hazards regression models. Results were adjusted for pre-existing somatic as well as psychiatric morbidity. Risk of dementia prior to AIH was evaluated with a logistic regression model.

Results: The majority of the included individuals were females (82%) and the median age at diagnosis of AIH was 56 years (range 18-104). Pre-existing dementia was not significantly associated with an increased risk of being diagnosed with AIH (OR 0.97; 95% CI:0.90-1.04). However, there was a higher prevalence of dementia following the diagnosis of AIH in cases as compared to controls, 3.6% *versus* 3.3%, respectively. In the Cox regression analyses, the risk of dementia was significantly increased in subjects with AIH (HR 1.22; 95% CI: 1.17-1.27), also after adjusting for degree of pre-existing somatic and psychiatric morbidity (HR 1.09; 95% CI: 1.05-1.14).

Conclusions: Being diagnosed with autoimmune hypothyroidism is associated with an increased risk of subsequently being diagnosed with dementia, even after adjusting for pre-existing morbidity. Investigation of other hypothyroidism phenotypes may shed light on the relative contribution of autoimmunity and hypothyroidism for this association.

		TSH, (mU/l)				
Cohort	**N**	**1st quintile**	**2nd quintile**	**3rd quintile**	**4th quintile**	**5th quintile**
1914-cohort	601	0.10-0.30	0.40-0.80	0.90-1.50	1.60-2.50	2.60-30.00
1936-cohort	918	1.10-1.40	1.50-1.50	1.60-2.20	2.30-3.60	3.70-32.10
Monica10	2647	0.01-0.51	0.52-0.76	0.77-1.03	1.04-1.46	1.47-67.40
Inter99	6341	0.01-0.91	0.91-1.22	1.23-1.60	1.61-2.20	2.21-75.00
Health2006	3358	0.01-0.90	0.90-1.22	1.23-1.59	1.60-2.18	2.19-53.10

OP-12-71

TARGETED IDENTIFICATION OF RESISTANCE TO EXOGENOUS T4 IN HUMANS

Cristian González-Guerrero[1], *Nerea Lacámara*[2], *Beatriz Lecumberri*[3], *Isabel González-Casado*[4], *Arantxa Escribano*[5], *Ilgin Yildirim*[6], *Juan Bernal*[7], *Pere Berbel*[8], *José C. Moreno*[9]

[1]Thyroid Molecular Laboratory, Institute for Medical and Molecular Genetics-INGEMM, La Paz University Hospital, Madrid, Spain; [2]Thyroid Molecular Laboratory, INGEMM, La Paz University Hospital; [3]Endocrinology. La Paz University Hospital; [4]Pediatric Endocrinology, La Paz University Hospital; [5]Pediatric Endocrinology, Virgen de La Arrixaca Hospital, Murcia, Spain; [6]Endocrinology and Metabolism, Ege University Hospital, Izmir, Turkey; [7]Instituto de Investigaciones Biomédicas, Csic, and Ciberer, Madrid, Spain; [8]Histology and Anatomy Department, Medical Faculty, Miguel Hernández University of Elche, Alicante, Spain; [9]Thyroid Molecular Laboratory, Instirute for Medical and Moleuclar Genetics-INGEMM, La Paz University Hospital, Madrid, Spain

Background: Thyroxine (T4) to triiodothyronine (T3) deiodination in hypothalamus/pituitary is mediated through *Dio2* expression. *Dio2*$^{(-/-)}$ mice show central resistance to levothyroxine (L-T4). In humans, euthyroid thyroidectomized patients with Ala92-DIO2 polymorphism receiving L-T4 show a slightly decreased serum T3, but within the normal range (nr). However, patients with hormone profiles consistent with central resistance to exogenous L-T4 (RETH) remain unidentified.

Objective: Our aim was the targeted identification of RETH patients and their characterization from a clinical, hormonal and genetic perspective.

Patients & Methods: Hypothyroid patients were recruited when thyrotropin remained elevated (TSH >5 mU/L) under regular L-T4 doses, and could only be normalized under high L-T4 doses leading to biochemical or clinical hyperthyroidism. TSH and free T4 (fT4) were determined by ELISA, and Total T3 (T3), T4 (T4), and reverse T3 (rT3) by radioimmunoassay. TSH/fT4 ratio at inclusion, and T3/T4, rT3/T4 and T3/rT3 ratios at follow-up were compared to those from patients with classical resistance to thyroid hormone (RTH) harboring *THRB* (thyroid hormone receptor-β) gene mutations. *DIO2, SECISBP2* and *THRB* genes were fully sequenced including the Ala92-DIO2 polymorphism and the entire SECIS element at the 3´-untranslated region.

Results: Eighteen hypothyroid patients (9 females, 3-59 years) were identified meeting the inclusion criteria. Etiology of hypothyroidism varied from thyroidectomy/radioactive thyroid ablation for Graves´ disease to autoimmune thyroiditis, severe thyroid hypoplasia or isolated hyperthyrotropinemia. At inclusion, patients showed elevated TSH (15.5±4 mU/L; nr: 0.4-4.5), fT4 (20.8±2 pmol/L; nr: 9-20) and TSH/fT4 ratio (0.74±0.25; nr: 0.03-0.13). TSH was only normalized after L-T4 increase from 1.7±1 to 2.4±1 µg/kg/day. At follow-up, L-T4 was progressively decreased to regain euthyroidism, at the expense of permanent hyperthyrotropinemia. In parallel, T3/T4 ratio were also decreased (9.2±2.4; nr: 11.3-15.3) whilst rT3/T4 increased (0.6±0.2; nr: 0.43-0.49). This suggests reduced T4 to T3 activation and increased T4 to rT3 inactivation, which does not occur in RTH patients. Genetic screens were normal. The Ala92-*DIO2* polymorphism was present in 7/18 patients (5 heterozygotes, 2 homozygotes) but without correlation with the RETH profile.

Conclusions: RETH characterizes by increased TSH/fT4 ratio at clinical suspicion, and decreased T3/T4, increased rT3/T4 and decreased T3/rT3 ratios at confirmatory diagnosis. Such profile comprehensively guides for a combined T4+T3 therapy in RETH patients. The absence of germline mutations in *DIO2* suggests that either aberrant hypothalamic/pituitary posttranslational D2 modifications or defects in other genes regulating the T4 to T3 conversion pathway could be involved in RETH.

OP-12-72

RESTORATION OF EUTHYROIDISM IN HYPOTHYROID WOMEN CHANGES BONE MICROARCHITECTURE BUT NOT BONE STRENGTH, AS INVESTIGATED BY HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY (HR-PQCT)

Maria Lohman Pedersen[1], *Pia Nicolaisen*[2], *Stinus Gadegaard Hansen*[3], *Kristian Hillert Winter*[2], *Anne Pernille Hermann*[2], *Niklas Rye Jørgensen*[4], *Laszlo Hegedüs*[2], *Thomas Brix*[2], *Steen Joop Bonnema*[2]

[1]The Department of Endocrinology, Odense, Denmark; [2]The Department of Endocrinology, Odense, Denmark; [3]The Department of Endocrinology, Denmark; [4]Department of Clinical Chemistry, Glostrup, Denmark

Objective: Studies on fracture risk in hypothyroid patients show discrepant results. Bone mass is typically increased, but since effects on bone microarchitecture and strength are unclarified, we investigated these parameters by High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT).

Methods: Two approaches were used: A) a cross-sectional study, comparing 32 hypothyroid (23 with subclinical hypothyroidism) women (mean age; 47±12 years) with 32 healthy women matched for age and menopause; B) a prospective study, where 27 of the 32 women were re-examined one year after obtaining euthyroidism with levothyroxine. HR-pQCT of the distal radius and tibia, and dual energy X-ray absorptiometry (DXA) of the lumbar spine and total hip were performed.

Results: Study A: In radius, the total (10.2%, $p<0.044$) and trabecular areas (12.9%, $p<0.038$) were higher and cortical volumetric bone mineral density (vBMD) was lower (-2.5%, $p<0.032$) in hypothyroid patients compared to controls. All indices of radius and tibia cortical and trabecular vBMD, microarchitecture and estimated bone strength were similar between groups, as was areal BMD (aBMD) measured by DXA.

Study B: In tibia, total vBMD decreased (-1.1%, $p<0.013$), primarily due to a decrease in cortical vBMD (-0.8%, $p<0.007$) and an increase in cortical porosity (9.8, $p<0.002$). The trabecular area (0.2%, $p<0.05$) increased. In radius, no change in total vBMD was detected, although both cortical (-0.9, $p<0.020$) and trabecular (-1.6%, $p<0.020$) vBMD decreased. The ratio trabecular bone volume to tissue volume decreased (-1.7%, $p<0.009$) and cortical porosity increased (22.3%, $p<0.016$). No changes in estimated bone strength in tibia or radius were detected. Lumbar spine aBMD, measured by DXA, decreased (-1.2%, $p<0.037$).

Conclusion: In hypothyroid women, as compared with healthy women, differences in bone microarchitecture were of only minor significance. Restoration of euthyroidism resulted in small changes in bone microarchitecture, reflected by decreased cortical bone indices, which did not affect bone strength.

OP-12-73

THYROID AUTOIMMUNITY AND INTRACYTOPLASMIC SPERM INJECTION OUTCOME: A SYSTEMATIC REVIEW AND META-ANALYSIS

Kris Poppe[1], *Candice Autin*[1], *Veltri Flora*[1], *Pierre Kleynen*[1], *Serge Rozenberg*[1], *Ameye Lieveke*[2]

[1]Chu Saint-Pierre (Université Libre de Bruxelles, ULB), Brussels, Belgium; [2]Bordet Institute (Université Libre de Bruxelles, ULB), Brussels, Belgium

Background: Since 2010, three meta-analyses have been published on the impact of thyroid autoimmunity (TAI) on pregnancy outcomes in infertile women treated with assisted reproductive technology (ART). The initially observed high risk of miscarriage became very low in the most recent meta-analysis published in 2016.

Objective: To investigate whether the lower risk of miscarriage in the latest meta-analysis was associated with the increased use of intracytoplasmic sperm injection (ICSI) in recent studies.

Data source: MEDLINE was searched from January, 1990, to May, 2017.

Study selection: Data from case-control and cohort studies, on ART (IVF/ICSI) pregnancy outcomes in women with and without TAI. Only studies were included in which women were treated with ICSI.

Data extraction and synthesis: Four studies were retained including 1855 ICSI cycles (290 with and 1565 without TAI). In women with a clinical pregnancy (114 ICSI cycles with TAI and 651 without), there was no difference in miscarriage or live birth rates: respective combined OR 0.95 (95% CI, 0.48 to 1.87) and 1.12 (95% CI, 0.62 to 2.03). There was no difference in age in women with and without TAI: combined mean difference of 0.13 years (95% CI, -0.51 to 0.76), but serum TSH was higher in women with TAI: combined mean difference of 0.20 mIU/L (95% CI, 0.07 to 0.33).

Conclusion: Infertile women with TAI treated with ICSI had no increased risk of a first trimester miscarriage compared with women without TAI.

OP-12-74

DRINKING WATER IODINE CONTENT IS ASSOCIATED WITH LONGEVITY IN OLDER ADULTS: 20 YEAR FOLLOW-UP OF THE RANDERS-SKAGEN STUDY

Johannes Riis[1], *Klaus M. Pedersen*[2], *Steen Terpling*[3], *Finn Iversen*[4], *Mathias Brix Danielsen*[5], *Gustav V.B. Sørensen*[5], *Louise Westergaard*[5], *Stine L. Andersen*[5], *Allan Carlé*[6], *Inge B. Pedersen*[6], *Christian Torp-Pedersen*[7], *Stig Andersen*[5]
[1]Aalborg University Hospital, Department of Geriatrics, Denmark; [2]Vejle Hospital, Department of Internal Medicine; [3]Aalborg University Hospital, Department of Infectious Diseases; [4]Skagen Hospital; [5]Aalborg University Hospital, Department of Geriatrics; [6]Aalborg University Hospital, Department of Endocrinology; [7]Aalborg University Hospital, Unit of Epidemiology and Biostatistics

Objective: Iodine intake affects the occurrence of thyroid dysfunction. However, the impact of iodine intake on longevity in older adults remains unknown. This led us to perform 20-year follow up on data from the Randers-Skagen (RaSk) study.

Methods: Residents in Randers born in 1920 (n = 210) and Skagen born in 1918-1923 (n=218) were included in 1997-1998. We collected baseline characteristics through questionnaires, clinical examination, measurement of iodine in urine and thyroid function tests from blood samples. Income data was gathered from Danish registries. Iodine contents in drinking water were 2 µg/l in Randers and 140 µg/l in Skagen. We gathered follow-up on mortality until 12-12-2017 using Danish registries.

Results: Twenty-year follow-up data was available on 426 of 428 participants (99.5%). At baseline, median estimated 24-hour urinary iodine concentration was 50 µg/24h in Randers and 177 µg/24h in Skagen. Participants had resided for an average of 35 and 53 years in Randers and Skagen, respectively. At the end of follow-up, 10 (5%) residents were alive in Randers and 26 (12%) were alive in Skagen ($P = 0.02$). Cox regression showed that living in Skagen compared to Randers was associated with decreased hazard of death in both age and sex adjusted analysis (HR 0.76, 95% CI: 0.60-0.97, $P = 0.03$) and when adjusted for age, sex, number of drugs, Charlson Comorbidity index, smoking, alcohol and income (HR 0.77, 95% CI: 0.60-0.99, $P = 0.04$). The results were unchanged by adding baseline TSH and baseline treatment of thyroid disease to the model (HR 0.76, 95% CI: 0.60-0.98, $P = 0.03$).

Conclusion: Residing in Skagen was associated with decreased mortality compared to residing in Randers, suggesting that long-term residency in an iodine sufficient environment may lead to increased longevity compared to residency in an iodine deficient environment.

Oral Session 13: Thyroid Cancer: From Bed Side to Bench

OP-13-75

MIRNA DIAGNOSTIC SIGNATURE OF HUMAN THYROID CANCER OUTPERFORMS CLASSICAL MUTATIONAL STATUS DETECTION

Manuel Saiselet[1], *Marie Quiriny*[2], *Alice Augenlicht*[1], *Joel Rodrigues Vitoria*[1], *Didier Dequanter*[3], *Alexandra Rodriguez*[3], *Ligia Craciun*[2], *Denis Larsimont*[2], *Guy Andry*[2], *Carine Maenhaut*[1]
[1]Interdisciplinary Research Institute of Brussels (IRIBHM), ULB, Anderlecht, Belgium; [2]Jules E. Bordet Institute, Pathology and Surgery Departments, ULB, Brussels, Belgium; [3]Chu Saint-Pierre, Endocrinology and Surgery Departments, ULB, Brussels, Belgium

Introduction: Thyroid cancer are the most frequent endocrine tumours with an increasing incidence. One of the major public health problems of thyroid tumours is the high frequency of nodules discovered by ultrasound of which only 5% are cancers. However, 15% to 30% of preoperative fine-needle aspiration biopsies (FNAB) yield inconclusive cytological findings. Many of these patients are therefore operated, three out of four unnecessarily. Recent studies showed that miRNA have the potential to discriminate begin from malignant nodules. The molecular tests already available in USA mainly use mutational status of the samples in order to determine clinical status. However, it has been shown that malignant and benign nodules may share common mutations that can decrease classifier performances.

Material & Methods: We performed miRNA profiling and mutational status determination of 140 thyroid nodule samples in order to train a classification algorithm. We gave the same weight to miRNA profiling (40 miRNA tested by qRT-PCR) and mutations detection (7 mutations tested). Then, we validated our algorithm using 150 independent FNAB samples. We analysed one of the largest thyroid nodule and FNAB cohort in Europe.

Results: We show that miRNA could be better thyroid cancer molecular markers that mutations. Only BRAF V600E mutation is relevant for malignant nodule detection. Furthermore, the best discrimination scores are obtained by several miRNA and predictive values are competitive.

Conclusions: Our observations open the field for the first European companion thyroid cancer molecular diagnostic test, at lower cost.

OP-13-76

CLONALITY STUDIES IN PAPILLARY THYROID CANCER: EVIDENCES OF INTRA-TUMOR HETEROGENEITY

Marina Muzza[1], *Gabriele Pogliaghi*[2], *Carla Colombo*[2], *Maria Carla Proverbio*[2], *Delfina Tosi*[3], *Laura Fugazzola*[4]
[1]Division of Endocrine Diseases, Milancusano Milanino, Italy; [2]IRCCS Istituto Auxologico Italiano, Division of Endocrine and Metabolic Diseases, Milan, Italy; [3]Asst Santi Paolo e Carlo, Milan, Unit of Pathology, University of Milan, Department of Health Sciences, Milan, Italy; [4]IRCCS Istituto Auxologico Italiano, Division of Endocrine and Metabolic Diseases, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy

Objectives: During last decades, there is a growing recognition of intra-tumor heterogeneity (ITH) within the same patient. Despite the potential high impact, ITH has been sparsely studied in thyroid cancer and the available literature indicates this tumor as a monoclonal disease. Aim of the study was to investigated ITH in papillary thyroid cancer (PTC). We have previously molecular characterized a large series of PTCs by a custom Mass Array (PTC-MA) panel able to detect 19 common genetic alterations and to provide, for each mutation, the allelic quantification. At least one mutation was found in 71% of PTCs, and in 19% of cases two or more mutations were detected. In most cases, the evaluation of the allelic frequencies normalized for the neoplastic cell content indicated the presence of the heterozygous mutation in virtually all the tumor cells. However, a minority of cases was found to harbor lower or higher allelic frequencies, consistent with ITH or with loss of heterozygosis (LOH), respectively.

Methods: HUMARA clonality assay and microsatellites analysis were performed in a subset of cases, to investigate ITH and LOH, respectively.

Results: We found that 16/24 (67%) of informative tumors were polyclonal. Interestingly, all tumors harboring mutations in two genes with different allelic frequency were polyclonal, highlighting the actual existence of different clones. Consistently, monoclonal tumors showed a mutated allelic frequency of about 50%, which was consistent with the presence of only one clone. On the other hand, LOH in *BRAF* and *TERT* gene was excluded in all the cases analyzed though the presence of copy number variations could not be excluded.

Conclusions: The present study adds evidence to the concept of intratumor heterogeneity in PTC. The heterogeneity found in some tumors warrants attention, since the occurrence of this phenomenon is likely to affect response to target-based drugs.

OP-13-77

SECRETION OF CANCER-ASSOCIATED MICRORNAS VIA EXOSOMES AFTER TSH STIMULATION OF THYROID CANCER CELLS

Jelena Jankovic[1], *Sara Muñoz-López*[2], *Julia A. Ramirez-Moya*[3], *Andrea Martínez- Cano*[4], *Pilar Santisteban*[5], *Garcilaso Riesco-Eizaguirre*[6]

[1]Institute for the Application of Nuclear Energy – Inep, Department for Endocrinology and Radioimmunology, University of Belgrade, Belgrade, Serbia; [2]Instituto de Investigaciones Biomédicas, Universidad Autónoma de Madrid, Madrid, Spain; [3]Biomedical Research Institute (CSIC-UAM), Ciberonc From Health Institute Carlos III, Madrid, Spain; [4]Instituto de Investigaciones Biomédicas, Madrid, Spain; [5]Instituto de Investigaciones Biomédicas, Universidad Autónoma de Madrid, Ciberonc, Instituto de Salud Carlos III, Madrid, Spain; [6]Hospital Universitario de Móstoles, Iib "Alberto Sols", Universidad Francisco de Vitoria, Móstoles, Spain

Introduction: MicroRNAs are hypothesised to be actively secreted by cancer cells via exosomes, whereby they can induce gene regulation in recipient cells and contribute to metastatic spread. Thyroid-stimulating hormone (TSH) stimulates the growth and development of papillary and follicular thyroid cancer. While TSH is known to influence the expression of microRNAs in normal thyroid cells, little is known on its influence on microRNA synthesis or secretion in thyroid cancer cells.

Objective: To determine whether TSH stimulation influences cellular microRNA expression and their active secretion through exosomes in thyroid cancer cells.

Material and methods: Four different human thyroid cancer-derived cell lines (TPC-1, FTC-133, OCUT-1, Nthy-ori 3.1), previously shown to be responsive to TSH, were stimulated with TSH and expression of selected thyroid cancer-related microRNAs (miR-21-5p, miR-34a-5p, miR-221-3p, miR-143-3p, miR-146b-5p, and miR-146b-3p) was detected by RT-qPCR, both the mature and precursor forms. Exosomes were isolated from cell medium through ultracentrifugation and characterised with immunoblot and nanoparticle tracking analysis.

Results: We found that TSH downregulated the cellular levels of miR-221-3p in TPC-1, but upregulated its levels in the exosomes derived from the same cells. On the contrary, the levels of its precursor, pre-mir-221-3p, showed the opposite pattern; TSH upregulated the cellular levels of pre-miR-221-3p but downregulated its levels in the exosomes. These differences between the cellular and exosomal levels of miR-221-3p and its precursor suggest that TSH promotes the expression of the miR precursor inside the cells, which is then secreted through exosomes and processed into its mature form outside the cells. We are currently testing the expression of miRs in patients' serum exosomes after TSH stimulation.

Conclusions:TSH stimulation regulates the levels of microRNAs in TPC-1 cells and exosomes. TPC-1 exosomal miR-221-3p may be processed from its precursor-microRNA into mature miR inside the exosomes, suggesting its potential role in thyroid cancer spread.

OP-13-78

FUNCTIONAL AND GENETIC STUDIES IN PTC TO ASSESS TKI EFFICACY

Miguel Angel Chenlo Miranda[1], *Sihara Perez-Romero*[1], *MCarmen Suarez-Fariña*[1], *Joana Rodrigues*[1], *Fernando Oroz-Gojar*[1], *Alberto Pradilla*[1], *Narciso Blanco-Freire*[2], *Mm Muzza*[3], *Jose Manuel Cameselle-Teijeiro*[4], *Laura Fugazzola*[3], *Clara V Alvarez*[1]

[1]Center for Research in Molecular Medicine and Chronic Diseases (CiMUS), University of Santiago de Compostela, Spain; [2]University Hospital of Santiago de Compostela (CHUS), Department of Surgery; [3]Division of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Italy; [4]University Hospital of Santiago de Compostela (CHUS), Department of Pathology

Papillary thyroid cancer (PTC) is a follicular epithelial cancer maintaining differentiated characteristics. It is the most common thyroid cancer, representing approximately 80% of cases and an increasing prevalence. Current treatment involves surgery and radioactive iodine therapy. In some cases, PTC persist or recurs becoming aggressive and unresponsive. Tyrosine kinase inhibitors (TKI) are an alternative treatment although its side effects. There are TKI tested for advanced PTC but there are not functional data that allow individual selection of the most convenient according to the mutational status.

Objectives: We aimed to compare the anti-proliferative effect of the TKI (Sorafenib, Lenvatinib, Sunitinib, Vandetanib, Cabozantinib) in primary cultures of PTC. In parallel the genetic mutation profile was obtained to related with anti-proliferative response.

Methods: Genetic test is performed through PTC-MA assay that allows the simultaneous detection of hotspot mutations (BRAF, KRAS, NRAS, HRAS, TERT, AKT1, PIK3CA, EIF1AX) and genetic rearrangements related to PTC (RET and TRK genes). Primary cultures were performed from patients' surgical thyroid surpluses following humanized h7H conditions established by our group (Bravo et al,JCEM2013). Relevant TKI concentrations are tested in vitro and proliferation evaluated through MTT assay.

Results: Up to now, we have tested five independent cultures**.** There are variations in the TKI efficiency in proliferation inhibition: Sunitinib was no effective, Lenvatinib and Vandetanib were effective in two cases and Cabozantinib was effective in one. PTC-MA assay allow the detection of point mutations and rearrangements in the same sample with high sensitivity, as well co-occurring mutations.Cases responding to Lenvatinib have similar mutational status.

Conclusions: Association between PTC genetic description and TKI assays performed in culture could be relevant for clinical management in terms of personalized selection of target TKI therapies. Work supported by FEDER, AEI (BFU2016-76973-R;P115-01501)

OP-13-79

GENDER DIFFERENCES IN TUMOR DEVELOPMENT AND TARGETED THERAPY IN A BRAFV600E-INDUCED MOUSE MODEL OF PAPILLARY THYROID CANCER

Elin Schoultz[1], *Mikael Montelius*[2], *Carmen Moccia*[3], *Therese Carlsson*[4], *Mikael Nilsson*[5]

[1]Sahlgrenska Cancer Center, Institute of Biomedicine, University of Gothenburg, University of Gothenburg, Sahlgrenska Cancer Center, Gothenburg, Sweden; [2]Institution for Clinical Science/Radiology Department, Gothenburg, Sweden; [3]Sahlgrenska Cancer Center, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden; [4]Institute of Biomedicine, Biomedicine, Sahlgrenska Academy, Gothenburg, Sweden; [5]Sahlgrenska Cancer Center, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden

Treatment of thyroid cancer battles against tumor growth and progression, and tumor cells ability to dedifferentiate. Braf-specific kinase inhibitor vemurafenib is currently evaluated for treatment of radioactive iodine (RAI) refractory tumors.

Magnetic Resonance (MR) is used clinically to monitor tumor size, progression and treatment effects. The value of MR in experimental thyroid cancer models e g to evaluate long-term therapy effects is poorly investigated.

We established a transgenic mouse model of sporadic papillary thyroid cancer (PTC), based on stochastic activation of mutant *Braf*. The advantages

are focal neoplasia in a natural microenvironment without elevated thyroid stimulating hormone (TSH).

Objectives: Evaluate the effect of Braf-kinase inhibitor vemurafenib on tumor development and progression in a PTC mouse model.

Methods: Conditional $Braf^{V600E}$ induction in *TgCreBraf*^{CA} mice by spontaneous Cre activation.

Mice administered with vemurafenib or control feed from 4 weeks or 6 months (mo) age.

Tumor size longitudinally evaluated by MR at 4-12 mo and thyroids excised.

Tissue processed for HE staining and immunohistochemistry.

Quantitative RT-PCR analysis of TSH-R, Tg, TPO and NIS at 6 mo.

Results: At 6 mo statistically significant gender differences ($p=0.0053$) in tumor volume; female/male ratio 2:1. Reduced expression of thyroid differentiation genes; by 86% in females and 70% in males. Recovery of gene expression by vemurafenib; females 52% and males >90%.

Long-term kinase inhibition partially decreased (by 40-55%) tumor volume, female/male ratio 1.6:1, at 4 mo, but conferred striking sex differences in tumor size at 12 mo: female/male ratio 19.5:1 ($n=4$), one female gland multiplying in volume by factor 50.

Histomorphologically 12 mo males exhibited a seminormalized follicular architecture staining positive for Tg. Corresponding female thyroids displayed papillary tumor phenotype of high heterogeneity and signs of dedifferentiation.

Conclusions: Evident gender differences in tumor growth, loss of thyroid specific gene expression, and therapeutic response to vemurafenib in a murine model of sporadic PTC.

OP-13-80

ANALYSIS OF COPY NUMBER VARIATION IN MEDULLARY THYROID CANCER AND CORRELATION WITH MUTATIONAL PROFILE AND RET EXPRESSION

Teresa Ramone[1], *Cristina Romei*[2], *Raffaele Ciampi*[3], *Alessia Tacito*[4], *Chiara Mulè*[5], *Rossella Elisei*[6]

[1]Dep of Clin and Exp Medicine, University of Pisa, Pisa, Italy; [2]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Dep of Clin and Exp Medicine, Pisa, Italy; [3]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [4]Department of Clinical and Experimental Medicine, University of Pisa, Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, Section of Endocrinology, Department of Clinical A, Pisa, Italy; [5]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa; [6]Endocrine Unit, Dept.of Clin and Exp Medicine, University Pisa, Pisa, Italy

Background: Medullary Thyroid Carcinoma (MTC) is related to *RET* proto-oncogene alterations: germline *RET* mutations are present in about 98% of hereditary cases and somatic mutations in 50-75% of sporadic cases. MTC is also associated with chromosome 10 amplification or loss.

Objective: Aim of the study was to evaluate the RET copy number variation (CNV) and to correlate CNV with mutational profile.

Methods and results: 175 sporadic cases, previously characterized with a NGS approach, have been reanalyzed with the ION Reporter software to reveal CNVs. In 29 cases RET CNV have been verified by MLPA. These data have been correlated with the mutational profile and with RET mRNA expression.

Seven cases (3.7%) were aploid (CNV≤1.5), 128 (72%) were diploid (1.5<CNV≤2.4) and 43 (24.3%) showed a *RET* amplification (CNV≥2.4). In silico data have been confirmed by MLPA in 23/29 cases (79.3%).

We demonstrated that the prevalence of RET CNV altered cases (deleted or amplified) was higher in RET (36/99, 36.4%) and RAS (10/43, 23%) positive cases while, in not mutated cases, the majority of tumors were diploid (30/33, 91%). No difference was found when analyzing different RET mutations and CNV. We then compared RET CNV with the allelic frequency (AF) of RET mutation and we found that AF was significantly higher in aploid cases (56.67%) than in diploid (36.45%) and amplified cases (37.9%). No correlation was found between CNV and RET expression levels.

Conclusions: We demonstrated that MTC is mainly diploid but aneuploidy can occur in a high percentage of cases particularly those with RET and RAS mutations. The evidence that AF is higher in RET aploid cases suggests that the deletion occurs on the wild type allele. The question of whether CNV is a late phenomenon in tumor development/progression or if it is a causative event remains to be answered.

OP-13-81

THE CLONALITY OF MEDULLARY THYROID CANCER COULD BE RELATED TO THE TYPE OF SOMATIC MUTATION AND ITS ALLELIC FREQUENCY

Cristina Romei[1], *Raffaele Ciampi*[2], *Alessia Tacito*[3], *Teresa Ramone*[4], *Alessandro Prete*[5], *David Viola*[6], *Valeria Bottici*[7], *Laura Agate*[8], *Eleonora Molinaro*[9], *Liborio Torregrossa*[10], *Clara Ugolini*[11], *Fulvio Basolo*[11], *Rossella Elisei*[12]

[1]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Dep of Clin and Exp Medicine, Pisa, Italy; [2]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [3]Department of Clinical and Experimental Medicine, University of Pisa, Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, Section of Endocrinology, Department of Clinical A, Pisa, Italy; [4]Dep of Clin and Exp Medicine, University of Pisa, Pisa, Italy; [5]University of Pisa, Unit of Endocrinology, Department of Clinical and Experimental Medicine, Pisa, Italy; [6]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Italy, 1department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy, Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy, Italy; [7]University of Pisa, Department of Clinical and Experimental Medicine, Endocrine Unit, Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy, Pisa, Italy; [8]University Hospital, 1department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy, Dept. of Endocrinology, Pisa, Italy; [9]University of Pisa, Endocrinology Unit, Department of Endocrinology, Pisa, Italy; [10]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [11]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, Pisa, Italy; [12]Endocrine Unit, Dept.of Clin and Exp Medicine, University Pisa, Pisa, Italy

Background: Medullary Thyroid Carcinomas (MTC) harbour *RET* and *RAS* somatic mutations in about 60% of cases while 40% has no mutations. The prevalence of *RET* mutation has been reported to be lower in smaller tumors (≤2 cm) and higher in more advanced cases.

Objective: Aim of this project was to evaluate differences of mutation distribution and frequency according to tumor size.

Methods and results: 133 sMTC were divided in 4 groups according to tumor size (TS): A (TS≤1cm); B (1cm<TS≤2cm); C (2cm<TS≤3cm); D (TS>3cm) and they were correlated with the presence of somatic mutations previously evaluated by NGS target sequencing. 53.4% of cases harbored somatic RET mutations, 26.3% somatic RAS mutations and 20.3% were negative. Mean mutation allele frequency (AF) was also correlated with the TS in the 4 groups. *RET* and *RAS* mutational profile was significantly different in the four groups ($p<0.0001$): the rate of *RET* mutations was higher in larger tumors: 35.3% in group A, 51.1% in group B, 64.3% in group C; 70.8% in group D. At variance, the percentage of *RAS* mutations was lower in larger tumors: 29.4% in group A, 31.2% in group B, 21.4% in group C; 16.7% in group D. A similar correlation was found in negative cases: 35.3%, 17%, 14.3%; 12.5% in groups A, B, C, D, respectively. Mean AF of *RET* mutations was also increasing according to tumor size ($P=0.0001$): 25.1% (A), 29.5% (B), 42.4% (C); 46.4% (D). No difference in RAS mutations AF was observed.

Conclusions: The overall rate of *RET* and *RAS* somatic mutations is lower in smaller MTCs and significantly increased in larger tumors. The higher AF in larger tumors suggests that smaller tumors are less clonal and more heterogeneous when compared to larger tumors.

OP-13-82

MESENCHYMAL STEM CELL - MEDIATED SODIUM IODIDE SYMPORTER (NIS) REPORTER GENE DELIVERY IN GLIOBLASTOMA

Carolin Kitzberger[1], *Rebekka Spellerberg*[1], *Kathrin A Schmohl*[1], *Mariella Tutter*[1], *Nathalie Schwenk*[1], *Roland E Kälin*[2], *Rainer Glaß*[2], *Peter J Nelson*[1], *Christine Spitzweg*[1]

[1]Department of Internal Medicine IV, University Hospital of Munich, LMU Munich, Munich, Germany; [2]Neurosurgical Research, Department of Neurosurgery, University Hospital of Munich, LMU Munich, Munich, Germany

The sodium iodide symporter (NIS) is one of the most promising theranostic genes for non-invasive radionuclide-based molecular imaging and therapy. We and others have investigated the potential of NIS to induce radioiodine accumulation in non-thyroidal tumors using different gene transfer vehicles. Based on their excellent tumor homing capacity, mesenchymal stem cells (MSCs) can be used as tumor-selective gene delivery vehicles. In the current study, we applied genetically engineered MSCs for tumor-targeted NIS gene transfer in glioblastoma multiforme (GBM), as a clinically highly relevant tumor with urgent need for novel therapy approaches.

Bone marrow-derived mouse and human MSCs, stably transfected with NIS driven by the constitutively active Cytomegalovirus promoter (CMV-NIS-MSC), showed functional NIS expression as demonstrated by ^{125}I uptake. Syngeneic and xenograft GBM mouse models were established by orthotopic or subcutaneous implantation of murine and human GBM cell lines. CMV-NIS-MSCs were systemically injected via the tail vein and tumoral iodide uptake was monitored by ^{123}I-scintigraphy or ^{124}I-PET imaging. Administration of the NIS inhibitor perchlorate or wildtype MSCs served as controls of NIS specificity. NIS-specific tumoral radionuclide accumulation was observed in syngeneic and xenograft subcutaneous GBM tumors after CMV-NIS-MSC application. Furthermore, promising preliminary experiments demonstrate strong recruitment of MSCs into orthotopic GBM in a syngeneic mouse model, establishing the use of NIS as a reporter gene to track MSC homing to GBM tumors. Resected tumors were further analyzed by *ex vivo* NIS staining revealing NIS-specific immunoreactivity after CMV-NIS-MSC application.

In future studies, we will extend our approach to clinically more relevant human primary cell line - derived GBM models and address the efficacy of our concept to deliver therapeutically active radionuclides (e.g.^{131}I) to brain tumors using NIS as theranostic gene.

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

European
Thyroid Journal

Presenting authors are underlined

Saturday, September 7th, 2019
Poster Session 1

Autoimmunity 1

P1-01-01
TAMOXIFEN CITRATE COULD BE THE DRUG OF CHOICE ON THE LONG TERM FOLLOW UP OF THE RIEDEL THYROIDITIS

Asena Gokcay Canpolat[1], Murat Cinel[1], Serpil Dizbay Sak[3], Işılay Taşkaldıran[4], Hakan Korkmaz[5], Özgür Demir[6], Reyhan Ersoy[7], Selçuk Dağdelen[8], Dilek Berker[9], Klara Dalva[9], Adile Begüm Bahçecioğlu[1], Murat Erdoğan[1]

[1]Ankara University Department of Endocrinology and Metabolism, Ankara, Turkey; [2]Ankara University, Department of Pathology, Ankara, Turkey; [3]Ankara Research and Training Hospital, Endocrinology Clinic, Ankara, Turkey; [4]Süleyman Demirel University, Department of Endocrinology and Metabolism, ısparta, Turkey; [5]Ankara University School of Medicine, Department of Endocrinology and Metabolic Diseases; Faculty of Medicine, Ankara, Turkey, Ankara, Turkey; [6]Yildirim Beyazit University, Faculty of Medicine, School of Medicine, Department of Endocrinology and Metabolism, Bilkent, Ankara, Turkey; [7]Hacettepe University, Department of Endocrinology and Metabolism, Ankara, Turkey; [8]Ankara City Hospital, Department of Endocrinology and Metabolism, Ankara, Turkey; [9]Ankara University, Department of Haematology, Ankara, Turkey

Introduction: Riedel's thyroiditis (RT), is a rare thyroiditis that is generally accepted as a thyroid manifestation of IgG_4 related systemic disease. Etiology and definite treatment of the disease are still unclear. Our aim was to investigate treatment modalities for RT.

Methods: We analyzed eight RT patients who were diagnosed and treated between 2015 and 2018.

Debulking surgery/isthmectomy has been performed, for diagnosis and to relieve obstruction in seven patients and thick needle biopsy in one.

Results: Glucocorticoids were given for remission induction in all patients as first-line therapy. However starting doses and the course of therapy were different (i.e. oral prednisone 0.6 mg/kg/d or 30-40 mg/d, for 4-8 weeks, followed by dose reduction, and cessation of the therapy generally in 3-6 months. Azathioprine and Colchicine were added to one patient who had concomitant polyserositis. Tamoxifen citrate 10-20 mg/day was given as the second-line agent to all patients for maintenance therapy following remission induction. All eight patients improved clinically and had a reduction in the size of the mass lesion and on tamoxifen therapy for (minimum 6 months-maximum 12 years) until now. None of the patients had a recurrence under tamoxifen therapy.

Conclusion: Since Riedel Thyroiditis is a very rare disease, a well established has not been described. Glucocorticoids are generally proven to be effective initial treatment. Tamoxifen, which is a nonsteroidal agent with antiestrogenic properties inhibits fibroblastic function through its influence on the production of TGFβ. There are no serious side effects regarding long term therapy with this agent since its common use in breast cancer for nearly a half-century. It seems to be a good option for the long term follow up maintenance therapy for these patients.

Duration and efficacy of the tamoxifen therapy on the long term can be determined in a prospective trial since most of the reported patients are in remission after several years of the follow-up with or without treatment. But for now, our proposed strategy is to use tamoxifen as long as the mass lesions exist.

P1-01-02
SERUM THYROID PEROXIDASE ANTIBODY AND INCIDENT HYPERTENSION IN EUTHYROID POPULATION: A NOVEL BIOMARKER

Aidin Baghbani-Oskouei[1], Maryam Tohidi[1], Atieh Amouzegar[2], Ladan Mehran[2], Farzad Hadaegh[1], Fereidoun Azizi[2]

[1]Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Aims: Dysfunction of the thyroid gland have profound effects on the cardiovascular system. We aimed to explore the relation of serum thyroid peroxidase antibody (TPO-Ab), as a marker of thyroid auto-immunity with incident hypertension among a euthyroid population.

Methods: A total of 3681 participants (1647 men) entered the study. Multivariate Cox proportional hazard models were conducted to estimate the association between TPO-Ab and incident hypertension.

Results: The mean age (SD) of the participants was 37.5 (12.8) years. During 12.2 years of follow-up, 511 men and 519 women developed hypertension. The multivariable hazard ratios (95% confidence interval) of 1-unit increase in ln TPO-Ab for incident hypertension in the fully-adjusted model were 1.09 (1.00-1.19), 1.03 (0.97-1.10), and 1.05 (1.00–1.11) for men, women, and total population, respectively.

Conclusion: Activation of humoral immunity against thyroid gland can contribute to the development of hypertension among euthyroid subjects over more than a decade long follow-up.

P1-01-03
WITHDRAWN

KARGER

E-Mail karger@karger.com
www.karger.com/etj

P1-01-04

INFLUENCE OF DIETARY PATTERN ON OXIDATIVE STRESS MARKERS IN HASHIMOTO'S THYROIDITIS

Rosaria Ruggeri[1], *Salvatore Giovinazzo*[2], *Giuseppe Giuffrida*[3], *Teresa Manuela Vicchio*[4], *Maria Teresa Cristani*[5], *Angela Alibrandi*[6], *Alfredo Campenni*[7], *Francesco Trimarchi*[8]

[1]Department of Clinical-Experimental Medicine and Pharmacology, Division of Endocrinology, University of Messina, Unit of Endocrinology, University Hospital of Messina, Messina, Italy; [2]Unit of Endocrinology, University Hospital of Messina, Messina, Italy; [3]Department of Clinical and Experimental Medicine, Unit of Endocrinology, University of Messina, Messina, Italy; [4]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [5]Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy; [6]Department of Economy Unit of Statistical and Mathematical Sciences, University of Messina, Italy; [7]Dep. of Biomedical and Dental Sciences, and Morfo-Functional Images, Nuclear Medicine Unit, University of Messina, Messina, Italy; [8]University of Messina, Accademia Peloritana, Accademia Peloritana Dei Pericolanti at University of Messina, Messina, Italy

Objective: Oxidative stress has been implicated in the pathogenesis of several immune-mediated disorders, including autoimmune thyroid disease. Aim of our study was to investigate the relationship between dietary habit and redox homeostasis, in relationship with thyroid autoimmunity.

Materials and Methods: We enrolled 200 healthy subjects (173 F, mean age 35±12). None of them was under any pharmacological treatment. Exclusion criteria: any infectious/inflammatory/autoimmune comorbidity, kidney failure, diabetes, cancer. In each subject, we measured; serum TSH, free thyroxine and anti-thyroid antibodies; plasma oxidative stress markers (Tab.1). A validated questionnaire on dietary habits, evaluating the intake frequencies of food groups (meat, fish, cereals, fruits and vegetables, dairy products) was submitted to each participant.

Results: Among the 200 recruited subjects, 81 (71 F, mean age 38 ± 11 yr) were diagnosed with euthyroid Hashimoto's thyroiditis (HT), the remaining 119 (102 F, mean age 33± 12 yr) served as controls. In HT subjects, AGEs, markers of oxidative stress, were significantly higher (P = 0.0001), and anti-oxidants GPX, TRX and TEAA lower (P = 0.02, P = 0.02, P = 0.002, respectively) than controls, clearly indicating a condition of oxidative stress (Tab.1). In questionnaires, HT subjects reported higher intake frequencies of animal foods (meat p = 0.0001; fish, p = 0.002; dairy products, p = 0.030) compared to controls, that, in turn, reported higher intake frequencies of plant foods (legumes, P = 0.010; fruits and vegetables, P = 0.030). Stepwise regression models demonstrated a significant dependence of oxidative stress parameters from consumption of animal foods: meat dietary intake was associated with low levels of GPX (p = 0.048) and TRX (p = 0.007), and dairy products intake was associated to low levels of TEAA (p = 0.020).

Conclusions: The present study provides further evidence that oxidative stress increases in euthyroid HT. Moreover, it suggests a positive influence of low intakes of animal foods on the oxidative/antioxidative balance, and a potential protective effect of such dietary habit towards oxidative stress-related disorders.

P1-01-05

THYROID DYSFUNCTION DURING IMMUNE-CHECKPOINT INHIBITOR TREATMENT

Clara Cunha[1], *Catarina Saraiva*[2], *Carlos Tavares Bello*[3], *Francisco Sousa Santos*[4], *Eugénia Silva*[5], *Joana Ferra*[6], *Cristina Matos*[7], *Margarida Falcão*[6], *Patricia Cavaco*[8], *Ana Martins*[8], *Fernando Nogueira*[6], *João Sequeira Duarte*[9], *Manuela Oliveira*[10]

[1]Department of Endocrinology, Hospital Egas Moniz, Lisbon, Portugal; [2]Department of Endocrinology, Hospital Egas Moniz, Lisbon, Portugal; [3]Hospital Egas Moniz, Lisbon, Portugal; [4]Hospital Egas Moniz, Lisbon, Portugal; [5]Department of Endocrinology, Hospital Egas Moniz, Lisbon, Portugal; [6]Department of Pneumology, Portugal; [7]Department of Pneumology, Lisbon, Portugal; [8]Department of Oncology, Hospital São Francisco Xavier, Lisbon, Portugal; [9]Department of Endocrinology, Hospital Egas Moniz; [10]Department of Endocrinology, Hospital Egas Moniz, Portugal

Introduction: Thyroid dysfunction has emerged as one of the most common immune-related adverse event associated with anti–PD-1 therapy.

Objective: To assess the incidence and characteristics of nivolumab and pembrolizumab-induced thyroid dysfunction.

Methods: We conducted a retrospective and observational study that included patients with advanced non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck and renal cell carcinoma who were treated with nivolumab or pembrolizumab at our institution between March 2016 and March 2019. All included patients had a normal thyroid function tests prior to immunotherapy treatment.

Results: We evaluated 55 patients (38 males) with a median age of 61 years and a median follow-up of 20.1 months. Nivolumab was prescribed to 36 patients (30 NSCLC, 4 renal cell carcinoma and 2 carcinoma of head and neck) and pembrolizumab to 19 patients with NSCLC. Patients received a median of 8 cycles of immunotherapy. The mean baseline TSH and fT4 levels were 1.98±1.26 mIU/L and 16.06± 2.14 pmol/L, respectively. The incidence of thyroid dysfunction was higher with nivolumab (27.7%) than with pembrolizumab (5.3%). Hypothyroidism developed in 9 cases, of which 4 were transient and 2 required levothyroxine replacement therapy. Thyrotoxicosis was documented in 2 patients, one of which was transient. A favorable response to immunotherapy was seen in the majority of patients with immune-checkpoint inhibitor-induced thyroid dysfunction (63.6%) and in 30.4% of patients without thyroid dysfunction.

Conclusions: Thyroid dysfunction is common in patients treated with nivolumab and pembrolizumab. Hypothyroidism and thyrotoxicosis related to inflammatory thyroiditis are the most frequent presentations. Serial measurements of thyroid function are indicated before and during and anti-PD-1 therapy in order to improve overall health-related outcomes.

Table 1.

	OXIDATIVE STRESS MARKERS § (mean ± SD)						
	AGEs	**AOPP**	**SOD**	**GPX**	**TRX**	**GR**	**TEAA**
	AU/g prot	**µmol EqCIT/L**	**U/ml**	**U/ml**	**U/ml**	**U/ml**	**mM TE**
HT	165.85	1.1335	4.8189	0.6100	1.7202	65.426	1.5322
(n = 81)	(±70.09)	(±0.35)	(±0.71)	(±0.12)	(±0.73)	(±20.27)	(±0.25)
Controls	114.51	1.0554	5.0598	0.6531	2.0809	71.525	1.5676
(n = 119)	(±55.97)	(±0.34)	(±1.05)	(±0.12)	(±0.90)	(±20.34)	(±0.10)
P*	0.0001	0.162	0.121	0.020	0.023	0.282	0.002

§AGEs: Advanced glycation End Products; AOPPs: Advanced Oxidation Protein Products; SOD: Superoxide dismutase; GPX: Glutathione Peroxidase; TRX: Thioredoxin; GR: Glutathione reductase; TEAA, Trolox-Equivalent Anti-oxidant Activity

P1-01-06

THE ASSOCIATION OF AUTOIMMUNE DISORDERS TO GRAVES' DISEASE AND HASHIMOTO'S THYROIDITIS IN AUTOIMMUNE POLYGLANDULAR SYNDROME

Greta Pham-Dobor[1], Laszlo Bajnok[2], Beata Bodis[3], Marin Gergics[2], Orsolya Nemes[3], Karoly Rucz[3], Emese Mezosi[2]

[1]Ist Department of Medicine, Division of Endocrinology and Metabolism, University of Pecs, Medical School, Szentágothai Research Centre, Pecs, Hungary; [2]Ist Department of Medicine, Division of Endocrinology and Metabolism, University of Pecs, Medical School, Szentágothai Research Centre, Pécs, Hungary; [3]Ist Department of Medicine, Division of Endocrinology and Metabolism, University of Pecs, Medical School, Pécs, Hungary

Introduction: In autoimmune polyglandular syndrome (APS) both types of Autoimmune Thyroid Disorders (AITDs), i.e. Hashimoto's thyroiditis (HT) and Graves' disease (GD) can be manifested. The pattern of autoimmune reaction is Th1 in HT, whereas the predominance of Th2 cytokines in GD indicates humoral immunity. The aim of this study was to investigate the potential differences in the associations of other autoimmune disorders to HT and GD in APS patients.

Patients and method: In the database of Ist Dept. of Medicine, University of Pecs 135 APS patients could be identified, of which 120 had either form of AITDs (89% of this population).

Results: HT or GD were present in 89 and 31 patients (74,1% vs. 25,9% of AITDs), respectively. HT was associated with 4 other autoimmune endocrinopathies, 10 non-endocrine organ specific autoimmune disorders and six systemic autoimmune diseases. The distribution of associated autoimmune conditions was similar in GD: 3 endocrinopathies, 7 non-endocrine organ-specific and 4 systemic autoimmune diseases. Addison's disease and T1 diabetes mellitus were the most common associated disorders. The prevalence of other autoimmune conditions was not different in HT and GD except coeliac disease which was more common in GD ($p = 0,049$). HT and GD were diagnosed as first manifestation in 31 and 9 cases, respectively. The combinations of two, three, four and five autoimmune diseases were found in 85, 29, 5 and 1 cases, respectively. The number of associated conditions was similar in HT and GD.

Conclusions: In APS, the various forms of autoimmune diseases are combined with either form of AITDs in 90% of cases. Except coeliac disease which was more prevalent in GD, we did not find major differences in the prevalence of other endocrine and non-endocrine autoimmune disorders between HT and GD.

P1-01-07

EPITOPIC SPECIFICITY OF ANTIBOIES TO THYROGLOBULIN IN PATIENTS WITH COMBINATION OF RHEUMATOID ARTHRITIS AND AUTOIMMUNE THYROIDITIS

Anton Dvorovkin[1], Vitali Odin[1], Vadim Tyrenko[1], Michael Toporkov[1], Olga Shashkova[2]

[1]Military Medical Academy Named after S.M. Kirov, Saint Petersburg, Russian Federation; [2]Hybrid Technology Lab, Russian Scientific Center for Radiology and Surgical Technologies Named after Academician A.M. Granov, Russian Federation

Background: It is known that antibodies to thyroglobulin (AT to TG) are detected in the blood of patients with rheumatoid arthritis (RA), including in the absence of autoimmune thyroiditis (AIT). Detection of monoclonal antibodies to various thyroglobulin epitopes allows us to study the heterogeneity problem of immunopathological and physiological variants of rheumatoid arthritis.

Objectives: To assess the detectability of monoclonal antibodies to various epitopes of thyroglobulin in patients with RA only and in patients with a combination of RA and AIT.

Methods: The study included two groups of patients. The main group of patients who had a combination of RA and AIT included 53 people (49 women and 4 men, average age - 63.92 ± 1.60 years, mean duration of RA10.0 ± 1.11 years). The control group of patients who had RA only included 61 people (57 women and 4 men, the average age was 62.83 ± 1.60 years, mean duration of RA 9.69 ± 1.18 years). All patients underwent general clinical and special examination, including specific immunological examination. The diagnoses of RA and AIT were established according to generally accepted criteria. As an antigen for determining titers and epitopic specificity of autoantibodies (autoAB) against thyroglobulin (TG) in blood sera, a preparation of purified human TG was used, obtained from thyroid gland tissue homogenates by gel filtration chromatography. To determine the epitope specificity of autoAB against TG, 7 monoclonal antibodies (MCA) against human TG were used. Determination of the interference of autoAB against TG with the MCA against TG was carried out using the competitive ELISA method.

Results: In the RA + AIT group, three patients were identified with different types of monoclonal antibodies to different epitopes of thyroglobulin molecule, in the RA group - one patient. Most often, among the two groups studied, different monoclonal antibodies are detected among patients with a combination of RA and AIT. The most common monoclonal antibody, which is found in patients with RA only and in patients with a combination of RA and AIT is MCAT 1F10. At the same time, MCA 4T4, 5F5, 5F9, 8E11 met in patients with RA + AIT, which were absent in patients with RA only.

Conclusions: Thus, the definition of monoclonal antibodies of the ciphers studied showed insufficient information to identify any patterns. Further study of this issue is required in a much larger sample of the persons surveyed.

P1-01-08

THE PRESENCE OF SS-A ANTIBODIES IS ASSOCIATED WITH SEVERELY DECREASED FREE THYROXINE LEVELS DUE TO INHIBITING THYROID HORMONE SYNTHESIS IN SYSTEMIC AUTOIMMUNE MIXED CONNECTIVE TISSUE DISEASE

Dr. Ildikó Molnár[1], *Dr. Edit Bodolay*[2]
[1]Endomed Debrecen Kft, Debrecen, Hungary; [2]University of Debrecen, Division of Clinical Immunology, Debrecen, Hungary

The specific autoantibody of MCTD is U1-RNP, however, several antibodies may be present in the patient serum, such as anti-SSA, anti-TPO, anti-Tg, which may be associated with autoimmune thyroid disease.

Thirty-three patients with MCTD, of whom 12 had overlap autoimmune thyroiditis (mean age 39±10 years, 32 females) and 34 controll (29±14 years, 31 females) were studied. Thyroid hormone levels (TSH, FT4, FT3), antibodies against thyroid peroxidase (TPO), thyroglobulin (Tg) and SS-A were investigated using chemilu¬mi¬nescence or enzyme-linked immunoassays.

SS-A antibodies were found in 6/21 (no thyroiditis) and 6/12 (yes thyroiditis) patients with MCTD. SS-A antibody positivity decreased serum FT4 levels compared with those in controls and MCTD patients who had no thyroiditis (5.5 pmol/l [CI95% 2.83-10.59] vs 10.82 pmol/l [CI95% 8.87-13.19], P = 0.001 and 11.26 pmol/l [CI95% 8.18-15.48], P = 0.003 demonstrating in geometric mean (GM) and 95% confidence interval (CI95%). GM values of TSH levels and FT3/FT4 ratios were increased 3.27 mIU/l vs 1.63 mIU/l, P = 0.001 and 2.38 mIU/l, NS for TSH levels, as well as 0.51 vs 0.27, P = 0.005 and 0.22, P = 0.004 for FT3/FT4 ratio. Serum FT3 levels were decreased in SS-A antibody negativity compared with those in their positivity in MCTD patients without (2.43 pg/ml [CI95% 1.78-3.33] vs 2.81 pg/ml [CI95% 1.93-4.13], NS and with thyroiditis 2.37 pg/ml [CI95% 1.83-3.07] vs 2.98 pg/ml [CI95% 2.37-3.76], NS. In SS-A antibody positivity, serum FT4 levels inversely correlated with anti-TPO (P = 0.01, r = -0.71) or anti-Tg (P = 0.002, r = -0.8) antibo-dies, but in their negativity gave positive correlation between FT4 and anti-TPO (P = 0.02, r = 0.51) or anti-Tg (NS) antibodies.

In summary, serum FT_3 levels decreased in MCTD patients independently of thyroiditis. Serum FT_4 levels significantly decreased in SS-A antibody positivity with increased TSH levels or FT_3/FT_4 ratios in MCTD patients without thyroiditis, and any thyroid hormone supplementation.

P1-01-09

FREQUENCY OF ANTI-THYROID AUTOANTIBODIES IN PATIENTS WITH MYASTHENIA GRAVIS: RESULTS OF A CROSS-SECTIONAL STUDY

Ilaria Ionni[1], *Marenza Leo*[1], *Giovanna Rotondo Dottore*[1], *Michelangelo Maestri*[2], *Roberta Ricciardi*[2], *Melania Guida*[2], *Anna De Rosa*[2], *Paolo Vitti*[1], *Michele Marinò*[1]
[1]Department of Clinical and Experimental Medicine, Endocrinology, University of Pisa, Italy; [2]Path of Myasthenia and Thymus Surgery, University of Pisa, Italy

Objectives: The association between myasthenia gravis (MG) and autoimmune thyroid diseases is well known. In previous studies, a mild clinical expression of MG was observed in patients with associated autoimmune thyroid diseases, with a higher prevalence of ocular than generalized MG. Overall, thyroid diseases are the autoimmune conditions most frequently associated with MG, with a prevalence ranging from 5 to 10%. However, the frequency of anti-thyroid autoantibodies in patients with MG in the absence of thyroid dysfunction is not known, but it would be rather important to estimate it as a possible predictor of the development of clinically overt thyroid diseases, which we investigated here.

Methods: We performed a cross-sectional study in all consecutive patients with a first diagnosis of MG and a normal thyroid function who came at our observation over a period of 36 months. From March 2016 to February 2019, 133 patients with MG were evaluated (59 men and 74 women, age: 50.8 ± 18.6 yr). Serum anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb) antibodies were measured in all patients.

Results: Twenty-four patients (18.0%) had detectable TgAb and/or TPOAb. The frequency of TgAb was 9.7% (13/133), whereas the frequency of TPOAb was 15.0% (20/133). In 9 patients (6,7%) both TgAb and TPOAb were detectable.

Conclusions: Approximately 20% of euthyroid patients with MG have positive serum anti-thyroid antibodies. It remains to be established whether this positivity is predictive for the development of an overt thyroid dysfunction and the possible role of immunosuppressive therapy to which these patients undergo for MG in determining the clinical outcome of these serological findings. In this regard, a follow-up of the study is ongoing.

P1-01-10

VASCULARIZATION CHARACTER AND SYSTOLIC VELOCITY OF BLOOD FLOW IN PATIENTS WITH AUTOIMMUNE THYROIDITIS

Olga Goroshko[1], *Elina Gasparyan*[2]
[1]Medical Centre “Professor”, Russian Federation; [2]Medical Centre “Professor”, “Professor” Medical Center, Saint-Petersburg, Russian Federation

Aim: Evaluation of vascularization character and systolic velocity of blood flow (SVBF) in patients with autoimmune thyroiditis (AIT) in the state of hypothyroidism and euthyroidism in order to determine their diagnostic significance.

Material and Methods: In our medical centre 91 patients with AIT and 167 patients with diffuse toxic goiter (DTG, the group of comparison), aged 29–70, were observed. All patients underwent usual clinical, laboratory, hormonal and instrumental tests. In ultrasound examinations of thyroid gland with B- and Colour Doppler regimes, SVBF in upper thyroid artery in cm/s in Doppler regime, were estimated. 58 patients out of 91 with AIT showed subclinical and overt hypothyroidism, 33 patients were in the state of euthyroidism. 53 patients out of 167 with DTG showed thyrotoxicosis, with 114 patients - euthyroidism.

Results: We have noticed the dependence of these indexes on thyroid functional state only in patients with DTG. 100% of patients with thyrotoxicosis showed a considerable increase of vascularization, or hypervascularization of thyroid gland. At the same time, SVBF was 42–86 cm/s (with its norm being 16–36 cm/s). Euthyroidism in patients with DTG was characterized with gradual normalization of thyroid vascularization and SVBF (average 28.0±8.0 cm/s). However, in all patients with AIT in the state of hypothyroidism and euthyroidism (with or without therapy) vascularization character was different: from relatively high to normal, low or negative. We must mention that SVBF indexes were normal in all patients, without showing any dependence on vascularization character, they were on average 22.0±6.0 cm/s, which is definitely lower than those in patients with thyrotoxicosis.

Conclusions:

* Thyroid hypervascularization and high indexes of SVBF, observed in all patients on the stage of thyrotoxicosis, have diagnostic significance.

* In patients with AIT at the stage of hypothyroidism and euthyroidism vascularization indexes were different at normal SVBF; they do not have any diagnostic significance.

* Normal SVBT indexes in patients with AIT in case of increased vascularization can be used for exclusion of thyrotoxicosis.

P1-01-11

ADIPONECTIN AND ITS RECEPTORS CORRELATE WITH SERUM TSH IN AUTOIMMUNE HYPOTHYROIDISM

Lachezar Lozanov[1], *Radka Argirova*[2], *Bojan Lozanov*[2], *Dessislava Gorcheva*[2], *Boyka Kostova*[2]
[1]Tokuda Hospital Sofia, Endocrinology Deprtment, Acibadem Cityclinic, Sofia, Bulgaria; [2]Acibadem City Clinic Tokuda Hospital

The aim of the study was to examine the serum levels of AdipoR1 and AdipoR2 in relation to circulating adiponectin and TSH in autoimmune hypothyroidism. 77 participants were enrolled regarding the serum adiponectin (45 hypothyroid patients with Hashimoto's disease and 32 healthy subjects). Both groups were matched for age (43 -37 y), had a normal body weight (BMI 22.4 vs 23.0 kg/m2), but with TSH of 11.5 and 1.8 mU/L respectively. Adiponectin in the hypothyroid group (15.6 9.5 µg/ml) was much higher than in healthy persons (8.03 ± 4.6 µg/ml, $p < 0.001$).

AdipoR1 and AdipoR2 (ELISA) were measured in 40 persons (20 of each group).The data revealed a significant difference of adiponectin receptors between both groups of studied persons. AdipoR1 and AdipoR2 in serum of the hypothyroid group were 5.1 and 2.7 ng/ml vs < 0.781 ng/ml respectively in the healthy control group ($p < 0.001$). It could be assumed that increased levels of adiponectin and its receptors appeared as a compensatory phenomenon promoted by the chronic autoimmune inflammation and oxidative stress in patients with Hashimoto's disease. Another explanation is that higher AdipoR1 may be "saturated" with the higher level of adiponectin so becoming fully or partially unable to link to adiponectin. This can be considered as a secondary adiponectin resistance due to hypothyroidism.

Key Words: Adiponectin, AdipoR1, AdipoR2, TSH, Hypothyroidism, Hashimoto's disease

Cancer Basic

P1-02-12

PROSPECTIVE EVALUATION OF THE THYROSPEC MUTATION PANEL FOR THE DIAGNOSIS OF INDETERMINATE THYROID FINE NEEDLE ASPIRATION CYTOLOGIES (FNAC) IN THE CALGARY/SOUTHERN ALBERTA HEALTH CARE REGION

Paul Stewardson[1], *Markus Eszlinger*[2], *Sana Ghaznavi*[1], *Chris Symonds*[1], *Douglas J Demetrick*[1], *Moosa Khalil*[1], *Ralf Paschke*[3]
[1]University of Calgary, Calgary, Canada; [2]Departments of Oncology, Pathology and Laboratory Medicine, Biochemistry and Molecular Biology, and Arnie Charbonneau Cancer Centre, Cumming School of Medicine, University of Calgary, Cumming School of Medicine, Calgary, AB, Canada; [3]Dept. of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Canada

Up to 30% of thyroid nodule fine needle aspiration cytologies (FNAC) are indeterminate. Molecular diagnosis may risk stratify these nodules to obviate diagnostic surgery. We previously demonstrated the applicability of MALDI-TOF mass spectrometry-based mutation detection (MassARRAY) to indeterminate FNAC to provide diagnostic information for clinical decision making.

A MassARRAY panel (ThyroSPEC™) was developed to interrogate 115 single nucleotide variants (SNVs) and 23 rearrangements, covering all genetic alterations described more than once in thyroid carcinoma in COSMIC v83. ThyroSPEC™ was applied to residual material from 75 indeterminate liquid FNACs with available histology in the region of Southern Alberta with centralized cytology assessment. To identify diagnostically relevant variants missed by ThyroSPEC™, seven histologically malignant, ThyroSPEC™ negative thyroid carcinomas were analyzed by whole exome sequencing (WES).

ThyroSPEC™ detected 29 SNVs and 1 rearrangement resulting in a 59% sensitivity and an 83% specificity across indeterminate categories Bethesda III and IV. This includes 49 Bethesda III FNACs for which sensitivity and specificity are 63% and 88% respectively. In our setting, Bethesda III and IV comprise 15% and 3% respectively of all FNAC. According to the 26% malignancy rate of Bethesda III nodules in our setting, the determined ThyroSPEC™ performance would result in a 65% PPV and an 87% NPV in this category. WES of the seven ThyroSPEC™-negative, malignant tumors revealed no somatic SNVs which are known driver mutations or diagnostically relevant variants for thyroid cancer.

The FNAs analyzed were collected prospectively and consecutively over two years, representing the first patients who underwent diagnostic surgery within the larger cohort. These specimens are enriched for malignancy, as demonstrated by the 49% malignancy rate in the 49 Bethesda III samples. Compared to other available tests the ThyroSPEC™ has much lower cost and greater cost efficiency. WES showed that no diagnostically relevant SNVs were missed by the ThyroSPEC™ panel.

P1-02-13

NANOCARRIER-MEDIATED SODIUM IODIDE SYMPORTER (NIS) GENE TRANSFER IN GLIOBLASTOMA MULTIFORME

Rebekka Spellerberg[1], *Teoman Benli-Hoppe*[2], *Carolin Kitzberger*[1], *Simone Hager*[2], *Nathalie Schwenk*[3], *Roland Kälin*[4], *Rainer Glaß*[4], *Ernst Wagner*[2], *Christine Spitzweg*[1]
[1]Ludwig Maximilian University Munich, Department of Internal Medicine IV, Munich, Germany; [2]Ludwig Maximilian University Munich, Department of Pharmaceutical Biology, Munich, Germany; [3]Ludwig Maximilian University, Department of Internal Medicine IV, Munich, Germany; [4]Ludwig Maximilian University Munich, Department of Neurosurgical Research, Munich, Germany

Glioblastoma multiforme (GBM) is a clinically highly relevant tumor with an urgent need for novel therapy approaches. Currently the median survival time after diagnosis is 12 to 15 months. In previous studies, the sodium iodide symporter (NIS) as well-characterized theranostic gene allowed detailed molecular imaging of transgene expression and effective application of therapeutic radionuclides. As an essential step towards clinical application, we are now building on and expanding these studies to the optimization and individualization of NIS-based gene therapy for GBM.

Tumor-targeted polyplexes based on sequence-defined lipo-oligomers were used as systemic NIS gene delivery vehicles. The lipo-oligomers are functionalized with azide groups and allow surface functionalization via a copper-free click reaction with ligands to target a NIS-expressing plasmid to GBM. For tumor targeting, we use the synthetic peptide GE11 as an epidermal growth factor receptor (EGFR)-specific ligand. To cross the blood-brain-barrier by active mechanisms we are focussing on a specific transferrin (TfR)-ligand with a retro-enantio approach to initiate receptor-mediated transcytosis of polyplexes.

In vitro receptor screening and iodide uptake studies with different human and murine GBM cell lines demonstrated high transduction efficiency and EGFR- or TfR-specifity of the respective polyplexes. Preliminary results of *in vivo* three-dimensional high-resolution ^{124}I-PET-imaging experiments in an orthotopic GBM xenograft mouse model (U87MG cells) showed significant tumor-specific accumulation of radioiodine using the EGFR-targeted polyplexes.

In conclusion, our preliminary data clearly demonstrate the enormous potential of tumor-targeted synthetic polyplexes for systemic non-viral NIS gene delivery to GBM, a tumor what is notoriously difficult to target.

P1-02-14

CDK4 PHOSPHORYLATION STATUS AND RATIONAL USE OF CDK4/6 INHIBITORS IN ADVANCED THYROID CANCERS

Jaime M Pita[1], *Katia Coulonval*[1], *Sabine Paternot*[1], *Giuseppe Costante*[2], *Decaussin Myriam*[3], *Laura A. Marlow*[4], *John A. Copland*[4], *Carine Maenhaut*[1], *Jacques E. Dumont*[1], *Pierre P. Roger*[1], *Eric Raspé*[1]

[1]Iribhm, Campus Erasme, Université Libre de Bruxelles, Brussels, Belgium; [2]Institut Jules Bordet, Université Libre de Bruxelles, Medicine, Brussels, Belgium; [3]Hospices Civils de Lyon, Laboratoire D'anatomie Pathologique, Pierre Benite, France; [4]Department of Cancer Biology, Mayo Clinic, Jacksonville, USA

The cyclin-dependent kinases CDK4/6 are key regulators of the cell cycle entry, by phosphorylating the onco-suppressor retinoblastoma protein (pRb). CDK4/6 inhibitors (CDK4i), which are already approved to treat advanced ER+ breast tumors, emerge as new drugs to treat various pRb-proficient chemotherapy-resistant cancers. Presence of activating T172-phosphorylation of CDK4 in breast tumors correlates with their sensitivity to CDK4i. Recent genomic analyses of poorly differentiated (PDTC) and anaplastic thyroid carcinomas (ATC) suggest that CDK4-pRb axis is a key integrating node of the main deregulated signalling pathways in these tumors.

We aimed to investigate the CDK4 activation state in thyroid follicular cell-derived tumors (FDTC) and its relationship with the sensitivity to CDK4i.

CDK4 post-translational modifications were studied in primary tissues using 2D-gel electrophoresis. Consistent with the quiescent state of the thyroid tissue, phosphorylated CDK4 could not be detected in non-malignant thyroid tissues (n = 13). CDK4 phosphorylation was detected in well-differentiated (WDTC) tumors (n = 14) and lymph node metastases (n = 7), in PDTCs (7/8) and in ATCs (5/11). Sensitivity to three CDK4i was assessed (by BrDU incorporation and viability assays) in 11 ATC- and 9 WDTC-derived cell lines. All except 2 WDTC cell lines were sensitive to CDK4i with either full or partial inhibition of DNA synthesis. Since drug responses were lower using viability assays, these compounds probably exert a mainly cytostatic effect. Detection of CDK4 T172-phosphorylation in thyroid cancer cell lines was associated to CDK4i sensitivity.

These data suggest that the presence of the phosphorylated CDK4 (the actual CDK4i target) could represent a biomarker of response to CDK4i in FDTCs and support CDK4i as a potential treatment for these cancers including a subset of most aggressive forms.

P1-02-15

INVOLVEMENT OF IQGAP PROTEINS IN THYROID TUMORIGENESIS

Miguel Zaballos[1], *Carlos Carrasco López*[2], *Pilar Santisteban*[3]

[1]Instituto de Investigaciones Biomédicas Alberto Sols, Ciberonc, Madrid, Spain; [2]Instituto de Investigaciones Biomédicas (CSIC-UAM), Ciberonc, Instituto de Salud Carlos III, Madrid, Spain, Instituto de Investigaciones Biomédicas "Alberto Sols", Madrid, Spain; [3]Instituto de Investigaciones Biomédicas, Universidad Autónoma de Madrid, Ciberonc, Instituto de Salud Carlos III, Madrid, Spain

Background: IQGAP scaffold proteins function as platforms for activation of MAPK and PI3K pathways, providing specific subcellular localization and controlling multiple cellular processes through interaction with a variety of effectors. In human cancer increased expression of IQGAP1 and decreased expression of IQGAP2 have been associated to tumor progression in different tissues, including the thyroid.

Methods: Analysis of The Cancer Genome Atlas Network cohort of human papillary thyroid carcinoma. Determination of cell viability, migration and invasion in human thyroid tumor derived cell lines with silenced IQGAP1 expression. MAPK and PI3K activation were studied by western-blot assay. Metastatic properties were analyzed in an orthotopic chicken embryo model.

Results: IQGAP1 is upregulated in human PTC and is associated with decreased IQGAP2 expression, BRAFV600E mutation and aggressiveness of different clinicopathological features. On the contrary IQGAP2 expression is increased in RAS mutant cells and is associated with the follicular variant of PTC. Depletion of IQGAP1 in human thyroid tumor derived cell lines dysregulates MAPK and PI3K signaling and modifies migratory and invasive properties while it does not affect cell viability. IQGAP1 silencing does not affect the growth rate of the primary tumor, but intravasation and lung and brain metastases were severely suppressed.

Conclusion: The expression of IQGAP proteins is dysregulated in human thyroid cancer and may serve as a diagnostic and prognostic marker. A specific mutant background is associated with a specific expression of the different members of the family and therefore IQGAP1 suppression differentially affects signaling and cellular processes depending on the driver mutation of the cells. IQGAP1 could serve as a therapeutic target, especially in BRAF mutant tumors, where it confers metastatic and aggressive properties to tumor cells.

P1-02-16

INCREASED LONG NONCODING RNA LOC400794 EXPRESSION AND ITS POTENTIAL ROLE IN PAPILLARY THYROID CANCER

Daham Kim[1], *Kyungwon Kim*[1], *Hyein Jung*[1], *Kyeong Hye Park*[2], *Cheol Ryong Ku*[1], *Dong Yeob Shin*[1], *Young Suk Jo*[1], *Eun Jig Lee*[1]

[1]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Rep. of South Korea;* [2]*Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Gyeonggi, Rep. of South Korea*

Objective: Emerging evidence indicates that long noncoding RNAs (lncRNAs) play an important role in tumorigenesis. Many studies have analyzed data from Gene Expression Omnibus (GEO) or The Cancer Genome Atlas (TCGA) to identify promising biomarkers for diagnosis and prognosis of papillary thyroid cancer (PTC). However, the role of cancer related lncRNAs in PTC is not fully elucidated.

Methods: We downloaded the genomic and corresponding clinical data of PTC from TCGA. We compared lncRNAs expression profiles between paired PTC and adjacent normal tissues. We selected the most increased lncRNA and its clinical significance was analyzed. To identify its potential role, genes which highly correlated in total cancerous tissues and significantly different expressed between subgroups were selected and constructed into a co-expression network using Cytoscape.

Results: LOC400794 was the most elevated lncRNA in PTC compared with normal adjacent tissues. Expression levels of LOC400794 were much higher in metastatic lymph nodes than in normal thyroid tissues. When we compared its clinicopathologic characteristics, high LOC400794 expression was associated with extrathyroidal extension, lymph node metastasis and the BRAF V600E mutations. The thyroid differentiation score (TDS) was negatively associated with high LOC400794 expression. Differently expression genes (DEGs) depending on LOC400794 expression were mainly enriched in Cell adhesion molecules, Pathways and Transcriptional misregulation in cancer.

Conclusion: LOC400794 was differentially expressed in thyroid cancer compared with normal adjacent tissues and it was associated with aggressive tumor behavior. LOC400794 can be considered as a potential diagnostic and prognostic biomarkers in PTC.

P1-02-17

ANALYSIS OF TUMOR MUTATIONAL BURDEN IN POORLY DIFFERENTIATED AND ANAPLASTIC THYROID CARCINOMAS

Efisio Puxeddu[1], *Sonia Moretti*[1], *Elisa Menicali*[1], *Nicole Nucci*[1], *Silvia Morelli*[1], *Riccardo Giannini*[2], *Clara Ugolini*[2], *Elisabetta Macerola*[2], *Renato Colella*[3], *Fulvio Basolo*[2]

[1]University of Perugia, Department of Medicine, Perugia, Italy; [2]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, Pisa, Italy; [3]University of Perugia, Department of Experimental Medicine, Perugia, Italy

Objective: Aim of the present study was to evaluate the tumor mutational burden (TMB) in advanced thyroid carcinomas.

Methods: Twenty seven DNA samples (14 PDTC and 13 ATC), extracted from FF-PE tissue section, were analyzed using NEOplus v2 RUO, a hybrid-capture based next-generation sequencing assay, covering 340 genes to analyze TMB. DNA samples were subjected to an initial QC check. Good quality DNA was sheared (Covaris) and subjected to NEO plusv2 analysis (NEO

New Oncology GmbH, Cologne, Germany). Computational analysis was performed using NEO New Oncology's proprietary computational biology analysis pipeline to detect relevant genomic alterations in a quantitative manner and calculate TMB.

Results: Among the 27 DNA samples provided to NEO New Oncology for analysis, 3 DNA samples showed insufficient DNA material in the primary QC check, 5 samples showed insufficient exonic territory coverage for robust TMB calling, 1 sample failed and therefore could not be analyzed. Informative cases (7 PDTC and 11 ATC) allowed to calculate a mean TMB of 7.40±5.72/Mb in PDTC and 4.41±2.86/Mb in ATC ($p = 0.428$). Conversely, quantification of heterozygous missense mutations with an allelic frequency of 30-50% in the considered 340 genes, showed a statistically significant difference between PDTC and ATC (PDTC mean mutation rate 16.70±15.98 vs ATC mean mutation rate 32.20±9.84, $p = 0.018$). These mutations included alterations of known thyroid cancer driver genes such as BRAF, RAS and TERT. Very few nonsense, indel, splice site mutations could be detected.

Discussion: Interestingly, the TMB did not show any significant difference between PDTC and ATC. Both hystotypes presented a mean TMB at least 10 times higher than the mean TMB (0.41/Mb) described for PTC in the TCGA study. These data indicate a high mutational rate in both PDTC and ATC. However, ATC showed a higher rate of heterozygous missense mutations that may involve genes that drive the extreme progression. These data confirm that increase of TMB is associated to thyroid cancer progression. A deeper analysis of the heterozygous mutations will allow to obtain a more comprehensive view of the mutational landscape of advanced thyroid carcinomas.

P1-02-18

DETECTION OF MULTIPLE MUTATIONS IN PAPILLARY THYROID CARCINOMA

Vlasta Sykorova[1], *Sarka Dvorakova*[1], *Eliska Vaclavikova*[1], *Barbora Pekova*[1], *Jitka Moravcova*[1], *Josef Vcelak*[1], *Daniela Kodetova*[2], *Petr Lastuvka*[3], *Jan Plzak*[3], *Petr Bavor*[4], *Jiri Hoch*[4], *Petr Vlcek*[1], *Pavla Sykorova*[5], *Jana Drozenova*[6], *Martin Chovanec*[7], *Bela Bendlova*[1]

[1]Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic; [2]Departments of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [3]Department of Otorhinolaryngology and Head and Neck Surgery, 1st Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [4]Department of Surgery, 2nd Faculty of Medicine Charles University and Motol University Hospital, Prague, Czech Republic; [5]Department of Nuclear Medicine and Endocrinology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [6]Department of Pathology, 3rd Faculty of Medicine, Charles University in Prague, Royal Vinohrady Teaching Hospital, Prague, Czech Republic; [7]Department of Otorhinolaryngology and Head and Neck Surgery, 3rd Faculty of Medicine, Charles University in Prague, Royal Vinohrady Teaching Hospital, Prague, Czech Republic

Objectives: In papillary thyroid carcinoma (PTC), main genetic changes are mostly exclusive, except for TERT mutations, that are often found together with other mutations. The coexistence has a synergistic effect in activation of signalling pathways. Aim of our study was to investigate clinical parameters in patients with multiple mutations.

Methods: Our cohort consisted of 477 patients with PTC. DNA from fresh frozen PTC samples was used for sequencing of TERT promoter (CEQ8000) and for next generation sequencing for detections of BRAF and RAS mutations (Nextera XT/THYRO-ID, MiSeq). RNA was used for detection of RET/PTC1 and RET/PTC3 rearrangements using Real Time PCR.

Results: Multiple mutations were detected in 45 patients (9.4%), all patients had TERT mutation (37xC228T and 8xC250T) together with V600E mutation in the BRAF gene in 42 patients, RET/PTC1 rearrangement in two patients and Q61K mutation in the NRAS gene in one patient. TERT mutations alone were detected in 10 patients (2.1%), BRAF mutations in 196 patients (41.1%), RET/PTC rearrangements in 27 patients (5.7%), RAS mutations in 31 patients (6.5%) and no mutation in 168 patients (35.2%). Patients with multiple mutations had significantly more frequent lymph node metastasis (63.9% vs. 24.8% in negative samples), extrathyroidal extension (81.3% vs. 18.8% in negative samples), more advanced T categories T3 a T4 (71.1% vs. 21.3% in negative samples), recurrence or persistence (52.2% vs. 9.2% in negative samples) and mortality (43.8% vs. 6.3% in negative samples).

Conclusions: The multiple mutations are associated with more aggressive features and the worst prognosis of PTC and this knowledge could help to select the patients with the poor prognosis of PTC.

Supported by AZV 16-32665A and MH CR RVO 00023761.

P1-02-19

BRN3A/POU4F1 FUNCTIONS AS A TUMOR SUPPRESSOR IN THYROID CANCER THROUGH TARGETING STAT3 SIGNAL

Lihua Liu[1], *Seung-Nam Jung*[2], *Chan Oh*[1], *Jae Won Chang*[2], *Yea Eun Kang*[3], *Bon Seok Koo*[4]

[1]Department of Medical Science, College of Medicine, Chungnam National University, Daejeon, Republic of Korea; [2]Department of Otolaryngology-Head and Neck Surgery, Research Institute for Medical Science, Chungnam National University College of Medicine, Daejeon, Republic of Korea; [3]Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, Chungnam National University, Daejeon, Republic of Korea, Division of Endocrinology and Metabolism, Department of Internal Medicine, Chungnam National University, College of Medicine, Daejeon, Republic of Korea; [4]Department of Otolaryngology – Head & Neck Surgery, Chungnam National University, School of Medicine, Department of Otolaryngology-Head and Neck Surgery, Research Institute for Medical Science, Chungnam National University College of Medicine, Daejeon, Republic of Korea, Daejeon, Rep. of South Korea

Objectives: In our study, the promoter hypermethylation of Pou4f1 was found in patients of aggressive thyroid cancer compare to non-cancer. We investigated the role of Pou4f1 in thyroid cancer cell progression and its clinical implication.

Materials and methods: For functional in vitro analysis, proliferation, migration, invasion assay, PCR and western blotting were performed after overexpression or suppression of Pou4f1. To investigate the exact mechanism of Pou4f1 in thyroid cancer, comparison of clinic-pathologic findings and IPA analysis were performed using TCGA database.

Results: In TCGA database, low Pou4f1 expression group revealed more aggressive phenotype, including lymph node metastasis and extrathyroidal extension compared to high Pou4f1 expression group. Pou4f1 was downregulated in thyroid cancer cell lines. Pou4f1 overexpression suppresses cell migration and invasion by EMT. In conversely, Pou4f1 knockdown promotes cell migration and invasion by EMT in B-CPAP cells. Pou4f1 also downregulates the protein expression and phosphorylation of STAT3, commonly functions as an oncogenic driver, to promote cancer metastasis.

Conclusion: Our findings reveal a novel mechanism of action for Pou4f1 in thyroid cancer cells. Taken together, these results identify Pou4f1 as a tumor suppressor in thyroid cancer that is essential for thyroid cancer therapy.

P1-02-20

PREFERENTIAL KILLING OF HUMAN THYROID CANCER CELL LINES WITH MITOCHONDRIAL DYSFUNCTION BY NON THERMAL PLASMA

Chan Oh[1], *Seung-Nam Jung*[2], *Yea Eun Kang*[3], *Mi Ae Lim*[2], *Jae Won Chang*[4], *Bon Seok Koo*[5]

[1]Department of Medical Science, College of Medicine, Chungnam National University, Daejeon, Republic of Korea; [2]Department of Otolaryngology-Head and Neck Surgery, Research Institute for Medical Science, Chungnam National University College of Medicine, Daejeon, Republic of Korea; [3]Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, Chungnam National University, Daejeon, Republic of Korea, Division of Endocrinology and Metabolism, Department of Internal Medicine, Chungnam National University, College of Medicine, Daejeon, Republic of Korea; [4]Department of Otolaryngology-Head and Neck Surgery, Research Institute for Medical Science, Chungnam National University, College of Medicine, Daejeon, Republic of Korea; [5]Department of Otolaryngology – Head & Neck Surgery, Chungnam National University, School of Medicine, Department of Otolaryngology-Head and Neck Surgery, Research Institute for Medical Science, Chungnam National University College of Medicine, Daejeon, Republic of Korea, Daejeon, Rep. of South Korea

Objectives: Non thermal plasma (NTP) is generated by ionization of neutral gas molecules, which has led to its application in the treatment of various diseases, including cancer. However, the molecular mechanisms of NTP-induced cancer cell death are unclear. The purpose of this study was to evaluate the molecular mechanism of NTP in the regulation of tumor cell viability in thyroid cancer.

Methods: The effects of NTP on thyroid cancer cells were investigated using RNA seq, cell viability assay, OCR/ECAR measurements and western blot analysis. The distinctive cellular and mitochondrial dysfunctions of two human thyroid cancer cell lines with BRAF mutation (BCPAP and 8505C) from human thyroid normal cell line (Nthy-ori3-1) were also studied by NTP treatment.

Results: The cell number of thyroid cancer cells has been significantly reduced more than that of the thyroid normal cells. Transcriptomic analysis in thyroid cancer cells revealed the upregulation of mitochondrial stress response signaling and mitochondrial stress induced transcription factor after NTP therapy. Interestingly, NTP reduced mitochondrial function in thyroid cancer cells and increased the expression of EGR1, which was known as the tumor suppressor gene.

Conclusion: These results suggest that NTP could be a potential therapy targeting mitochondrial stress response and mitochondrial function for the treatment of thyroid cancer.

P1-02-21

A NEW PATIENT-DERIVED ANAPLASTIC THYROID CANCER CELL LINE OBTAINED FROM A FINE-NEEDLE CYTOLOGY OF A PATIENT WITH AN UNRESECTABLE TUMOUR

Ana T. Pinto[1], *Marta Pojo*[1], *Joana Simões-Pereira*[2], *Rúben Roque*[3], *Ana Saramago*[1], *Lúcia Roque*[1], *Carmo Martins*[1], *Saudade André*[4], *José Cabeçadas*[3], *Valeriano Leite*[5], *Branca Cavaco*[6]

[1]Unidade de Investigação Em Patobiologia Molecular, Instituto Português de Oncologia de Lisboa Francisco Gentil, Portugal; [2]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Unidade de Investigação Patobiologia Molecular, Instituto Português de Oncologia de Lisboa Francisco Gentil, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal; [3]Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Portugal; [4]Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E., Serviço de Anatomia Patológica, Lisbon, Portugal, Portugal; [5]Servico de Endocrinologia, Instituto Português de Oncologia de Lisboa, Nova Medical School | Faculdade de Ciências Médicas, Lisboa Codex, Portugal; [6]Unidade de Investigação Em Patobiologia Molecular (Uipm), Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal

Introduction: Anaplastic thyroid cancer (ATC) although rare, is one of the most lethal tumours, due to its unresectability, local invasiveness and refractoriness to standard therapies. ATCs are genetically heterogeneous, being mandatory to better understand the mechanisms underlying their aggressiveness. In this study we aimed to establish an ATC cell line obtained from a fine-needle aspiration cytology (FNAC).

Methods: We obtained cells from FNAC of a patient with an unresectable ATC and established an ATC primary cell culture, named C3948. This cell line was then characterized in terms of morphology, expression of epithelial and thyroid markers, molecular cytogenetics, mutational and global gene expression profile, doubling time and drug resistance profile, using different methodologies: immunostaining, karyotype analysis, comparative genomic hybridization (CGH), next-generation sequencing, Sanger sequencing, gene expression microarrays, cell counting and IC_{50} determination.

Results: C3948 retained the cytological characteristics of the original ATC cells: both FNAC-original specimen and -derived C3948 cell line expressed AE1/AE3 and Cam5.2, but not cytokeratin 19, thyroglobulin, calcitonin, PAX8 or TTF-1. Furthermore, C3948 harbors mutations in *TP53*, *STK11* and *DIS3L2* genes, an aberrant karyotype with many chromosomal losses and gains and a gene expression profile similar to C643 ATC commercial cell line. Doubling time and drug resistance profile for paclitaxel, doxorubicin and cisplatin were also identical to the commercial cell line C643.

Discussion: This experiment allowed us to establish a new ATC cell line from cells obtained through a routine FNAC, demonstrating that this can be considered a useful approach to obtain cell lines from unresectable tumours. We believe that this new model of study will help to better understand the biology and drug resistance of ATC. In the near future, these tumour models are expected to better predict and support the selection of the most effective therapeutic approach to each ATC.

P1-02-22

GENE EXPRESSION PROFILE OF PAPILLARY THYROID CARCINOMAS HARBORING TERTP MUTATION- DOES IT DIFFER FROM GENE EXPRESSION PROFILE OF BRAF-POSITIVE PTCS?

Dagmara Rusinek[1], Marta Cieslicka[2], Aleksandra Pfeifer[2], Sylwia Szpak-Ulczok[2], Jolanta Krajewska[2], Malgorzata Kowalska[2], Jadwiga Zebracka-Gala[2], Tomasz Tyszkiewicz[2], Monika Halczok[2], Ewa Chmielik[2], Ewa Zembala-Nozynska[2], Malgorzata Oczko-Wojciechowska[2], Barbara Jarzab[2], Agnieszka Czarniecka[2]

[1]Maria Sklodowska-Curie Institute - Oncology Center, Gliwice Branch, Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Institute - Oncology Center Gliwice Branch, Gliwice, Poland; [2]Maria Sklodowska-Curie Institute - Oncology Center, Gliwice Branch, Poland

Objectives: *BRAF* V600E mutation is the most common genetic alteration in papillary thyroid carcinoma (PTC), however, its prognostic significance is controversial. There are evidences that co-existence of *BRAF* V600E and *TERT* promoter (*TERT*p) mutations have negative impact on clinical outcomes in patients with PTC. Although, single studies show that *TERT*p mutations alone are responsible for aggressive course of the disease. The aim of our study was the search of potential differences in PTCs gene expression profiles that resulted from *TERT*p mutations occurrence.

Methods: The PTC cohort consisted of a total of 54 cases [16 being BRAF(+), 8 BRAF and TERTp(+) and 30 PTCs without detected *BRAF* and *TERT*p mutations]. Affymetrix Human Gene 1.0 ST were used. Microarray data has been pre-processed using the fRMA and ComBat algorithms. The t-Student test was used in analysis of genes expression. PTCs with *BRAF*V600E, with *TERT*p mutation and without these genetic alterations were compared to each other for potential differences in gene expression profile. Additionally, BRAF-like, RAS-like score (BRS) and Thyroid Differentiation Score (TDS) were calculated.

Results: When comparing BRAF(+) and BRAF(-) PTCs more than 2500 genes were obtained as being significantly differentiated (FDR<0.05). However, in the comparison of BRAF(+) and BRAF&TERTp(+) cases only 9 genes with statistically significant difference in expression were obtained. *TERT*p mutations did not affect the TDS or BRS scores.

Conclusions: The presence of *TERT*p mutations in PTCs is believed to be responsible for poorer outcome. Obtained results, although, do not show major changes in gene expression profile in TERTp(+) PTCs comparing to BRAF(+) ones, cannot exclude existence of molecular differences that are a consequence of mutated *TERT*p. Lack of cases with the presence of only *TERT*p mutation significantly impairs our analysis of these mutations impact. Further studies are needed.

Supported by the National Centre for Research and Development project MILESTONE (STRATEGMED2/267398/4/NCBR/2015).

Cancer Clinical 1

P1-03-23

THE OUTCOME OF METASTATIC DIFFERENTIATED THYROID CANCER IS SIMILAR IN PATIENTS PREPARED FOR 131-I THERAPY WITH RECOMBINANT TSH OR HYPOTHYROIDISM

Maria Cristina Campopiano[1], Debora Podestà[2], Elisabetta Addante[2], Carlotta Giani[2], Francesca Bianchi[2], Laura Agate[2], David Viola[2], Rossella Elisei[2], Eleonora Molinaro[2]

[1]Unit of Endocrinology, Pisa, Italy; [2]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Objective and aim: Although not approved for 131-I therapy in metastatic thyroid cancer, recombinant human TSH (rhTSH) can be used in compassionate cases. We aimed to evaluate if the rhTSH preparation to 131I-therapy, compared to LT4 withdrawal (HYPO), had an impact on the outcome of metastatic DTC.

Methods: among >300 patients treated for metastases with 131-I, we identified a group of DTC patients treated several times with 131-I for metastatic disease and always prepared with rhTSH (compassionate use). We than matched a similar group who was prepared with HYPO.

Results: We selected 77 DTC patients with metastatic disease after total-thyroidectomy and 131I remnant-ablation (RRA). Fourty-3/77(55%) patients represented the rhTSH-group and 34/77(45%) the HYPO-group. As expected from the matching procedure, clinical-pathological data (age, sex, TNM, aggressive variants and ATA risk classes) were similar. The only difference was that at whole-body-scan (WBS) post-RRA, the rhTSH-group showed a higher prevalence of 131-I avid metastases (31/43[72%] *vs* 15/34[56%], p = 0.01). Nevertheless, a similar cumulative 131I-activities were administered in the two groups (17242±5994 MBq and 18130±5180 MBq, p = 0.1). The last WBS post-131I showed metastases in 34/43(79%) patients of rhTSH-group and 24/34(71%) patients of HYPO-group (p = 0.4). In particular, 13/34(39%) and 10/24(42%) had lymph-node metastases; 21/34(61%) and 14/24(58%) had distant metastases (p = 0.8). After 4 years of follow-up there was no difference in the outcome between the two groups: 1/43(2%) in rhTSH-group and 1/34(3%) in HYPO-group had excellent response, 7/43(19%) in rhTSH-group and 9/34(26%) in HYPO-group had biochemical persistence, 34/43(79%) in rhTSH-group and 24/34(71%) in HYPO-group had structural disease (p = 0.53).

Conclusions: the final outcome of two groups of metastatic DTC patients prepared for 131-I with rhTSH or HYPO, well matched for all the clinical-pathological features, was similar. These results are strongly suggestive that the type of stimulation does not affect the results of the 131-I therapy.

P1-03-24

IMPACT OF PROPHYLACTIC CENTRAL COMPARTMENT LYMPH NODE DISSECTION (PCCLND) ON THE OUTCOME OF PATIENT WITH PAPILLARY THYROID CARCINOMA (PTC) AND SYNCRHRONOUS IPSILATERAL LATERO-CERVICAL LYMPH NODE METASTASES (SILCLN)

Luigi De Napoli[1], Antonio Matrone[2], Karin Favilla[3], Aleksandr Aghababyan[3], Carlo Enrico Ambrosini[4], Piermarco Papini[1], Liborio Torregrossa[5], Fulvio Basolo[6], Paolo Vitti[7], Rossella Elisei[8], Gabriele Materazzi[9]

[1]Department of Surgical, Medical, Molecular Pathology and Critical Area, Unit of Endocrine Surgery, University Hospital of Pisa, Department of Surgery, Pisa, Italy; [2]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [3]Department of Surgical, Medical, Molecular Pathology and Critical Area, Unit of Endocrine Surgery, University Hospital of Pisa, Italy; [4]Department of Surgical, Medical, Molecular Pathology and Critical Area, Unit of Endocrine Surgery, University Hospital of Pisa, Pisa, Italy; [5]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [6]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, Pisa, Italy; [7]Endocrinology, Department of Clinical and Experimental Medicine, Endocrinology Unit, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy; [8]Endocrine Unit, Dept of Clin and Exp Medicine, University Pisa, Pisa, Italy; [9]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, University Hospital of Pisa, Pisa, San Giuiano Terme, Italy

Introduction: pCCLND is linked to recurrent laryngeal nerve palsy and hypoparathyroidism. Little is known about the prognostic implication of pCCLND on the clinical outcome of PTC patients with sILCLN. The aim of our study has been to evaluate the impact of pCCLND on clinical outcome of PTC pts with sILCLN proven metastases.

Material and methods: We collected the data of 169 consecutive pts affected by PTC and sILCLN, without ultrasonographic evidence of CCLND metastases, from 2004 to 2015. All of them, were surgically treated at the Endocrine-Surgery Unit and followed by the Endocrinology Unit of Pisa

University. Patients were divided in Group A (TTx+ipsilateral LCLN dissection) (114/169 – 67.5%) and Group B (TTx+ipsilateral LCLN dissection and pCCLND) (55/169 – 32.5%). Clinical outcome was evaluated at the end of follow-up (median 5 years).

Results: Group A and B were similar for age and gender, histological variant and tumor dimension. Moreover, no difference in the number of dissected LCLN and in number and dimension of metastatic LCLN, were noted. The activity of ^{131}I at time of RRA was similar between the two groups. Clinical outcome (i.e., excellent, biochemical incomplete, structural incomplete and indeterminate response) did not differ between the groups. No significant differences were reported, in terms of recurrent laryngeal nerve permanent palsy. At variance, permanent hypoparathyroidism was significantly higher in Group B vs A (20 vs 5.3% - p<0.01). Surgical retreatment for recurrence in the CC compartment (1.75% in group A vs 1.8% in group B – p = ns) was not different in the two groups.

Conclusions: This study showed that, the pCCLND does not improve the outcome of pts with PTC and sILCLN, regardless of number of dissected LCLN and number and dimension of metastatic LCLN. Conversely, the risk of permanent hypoparathyroidism significantly increased in Group B.

P1-03-25

IS ROUTINE NECK ULTRASOUND SURVEILLANCE NEEDED IN FOLLOW-UP OF PTC PATIENTS WITH NO EVIDENCE OF DISEASE AT THE 1-YEAR EVALUATION?

Cosimo Durante[1], *Giorgio Grani*[2], *Valeria Ramundo*[3], *Livia Lamartina*[3], *Marco Biffoni*[3], *Laura Giacomelli*[3], *Rosa Falcone*[2], *Laura Ciotti*[2], *Cristiano Lomonaco*[2], *Sebastiano Filetti*[3]

[1]Dep. Translational and Precision Med, Rome, Italy; [2]Sapienza University of Rome, Dept. of Translational and Precision Medicine, Rome, Italy; [3]Sapienza University of Rome, Italy

Objectives: Ultrasound examination of the neck is commonly used in the follow-up of thyroid cancer patients, as it is considered the best tool to detect persistent or recurrent disease. The aim of this study was to clarify the usefulness of routine neck sonographic surveillance in low- and intermediate-risk papillary thyroid cancer patients with negative sonographic findings at the initial post-thyroidectomy assessment and unstimulated serum Tg levels < 1 ng/mL.

Methods: A retrospective analysis of prospectively recorded data, during the long-term follow-up was performed at an academic referral center. All patients underwent yearly biochemical evaluation (unstimulated serum thyroglobulin [Tg], anti-thyroglobulin antibodies, and TSH levels), and neck ultrasound examination. A cohort of 226 patients with no evidence of disease at 1-year evaluation was considered for the final analysis, after exclusion of high-risk patients (according to the American Thyroid Association initial risk estimation). The rate of abnormal sonographic findings at 3-year follow-up visit and at the last follow-up visit was calculated.

Results: The rate of abnormal lymph nodes in patients with initially undetectable Tg was 1.2% at 3 years and 1.8% at the last visit, corresponding to a negative predictive value (NPV) of 98.8% (95% CI 95.8–99.9%) and 98.2% (95–99.6%), respectively. In patients with detectable Tg, but <1 ng/ml, the NPV were similar: 98.2% (90.3–99.9%) and 94.5% (84.9-98.9%) at 3-year and last visit, respectively.

Conclusions: Low- and intermediate-risk patients whose initial assessment reveals no evidence of disease can be safely followed with regular clinical assessments and unstimulated serum Tg assays. Repeat neck sonography should be reserved for patients with rising Tg antibodies titers or Tg levels increasing above 1 ng/mL.

P1-03-26

EFFECT OF CHRONIC LYMPHOCYTIC THYROIDITIS FOR RECURRENCE IN CN0 PAPILLARY THYROID CANCER

Young Jae Ryu[1], *Jung Han Yoon*[1]

[1]Chonnam National University Hwasun Hospital and Medical School, Gwangju, Rep. of South Korea

Background: Clinical outcomes of chronic lymphocytic thyroiditis (CLT) in patients with papillary thyroid carcinoma (PTC) remained controversial. The aim of this study was to evaluate clinicopathological variables according to CLT and analyze risk factors for recurrence in clinically lymph node (LN) negative PTC.

Methods: We thoroughly examined medical records of 850 PTC patients who underwent prophylactic bilateral central neck dissection as well as total thyroidectomy from 2004 to 2010 during a median follow-up of 95.5 months (range, 12−158 months).

Results: Female gender, preoperative thyroid stimulating hormone level more than 2.5 mU/L, size of primary tumor less than 1cm, no gross extrathyroidal extension, high number of harvested LN, low number of metastatic LN, and positive anti-thyroglobulin (Tg) antibody at one year after initial treatment were significant associated with CLT in PTC patients. In the finding of multivariate analysis according to recurrence, patients with N1a stage (vs. N0 stage; hazards ratio [HR], 3.255; 95% confidence interval [CI], 1.290−8.213; p = 0.012) and positive anti-Tg antibody at one year after initial treatment (vs. negative anti-Tg antibody; HR, 5.118; 95% CI, 2.130−12.296; $p < 0.001$) had worse recurrence-free survival (RFS) while patients with CLT (vs. no CLT; HR, 0.357; 95% CI, 0.157−0.812; p = 0.014) had favorable RFS.

Conclusions: CLT was associated with less aggressive tumor characteristics and LN status. Clinically LN negative PTC patients with CLT had more favorable RFS compared with those without CLT.

Keywords: Papillary thyroid cancer, Chronic lymphocytic thyroiditis, Recurrence.

P1-03-27

PAPILLARY THYROID CANCERS OF THE THYROID ISTHMUS: THE PATTERN OF NODAL METASTASIS AND THE SIGNIFICANCE OF EXTRATHYROIDAL EXTENSION

Jungirl Seok[1], *Hyeong Won Yu*[1], *June Young Choi*[1], *Young Ho Jung*[1], *Soon-Hyun Ahn*[2], *Woo-Jin Jeong*[1]

[1]Seoul National University Bundang Hospital; [2]Seoul National University Hospital

Background: Cancers of the thyroid isthmus are less frequent compared to the lobar cancers, yet has its own unique clinicopathological characteristics. Herein, we sought to examine the isthmic papillary thyroid carcinomas (PTCs) for the pattern and risk factors for nodal metastasis and the significance of extrathyroidal extension (ETE).

Methods: The medical records of 3,138 patients diagnosed with solitary PTC who had undergone surgery were retrospectively reviewed. Of these, 122 isthmic PTCs were matched to common lobar PTCs at a ratio of 1:3 for age, sex, and nodule size. Patient demographics, surgical findings, and pathology reports were analyzed.

Results: Solitary isthmic PTCs comprised 4.6% of all PTCs. Isthmic PTCs had more lymphatics invasion (22.1% vs 13.4%, P = .021), ETE (73.0% vs 57.1%, P = .002), and perithyroidal node metastasis (18.0% vs 9.0%, P = .006) compared to lobar PTCs. However, there were no significant differences in the rate of central and lateral neck node metastasis between the two groups. ETE was identified not to be a risk factor for isthmic PTCs for central and lateral node metastasis, in contrast to lobar PTCs in which ETE was a significant risk factor (OR [95% CI]: 3.18 [1.89-5.34], 4.72 [1.04-21.41]).

Conclusion: The rate of central and lateral neck node metastasis of isthmic PTCs are comparable to lobar PTCs despite higher rate of ETE in the isthmic counterpart. Although the extent of surgery for isthmic PTCs remains to be investigated, careful dissection of perithyroidal nodes may be necessary for isthmic PTCs.

P1-03-28

RISK OF THYROID CANCER IN 1504 PATIENTS REFERRED FOR THYROID SURGERY WITH ASSUMED BENIGN HISTOLOGY

Signe Gram[1], *Ulla Feldt-Rasmussen*[2], *Jens Bentzen*[3], *Giedrius Lelkaitis*[4], *Christian von Buchwald*[1], *Christoffer Holst Hahn*[1], *Jacob Rasmussen*[1]

[1]Rigshospitalet, Copenhagen University, Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Copenhagen, Denmark; [2]Copenhagen University Hospital, Rigshospitalet, Dept of Endocrinology, Pe 2132, Copenhagen, Denmark; [3]Herlev Hospital, Copenhagen University, Department of Oncology, Denmark; [4]Rigshospitalet, Department of Pathology, Rigshospitalet, Copenhagen University, Denmark

Objectives: The aims of this study were to report the risk of thyroid malignancy in case of either benign fine-needle aspiration (FNA) or without FNA performed, and to investigate possible predictive factors for thyroid malignancy in a population with recent moderately low iodine intake.

Methods: All patients referred for thyroid surgery in a tertiary cancer centre from 2000-2016 were included (N = 3703). After excluding cases indicating malignant histology, we included group 1: patients with benign FNA (N = 764), and group 2: patients without FNA (N = 740), leaving 1504 eligible for further investigation. Information on age, gender, tracheal compression or dislocation, thyroid specimen weight, scintigraphy, ultrasound, medically treated thyrotoxicosis, serum stimulating thyroid hormone, indication of surgery, TNM classification, stage and outcome were retrieved.

Results: The malignancy risk was 7.6% (58/764) in group 1 and 6.8% (50/740) in group 2. Patients with T2-4 tumours constituted 2.2% (33/1504). In the combined groups, ultrasound verified that solitary solid tumour was predictive for malignancy ($p = 0.01$ by Chi2, and OR = 1.69, $p = 0.02$ in multiple logistic regression). For group 1 patients, thyrotoxicosis, which in this case was medically treated, was a significant predictive factor for malignancy ($p = 0.04$).

Conclusions: The risk of malignancy of 7.6% and 6.8% was high, considering that patients with malignant FNA, suspicious FNA or clinical findings indicating malignancy were excluded, and 2.2% of these malignancies were stages T2-4. In cases with solitary solid tumour on ultrasound, the risk of malignancy should not be ignored, even with benign FNA.

P1-03-29

RADIATION EXPOSURE IN THYROID CARCINOMA TREATED WITH RADIOIODINE-WHICH FACTORS ARE DECISIVE?

Anabela Martins[1], *Francisco Sobral do Rosário*[1], *Daniel Macedo*[2], *Cristina Loewenthal*[3], *Teresa Rézio*[1], *Rosário Vieira*[1], *Nuno Cordeiro Raposo*[4], *José Marçalo*[5]

[1]Hospital Da Luz, Lisboa, Portugal; [2]Hospital Da Luz, Hospital Da Luz, Hospital Da Luz, Lisboa, Portugal; [3]Hospital Da Luz, Lisboa; [4]Hospital Beatriz Ângelo, Hospital Beatriz Angelo, Lisbon, Portugal; [5]Hospital de Santa Maria

Introduction: Total thyroidectomy followed by radioiodine is the initial treatment of thyroid cancer. Hypothyroidism or recombinant human TSH (rTSH) are the stimulation methods. At discharge the radiation emitted by the patient is measured at 1,5 meter with a handheld radiation detector in order to determine radiation protective measures to others. Radiation exposure is important and warrants special care in order to decrease exposure of the general public.

Objective: Characterize the group of thyroid carcinoma patients submitted to radioiodine, with regards radiation half life and its related factors.

Material and Methods: Retrospective evaluation of thyroid carcinoma patients submitted to radioiodine therapy from 2011 to March 2018. Statistical analysis done with SPSS 21.

Results: 537 patients were submitted to radiodine therapy, 396 female (77,3%). 26 patients were submitted to two treatments and 3 have done a third. Mean age of 48,8 years (SD-13,2 17-86). 445 treatments were under rTSH and 91 under hypothyroidism. 159 presented with papillary thyroid carcinoma (PTC), common type, 231 PTC follicular variant, 31 PTC with poorly differentiated areas, 21 follicular carcinoma and 70 mixed variants. 182 patients presented regional lymph node metastases and 5 distant metastases. Higher levels of thyroglobulin and radioactivity at discharge occurred in the hypothyroidism group, when compared to the rTSH group ($p<0,01$).Higher levels of radioactivity at discharge and thyroglobulin are also more elevated in patients with bigger size tumour and with specific histological variants (PTC with poorly differentiated areas, PTC follicular variant, follicular carcinoma), but this effect is not independent from the stimulation method or radioiodine activity. Regional lymph node metastases are not correlated to radiation total-body effective half life.

Conclusions: Radiation exposure to the general population is an important issue. Patients submitted to radioiodine therapy with hypothyroidism presented higher radioactive emission levels at discharge and warranted longer periods of protective measures.

P1-03-30

DIFFERENCIATED THYROID CANCER IN A PEDIATRIC POPULATION: ESTIMATING THE RISK OF RECURRENCE AND EVOLUTION OVER TIME

Inês Damásio[1], *Daniela Dias*[2], *Sara Pinheiro*[3], *Rita Santos*[4], *Valeriano Leite*[5]

[1]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Portugal; [2]Instituto Português de Oncologia de Lisboa, Francisco Gentil, Endocrinology Department, Portuguese Cancer Institute, Lisbon, Portugal, Lisboa, Portugal; [3]Endocrinology Department, Portuguese Cancer Institute, Lisbon, Portugal, Portugal; [4]Institudo Português de Oncologia de Lisboa Francisco Gentil, Endocrinology Department, Instituto Portugues de Oncologia de Lisboa, Francisco Gentil, Lisbon, Portugal, Nova Medical School/ Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal, Lisboa, Portugal; [5]Servico de Endocrinologia, Instituto Português de Oncologia de Lisboa, Nova Medical School | Faculdade de Ciências Médicas, Lisboa Codex, Portugal

Introduction: Differentiated thyroid cancer (DTC) is the most common endocrine cancer during childhood and the prognosis is usually good. The 2015 American Thyroid Association (ATA) pediatric guidelines for DTC classifies patients in three categories (low, intermediate and high) that represent the risk or persistent/recurrent disease.

Aim: To characterize pediatric patients with DTC; to classify those patients according to 2015 ATA risk groups; to relate the risk group with the treatment response between year 1 and 2 of follow up and with the disease status at the end of follow up; to access the evolution of patients with persistent disease over time.

Methods: Retrospective analysis of pediatric patients (≤18 years) with DTC followed in our institution between 2007 and 2018. Patients with non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) were excluded.

Results: We found 39 patients, 29 were female with median age at diagnosis of 15 years old (range 5-18) and median follow-up of 40 months. Six patients were excluded for some analysis due to short follow up or missing data. It was possible to stratify 33 patients in ATA risk groups: 13 low-risk,11 intermediate-risk, and 9 high-risk. Between year 1 and 2, 16 patients had an excellent response, 3 had incomplete biochemical response, 7 had structural incomplete response and 7 were indeterminate. At the end of the follow up, 20 patients had no evidence of disease, 3 patients had biochemical evidence of disease, 6 patients had structural disease and 4 were indeterminate. There was a good correlation between risk groups, treatment response and disease status. All patients with persistent disease had stable or slowly decreasing serum thyroglobulin over time without any further treatment.

Conclusion: Defining risk categories and treatment response predicted disease status in our cohort. Most patients with persistent disease remain stable over time.

P1-03-31

RETROSPECTIVE ANALYSIS OF 123 PAPILLARY THYROID CARCINOMAS ≤ 1CM IN ONE SINGLE CENTER

Daniel Macedo[1], *Raquel Vaz de Castro*[2], *Ricardo Veiga*[1], *Anabela Martins*[1], *Carlos Fernandes*[1], *Ana Catarino*[1], *Francisco Sobral do Rosário*[1]

[1]Hospital Da Luz, Lisboa, Portugal; [2]Centro Hospitalar Lisboa Norte, Portugal

Introduction: Thyroid cancer incidence is increasing worldwide over the last decades. The widespread use of thyroid imaging, particularly ultrasound is partially responsible for this trend, but the causes are highly debated.

Although papillary carcinoma (PTC) is the most frequent thyroid carcinoma, this increase is mainly due to PTC ≤ 1cm (T1a).

The aim of this study was to analyze PTC ≤ 1cm prevalence and patterns, and to compare the groups with incidental vs non-incidental diagnosis, as well as the groups with a diagnosis before and after 2015 (according to the year of release of the ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer).

Methods: Retrospective analysis of the clinical files of CPT-T1a patients diagnosed in our center between 2008 and 2018. Patients were identified through the SNOMED papillary microcarcinoma codification. Patients were then divided in 2 groups: incidental vs non-incidental diagnosis; histological diagnosis before 2015 and after 2015.

Results: 123 PTC-T1a patients were identified. The mean age at diagnosis was 50.3 years (21-84). 81.3% were female. Mean tumor diameter was 6.2mm. 25.2% were multifocal; 13.8% had extra-thyroidal extension; 13.8% had lymph node metastases; 2.4% had angioinvasion; 1.6% had positive surgical margins and 10.6% had high risk histological variants. 27.6% of the patients were submitted to ^{131}I therapy. The mean follow-up time was 53 months.

65 patients (52.8%) were diagnosed incidentally, with a mean tumor diameter of 4.5mm, versus the 7.8mm for non-incidentalomas. 13.8% of the incidentalomas were multifocal, contrasting with 37.9% of the non-incidentalomas ($p<0.05$). Only 7.7% of the incidentalomas had lymph node metastases while cervical metastases were found in 20.7% of the non-incidentalomas. 6.5% of the incidentalomas and 22.4% of the non-incidentalomas had extra-thyroidal extension. There were no patients diagnosed incidentally with angioinvasion. 7.7% of the incidentalomas were submitted to ^{131}I therapy, differing from 37.9% of the non-incidentalomas. More aggressive histological variants were identified in the incidentalomas group (12.3% vs 8.6%).

81.4% of the patients diagnosed before 2015 were submitted to total thyroidectomy, while 54.3% of those diagnosed from 2015 were submitted only to lobectomy. 2 patients submitted to lobectomy after 2015, needed to complete the thyroidectomy.

The percentage of patients submitted to ^{131}I therapy was higher in the group of patients diagnosed after 2015 (31.4% vs 25.6%).

Conclusion: Patients diagnosed incidentally with PTC-T1a appear to have less aggressive disease with a lower need of ablative ^{131}I therapy.

The trend to submit patients with tumors ≤ 1cm to lobectomy instead of total thyroidectomy is supported by our results.

P1-03-32

TEN YEAR SURVIVAL OF PATIENTS WITH WELL DIFFERENTIATED THYROID CANCERS - A RETROSPECTIVE ANALYSIS

Elizabeth M. Iype[1], *Shirish Patil*[1]

[1]Regional Cancer Institute, Head and Neck Oncosurgery, Trivandrum, India

Background: Well-differentiated thyroid carcinoma (WDTC) representsa group of thyroid cancers with excellent prognosis. The behavior of these cancers can be predicted by patient age, sex, tumor size, local invasion, angioinvasion, lymph node metastases, distant metastases, as well as tumor differentiation and ability to take up radioactive iodine.

Objectives:

1. To analyzes ten year overall and disease free survival of patients with well differentiated thyroid cancers treated at Regional Cancer Centre for two years during January 2006- December 2007 (400 patients).
2. To evaluate the various prognostic factors (Age, gender, Tumour stage, Nodal stage, Pathological variables, Extent of surgery and post operative adjuvant treatment taken) of well differentiated thyroid cancer patients treated at our centre.

Materials and methods: Oncological outcomes of patients in terms of disease-specific survival (DSS) and disease-free survival (DFS) was calculated by the Kaplan–Meier method, while multivariable analysis was done by the Cox proportional hazard model for assessing the independent influence of various prognostic factors.

Hypothyroidism

P1-04-33

PROSPECTIVE EVALUATION OF AUTOIMMUNE AND NON-AUTOIMMUNE SUBCLINICAL HYPOTHYROIDISM IN A LARGE COHORT OF CHILDREN AND ADOLESCENTS WITH DOWN SYNDROME

Malgorzata Wasniewska[1], *Giorgia Pepe*[2], *Domenico Corica*[3], *Luisa De Sanctis*[4], *Mariacarolina Salerno*[5], *Maria Felicia Faienza*[6], *Daniele Tessaris*[4], *Gerdi Tuli*[7], *Ida D'Acunzo*[5], *Tommaso Aversa*[8], *Angela Alibrandi*[9], *Filippo De Luca*[8]

[1]University of Messina, Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy, Department of Human Pathology of Adulthood Abd Childhood, University of Messina, Italy; [2]Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy; [3]Department of Human Pathology in Adulthood and Childhood, University of Messina, Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy; [4]Department of Public Health and Paediatric Sciences, University of Turin, Turin, Italy; [5]Department of Translational Medical Sciences, Federico II University of Naples, Naples, Italy; [6]Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy; [7]Department of Public Health and Paediatric Sciences, University of Turin, Turin, Italy; [8]Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy; [9]Department of Economics, University of Messina, Messina, Italy

Objectives: Subclinical hypothyroidism (SH) is the most common thyroid abnormality in Down Syndrome (DS) children (25-60%); its etiology remains still not completely clarified.

Aim of this prospective multicenter study was to evaluate prevalence and natural course of autoimmune and non-autoimmune SH in a large cohort of DS children and adolescents.

Methods: The study population included 101 DS patients with SH (TSH 5-10 mIU/L; FT4 12–22 pmol/L), aged 2-17 years at SH diagnosis. DS children with congenital hypothyroidism or early onset isolated hyperthyrotropinemia were excluded. Annual monitoring of TSH, FT4, BMI, height was performed for 5 years. Thyroglobulin and thyroid-peroxidase autoantibodies (TGAbs, TPOAbs) were tested at diagnosis and at the end of follow-up.

Results: 37/101 (36.6%) patients displayed autoantibodies positivity (**group A**); the remaining 64 (63.4%) were classified as non autoimmune SH (**group B)**, ($p = 0.0001$). Group A was characterized by higher median age at SH diagnosis and more frequent family history of thyroid disease (6.6 vs 4.7 years, $p = 0.001$; 32.4% vs 7.8%, $p = 0.001$ respectively), whereas congenital heart defects were more common in group B (65.6% vs 43.2%, $p = 0.028$). Gender, median BMI (SDS), height (SDS), FT4, TSH were similar between the two groups.

At the end of follow-up: 35.1% of group A patients developed an overt hypothyroidism (OH) vs 17.2% of group B ($p = 0.041$); 31.25% vs 10.8% became biochemically euthyroid ($p = 0.02$) respectively; 37.8% of group A vs 51.5% in group B maintained, over time, SH condition ($p = 0.183$). Overt hyperthyroidism was only observed in group A (16.2%, $p = 0.004$).

Logistic regression suggested autoimmunity (OR = 3.2) and baseline TSH values (OR = 1.13) as predictive factors of evolution from SH to OH.

Conclusions: In DS children, non-autoimmune SH showed higher prevalence and earlier onset. The risk of thyroid function deterioration, from SH to OH, is influenced by autoimmune etiology and higher baseline TSH values.

P1-04-34

CENTRAL NERVOUS SYSTEM METABOLIC CHANGES DURING HYPOTHYROIDISMO: COMPARISION WITH EUTHYROID STATE AND RTSH STIMULATION

Maria João Oliveira[1], *Catarina Machado*[2], *Jose Oliveira*[3], *Diogo Faria*[4], *Rita Afonso*[3], *Francisco Oliveira*[5], *Durval Costa*[6]

[1]Centro Hospitalar Vila Nova de Gaia/Espinho, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal; [2]Ch de Vila Nova de Gaia/Espinho, Centro Hospitalar Vn Gaia, Vila Nova Gaia, Portugal; [3]Hpp MM, Porto, Portugal; [4]Universidade de Aveiro, Portugal; [5]Fundacao Champalimaud, Lisboa, Portugal; [6]Fundação Champalimaud, Fundacao Champalimaud, Lisboa, Portugal

Background: Hypothyroidism is often associated with memory problems, behavioral and psychomotor symptoms. The relationship between thyroid hormone status and brain metabolism is not well understood. In this study we evaluated changes in CNS regional cerebral glucose metabolism with FDG-PET in total thyroidectomy (due to papillary thyroid carcinoma) patients, during hypothyroidism (levothyroxine – LT4 withdrawal) in comparison with euthyroidism and rTSH stimulation.

Methods: A set of neuropsychological tests and FDG PET-CT studies were performed in two groups of 6 total thyroidectomy patients on follow-up. Glucose metabolism profiles in cortical and subcortical cerebral areas were compared, on two different occasions, for each group, as follows:

- Hypothyroidism state versus euthyroidism (6 months later)
- rTSH stimulation versus euthyroidism (6 months later).

Statistical Parametric Mapping (SPM) was applied to search for statistically significant differences between each state on a voxel by voxel SUVr (standard uptake value ratio) comparison.

Results: There were no significant differences in neuropsycological tests between the two groups of patients although in 3 patients cognitive deficits (memory) and anxiety were observed during hypothyroidism that resolved on euthyroidism.

During rTSH stimulation there was higher cortical (bilateral frontal, bilateral parietal and right temporal cortices) metabolism than on euthyroidism (voxelwise $p \leq 0.005$);

During hypothyroidism, there was cerebral hypometabolism in bilateral frontal, parietal, temporal and insular cortices, as well as, in subcortical grey matter areas compared to euthyroidism (voxelwise $p \leq 0.005$);

Patients on hypothyroidism compared to those during rTSH stimulation had severe and more extended cerebral glucose hypometabolism in the frontal (dorsolateral and mesial), parietal and temporal cortices bilaterally (voxelwise $p \leq 0.001$).

Conclusions: Under hypothyroidism there is cerebral hypometabolism (cortical and subcortical) that reverts completely under euthyroidism. These results seem to concur to the idea that thyroid hormones enhance brain metabolism and therefore their withdrawal has to be considered carefull.

P1-04-35

A CLINICAL DECISION MODEL FOR PREDICTING THE SUCCESSFUL DISCONTINUATION OF HORMONE REPLACEMENT THERAPY IN PRIMARY HYPOTHYROIDISM

Kyong Yeun Jung[1], *Ha Na Kim*[2], *Hoon Sung Choi*[3], *Jee Hyun An*[4], *Young Joo Park*[2], *Sun Cho*[2], *Hyo-Jeong Kim*[1]

[1]Department of Internal Medicine, Eulji University School of Medicine, Rep. of South Korea; [2]Department of Internal Medicine, Seoul National University College of Medicine, Rep. of South Korea; [3]Department of Internal Medicine, Kangwon National University School of Medicine, Rep. of South Korea; [4]Department of Internal Medicine, Korea University College of Medicine, Rep. of South Korea

Background: Lifelong thyroid hormone replacement is usually recommended for patients with primary hypothyroidism. The aim of this study was to investigate the factors predicting the successful discontinuation of levothyroxine (L-T4) therapy in primary hypothyroidism.

Methods: A total of 382 patients with primary hypothyroidism, receiving L-T4 replacement therapy for 1 year or more, following gradual L-T4 tapering, were recruited from 3 referral hospitals and their medical records reviewed. The patients were divided into 3 groups according to the clinical outcome of L-T4 tapering: Failure, Reduction, and Discontinuation groups. The clinical, biochemical, and ultrasonographic findings were compared between groups. A decision tree for predicting successful L-T4 tapering was established.

Results: Among 382 patients, 22.5% and 58.4% had achieved the discontinuation and reduction of L-T4, respectively. Patients in the Discontinuation group received shorter duration of L-T4 therapy and lower L-T4 dose than the Failure group. Serum thyroid-stimulating hormone (TSH) levels and the presence of anti-thyroid peroxidase (%) at the time of L-T4 initiation were significantly lower in the Discontinuation group than in the Failure group. On thyroid ultrasonography, heterogeneous or severely hypoechoic parenchyma were less frequently observed in the Discontinuation, Reduction and Failure groups, sequentially (P for trend <0.05). A decision tree for predicting successful discontinuation of L-T4 therapy was created by the duration and dose of L-T4 therapy and serum TSH level at the time of L-T4 tapering.

Conclusion: Shorter duration of L-T4 therapy and lower TSH levels at the time of L-T4 tapering were favorable factors predicting successful discontinuation of L-T4 therapy in primary hypothyroidism.

P1-04-36

PREDICTORS OF IMPROVEMENT IN QOL WHEN TREATING HYPOTHYROIDISM

Bjarke Borregaard Medici[1], *Jeppe Lerche la Cour*[2], *Filip Krag Knop*[3], *Martin Krakauer*[4], *Luba Freja Michaelsson*[5], *Jens Faber*[6], *Torquil Watt*[7], *Birte Nygaard*[8]

[1]Department of Endocrinology, Herlev University Hospital, Center for Endocrinology and Metabolism, Department Internal Medicine, Herlev and Gentofte Hospitals, Herlev, Denmark, Department of Endocrinology, Gentofte University Hospital, Copenhagen, Denmark; [2]Center for Endocrinology and Metabolism, Department Internal Medicine, Herlev and Gentofte Hospitals, Herlev, Denmark, Hvidovre, Denmark; [3]Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [4]Department of Clinical Physiology and Nuclear Medicine, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark; [5]Herlev Hospital, København N, Denmark; [6]Herlev University Hospital, Dept. of Endocrinology, Faculty of Health and Medical Sciences, University of Copenhagen, Herlev, Denmark; [7]Department of Endocrinology, Copenhagen University Hospital Rigshospitalet, Denmark, Department of Internal Medicine F, Gentofte Hospital, Department of Endocrinology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; [8]Department of Endocrinology, Herlev University Hospital, University of Copenhagen, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Background: Primary hypothyroidism is characterised by reduced quality of life (QoL). Although thyrotropin (TSH) is utilised as the primary indicator of thyroid disease and treatment adequacy, studies point to no simple correlation between QoL and TSH.

Objectives: The aim was to investigate changes in clinically relevant predictors during initiation of levothyroxine (L-T4) therapy and their ability to predict improvement in QoL.

Method: Prospective cohort study on patients with newly diagnosed hypothyroidism, during the initial 12 months of L-T4 therapy, and 18 healthy controls. Quality of life was evaluated by the thyroid-related patient-reported outcome, ThyPRO-39, scored as Composite QoL scale and Tiredness and Emotional Susceptibility sub-scales (0-100, higher scores worse). Clinical variables (Resting energy expenditure (REE), body composition, thyroid function, L-T4 dose and cognitive function tests) were evaluated as predictors of improvement in QoL by linear and multiple regression analysis.

Results: Thirty-seven hypothyroid patients with a baseline median TSH of 30 mU/l and a median QoL score of 29 were included. After twelve months of L-T4 treatment, the ThyPRO-39 QoL-score had significantly improved to a median score of 14, while REE per kg fat free mass (FFM) increased significantly from a mean of 26.5 to 28.7 kcal/day/kg ($p<0.001$). Change in ThyPRO-39 was not correlated with change in REE/FFM ($p = 0.93$) but correlated positively with baseline body mass index (BMI) ($p = 0.002$), without correlating with weight loss ($p = 0.96$).

Conclusion: Improvement in QoL as measured by ThyPRO-39 after initiation of L-T4 therapy for hypothyroidism was not correlated with changes in REE. High baseline BMI, but not weight changes during therapy, was associated with improvement in QoL.

P1-04-37
WITHDRAWN

P1-04-38
INCREASED ARTERIAL WALL STIFFNESS IN PATIENTS WITH HYPOTHYROIDISM

Aasem Saif[1], *Shrook Mousa*[1], *Afaf Hemeda*[1], *Hamed Ghorab*[2], *Alaa Abdelhamid*[1]
[1]Cairo University, Cairo, Egypt; [2]Alexandria University Hospital, Alexandria, Egypt

Background and aim: Hypothyroidism is associated with an increased risk of atherosclerosis. Pulse wave velocity (PWV) is an index of arterial wall stiffness and can be used as an early marker of atherosclerosis. The aim of this work was to assess pulse wave velocity in patients with hypothyroidism.

Patients and methods: Eighty female patients with hypothyroidism, aged 18-55 years, were included (40 had subclinical hypothyroidism). Twenty age-matched females with normal thyroid functions were included as a control group. Doppler ultrasonography was used to calculate the heart-femoral pulse wave velocity (hfPWV).

Results: Pulse wave velocity was higher in patients with overt and subclinical hypothyroidism as compared with the control group (9.55±1.81 and 9.30±1.28, respectively vs 7.82±2.14, m/s, p< 0.001 for both). A significant positive correlation between TSH and hfPWV was found in patients with overt hypothyroidism (r = 0.348 & p = 0.028) and in those with subclinical hypothyroidism (r = 0.373 & p = 0.018).

Conclusion: Pulse wave velocity, as an index of arterial wall stiffness, is significantly higher in patients with overt and subclinical hypothyroidism as compared with normal control subjects. This denotes early increase in arterial wall stiffness in patients with hypothyroidism, even in the subclinical phase. A positive correlation between PWV and TSH was found in both groups of patients indicating that arterial wall stiffness is proportionate to the severity of hypothyroidism.

P1-04-39
MARKERS OF CARDIOVASCULAR RISK IN YOUNG PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

Olga Dygun[1], *Anna Volkova*[1], *Svetlana Dora*[1], *Inna Abramova*[1]
[1]Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation

Most studies of subclinical hypothyroidism (SH) have shown that minimal changes in laboratory cardiovascular risk parameters are detected.

Objective: to evaluate levothyroxine therapy effectiveness in young patients with SH based on changes in laboratory cardiovascular risk parameters.

Materials and methods: 101 patients with SH were included (mean age 36.62±9.92). After 3 months, TSH level of was reassessed in all patients. TSH level recovery was detected in 17 patients. Levels of homocysteine, the activity of superoxide dismutase (SOD), malondialdehyde oxidized LDL (MDA – oxLDL), anti-oxidized LDL autoantibodies (oLAB) were evaluated in groups of persistent SH and control group. The control group consisted of 22 people with normal TSH levels. Then, patients with persistent SH were randomized into 2 groups: levothyroxine treatment group (n = 42) and observation group (n = 42). After 1 year, laboratory values were reevaluated in these patients.

Results: Predictors of persistent SH were high TSH levels and positive antithyroid autoantibodies (p<0.05). A significant decrease in SOD activity was detected in SH group compared with control group (p <0.0001).

Clinical and laboratory parameters in patients with SH at baseline and after 1 year of observation

	Baseline TSH	TSH after 1 year	p
Observation group (n = 42)	5, 56 (4, 96 - 7,02)	6.34 [5.13; 6.91]	>0.05
Treatment group (n = 42)	5.46 [4.72; 6.97]	1.76 [1.32; 2.35]	<0.05
	Baseline oLAB	oLAB after 1 year	
Observation group (n = 42)	623.25 [293.72;1236.59]	529.78 [189.38-1002.99]	>0.05
Treatment group (n = 42)	650.21 [254.12;1175.35]	186.19 [97.79-653.63]	<0.05
	Baseline homocysteine	Homocysteine after 1 year	
Observation group (n = 42)	6.64 [5.51;8.49]	8.48 [6.06-9.65]	<0.05
Treatment group (n = 42)	6.76 [5.78-9.36]	5.78 [4.72; 6.21]	<0.05

Conclusion:
1. Decrease in SOD activity, increased levels of homocysteine and oLAB was detected in SH patients.
2. Levothyroxine treatment results in normalization of laboratory markers of cardiovascular risk in SH patients.

P1-04-40
MANAGEMENT OF HYPOTHYROIDISM IN INTERNAL MEDICINE IN ITALY: THE FADOI-TIAMO STUDY (FEDERAZIONE DELLE ASSOCIAZIONI DEI DIRIGENTI OSPEDALIERI INTERNISTI-TRATTAMENTO DELL'IPOTIROIDISMO NELL'AMBITO DELLA MEDICINA INTERNA OSPEDALIERA)

Davide Brancato[1], *Tiziana Marcella Attardo*[2], *Aldo Fierro*[3], *Maurizio Nizzoli*[4], *Gualberto Gussoni*[5], *Elisa Zagarri*[5], *Roberto Vettor*[6], *Mauro Campanini*[7], *Andrea Fontanella*[8]
[1]Ospedale Civico DI Partinico (Pa), Internal Medicine Unit, Regional Reference Center for Diabetology, Italy; [2]Ospedale Barone Lombardo DI Canicattì (Ag), Internal Medicine Unit; [3]Ospedale Sandro Pertini DI Roma, Internal Medicine Unit; [4]Ospedale G.B. Morgagni DI Forlì; [5]Centro Studi Fondazione Fadoi (Mi); [6]Università DI Padova, Department of Internal Medicine; [7]Aou DI Novara, Internal Medicine Unit; [8]Ospedale Fatebenefratelli (Na), Internal Medicine Unit

Background and Objectives: The clinical profile of patients affected by hypothyroidism and managed in the Internal Medicine (IM) setting in Italy it is not well known. The present study aims to: 1) take a real-life picture of these patients; 2) evaluate possible deviations from the clinical practice recommendations (CPRs) contained in evidence-based guidelines (EBGs), and 3) improve the management by a structured educational program (EP) based on outreach visits.

Materials and Methods: TIAMO study is a multi-center, prospective study, designed as replicate of two cross-sectional surveys (Phase 1 and 3) interspersed with an EP (Phase 2) to be conducted in half out of participating Centres. Were included in- and outpatients with diagnosis of hypothyroidism. Four EBGs on hypothyroidism management and 38 CPRs were considered, so to obtain 22 standards and their respective indicators.

Results: From June 2016 until to March 2018, we recruited 21 Centres (10 that underwent to the EP) and 1125 patients (588 hospitalised; 850 females; age = 69.5 years ± 17.6 years). We observed a variable adherence to each CPR, and 57% of indicators showed a value < 50%, considered unsatisfactory. However, EP was effective to increase the adherence to some relevant CPRs; for example, the adherence to the CPR 11 of 2016 Associazione Medici Endocrinologi Statement (about the treatment with either liquid or soft-gel formulations when there is a risk of hampered levothyroxine absorption)

increased significantly from 7 to 28% in inpatients ($p < 0.0002$) and from 6% to 37% in outpatients ($p < 0.002$), only when EP was implemented.

Conclusions: FADOI-TIAMO study is the first study that shows a detailed clinical picture of patients with hypothyroidism managed in IM in Italy; the adherence to CPR is unsatisfactory, and this is the first study showing the effectiveness of an EP based on outreach visits.

P1-04-41

THE SWITCH FROM ORAL L-T4 IN TABLET FORM TO L-T4 IN LIQUID FORMULATION LEADS TO A SERUM TSH LEVELS NORMALISATION IN PATIENTS WITH CELIAC DISEASE

Poupak Fallahi[1], Silvia Martina Ferrari[2], Giusy Elia[2], Francesca Ragusa[2], Sabrina Rosaria Paparo[2], Ilaria Ruffilli[2], Alessandro Antonelli[2]

[1]University of Pisa, Department of Translational Research of New Technologies in Medicine and Surgery, Pisa, Italy; [2]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy

The efficacy of the L-thyroxine (L-T4) treatment can be influenced by several factors that act on its absorbtion, such as patient's age, drugs interference, absorption kinetics, dietary habits or adherence to therapy. Patients with celiac disease (CD) could report issues in the L-T4 absorption, caused by drug malabsorption.

In our study we recruited twenty-five patients affected by CD following a treatment with L-T4 in tablet formulation, because of their high serum thyrotropin (TSH) levels.

All patients switched to a treatment with L-T4 liquid formulation, using the same dosage.

It has been observed a normalisation/reduction of the circulating TSH levels in all the patients after the switch from L-T4 in tablet formulation to an oral liquid one with the same L-T4 dosage.

TSH values fell back into the hypothyroid range in nine subjects who returned to receive L-T4 in tablets (maintaining the same dosage).

We suggest that the administration of the oral liquid L-T4 formulation could aid to overcome the malabsorption issues leading to a better management of hypothyroid patients affected by CD.

P1-04-42

SUBCLINICAL HYPOTHYROIDISM AND PROBABILITY OF CARDIOVASCULAR DISEASES

Anna Volkova[1], Olga Dygun[1], Olga Berkovich[1], Ludmila Belyakova[1]

[1]Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation

Increased TSH levels, especially in older patients, are detected quite often. According to a large meta-analysis of 18 prospective studies (n = 73000), it was shown that the risk of cardiovascular events increases significantly with TSH levels>7.0 mIU/l. Determining the threshold values of TSH associated with cardiovascular diseases is an important clinical task for optimizing treatment tactics in elderly patients with cardiovascular diseases and subclinical hypothyroidism.

Objective: determine the range of values of a thyroid-stimulating hormone associated with cardiovascular diseases in patients who went to a multidisciplinary hospital in Saint Petersburg.

Material and methods: 1340 patients of different sex and age were included with normal TSH value (0.4-2.5 mIU/l) and subclinical hypothyroidism. According to electronic case histories in all patients, cardiovascular diseases (hypertension, coronary heart disease, heart failure, arterial atherosclerosis of the lower extremities) and a history of cardiovascular events (unstable angina, acute myocardial infarction, stroke, and transient ischemic attack) were analyzed. Statistica v.12 was used for data analysis.

Results: In patients with subclinical hypothyroidism cardiovascular diseases were detected significantly more often than in patients with euthyroidism ($p<0.05$). Subclinical hypothyroidism increased the probability of cardiovascular diseases in the middle age group (OR 1.62 (1.39-1.89), in elderly patients - OR 3.84 (2.95-4.99), in the group of patients 75 years and older - OR 2.53 (1.84-3.50). Using the discriminant analysis, a mathematical model, which allows predicting the formation of cardiovascular diseases according to the level of TSH, was built (accuracy 66.7%, sensitivity 22.3%, specificity is 96.8%.). The estimated threshold of TSH was 6.68 mIU/l. TSH level of less than 6.68 mIU/l is probably not associated with cardiovascular disease (96.8%).

Conclusion: Association of subclinical hypothyroidism with coronary heart disease, hypertension, and cardiovascular diseases, in general, has been established. TSH level of less than 6.68 mIU/l is probably not associated with cardiovascular disease and does not require active treatment.

P1-04-43

PSYCHOEMOTIONAL STATUS, QUALITY OF LIFE AND LIPID PROFILE IN PATIENTS WITH SECONDARY AND PRIMARY HYPOTHYROIDISM RECEIVING REPLACEMENT THERAPY WITH LEVOTHYROXINE

Valentin Fadeyev[1], Tatyana Morgunova[1], Tatyana Kienia[1]

[1]I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation

Aim: To compare the psychoemotional status, quality of life and lipid profile in patients with secondary and primary hypothyroidism receiving replacement therapy with levothyroxine (L-T4).

Patients and methods: The study included 20 patients (8 men, 12 women, 18-60 years old) with secondary hypothyroidism (SH) due to transsphenoidal adenomectomy and 20 patients with primary hypothyroidism (PH). Also 10 patients had secondary adrenal insufficiency, 14 - secondary hypogonadism, 3 - diabetes insipidus. All patients received L-T4 for at least 1 year. We evaluated the TSH, free T4 (fT4), total cholesterol, low (high) density lipoprotein (LDL/HDL), triglyceride (TG) levels; anxiety and depression, symptoms of hypothyroidism, quality of life.

Results: There was no significant difference in age, sex, BMI levels between the groups with secondary and primary hypothyroidism. As expected, the level of TSH was significantly lower in patients with SH, and the dose of L-T4 in the group of patients with SH was lower ($p < 0.05$). In 9 out of 20 patients with SH the fT4 level was low-normal or even decreased. While comparing the lipid profiles there no difference in the total cholesterol, HDL, LDL, and TG levels between the groups ($p > 0.05$). The anxiety and depression levels were the same ($p > 0.05$). In patients with SH the severity of symptoms was significantly higher than in patients with primary hypothyroidism and the quality of life was lower ($p <0,05$).

Conclusions: In routine practice the patients with secondary hypothyroidism receive the dose of L-T4 less than patients with primary hypothyroidism, which lead to maintenance of low/low-normal level of fT4. However, this does not lead to a deterioration of lipid profile in comparison with compensated primary hypothyroidism but is accompanied by an increase in the severity of symptoms and some decrease in the quality of life.

P1-04-44

LINGUAL THYROID - A RARE CAUSE OF HYPOTHYROIDISM: A CASE REPORT

Miha Jesenko[1], Nina Ostaševski Fernandez[1], Edvard Pirnat[1], Simona Gaberscek[2], Katja Zaletel[1]

[1]Department of Nuclear Medicine, University Medical Centre Ljubljana, Slovenia; [2]Department of Nuclear Medicine, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Slovenia, Ljubljana, Slovenia

Introduction: Lingual thyroid is a rare developmental anomaly, caused by the failure of the gland to descend to its normal pretracheal location, appearing with a prevalence of 1:100,000. It accounts for 90% of all cases of ectopic thyroid tissue and occurs four times more frequently in females than in males. In 75%, the ectopic gland is the only functioning thyroid tissue in the body. Beside hypothyroidism, that occurs in 33-62% of cases, the condition may cause local symptoms such as foreign body sensation, dysphagia, dyspnea, or even haemorrhage.

Case report: A 42-year-old woman was diagnosed with hypothyroidism in 1996. Ultrasound examination showed a very small thyroid gland at the normal location in the neck. Serum level of TSH was slightly increased, whereas levels of free T4 and free T3 were normal. Thyroid antibodies were negative. Levothyroxine therapy was initiated. In 2018 she was referred to the

department of otorhinolaryngology after a mass at the base of the tongue was found accidentally upon examination of the oral cavity by general practitioner. Biopsy of the lesion was performed and the histological examination revealed the presence of thyroid tissue. At the thyroid department, on ultrasound examination, thyroid gland was not visible at the normal location. Thyroid scintigraphy with I-123 showed a marked I-123 uptake in the area of the tongue and no uptake in the neck. SPECT/CT with I-123 revealed a high density mass 22 x 20 x 23 mm in size at the base of the tongue with a marked I-123 uptake, representing lingual thyroid. The patient was euthyroid taking 50 mcg of levothyroxine daily and without local symptoms. Therefore, no additional treatment was needed.

Conclusion: Lingual thyroid is a rare condition that can manifest at any age. Suspicion should be raised when a mass is found at the base of the tongue or thyroid gland is not found at its normal location. No treatment is required when lingual thyroid is asymptomatic and the patient is euthyroid. Hypothyroid patients are treated with levothyroxine. Treatment options for patients with local symptoms are ablation with radioactive iodine 131 or surgical removal of the ectopic tissue.

Nodules 1

P1-05-45

LARGE THYROID NODULES - MALIGNANCY AND RELIABILITY OF ULTRASOUND GUIDED FINE-NEEDLE ASPIRATION

Nelson Cunha[1], Diana Catarino[2], Maria Leonor V. Gomes[3], Cristina Ribeiro[4], Sandra Paiva[2], Jose Melo[1], Lúcia Fadiga[2], Diana Alexandra Festas Silva[2], Joana Reis Guiomar[5], Inês Vieira[2], Mariana Lavrador[2], Isabel Paiva[2]

[1]Endocrinology Department, Centro Hospitalar e Universitário de Coimbra, Faculdade de Medicina Da Universidade de Coimbra, Coimbra, Portugal; [2]Endocrinology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [3]Hospitalis Da Universidade de Coimbra, Endocrinology Department, Dept Endocrinology, Coimbra, Portugal; [4]Serviço de Endocrinologia, Huc, University Hospital of Coimbra, Coimbra, Portugal; [5]Endocrinology, Diabetes and Metabolism Department, Coimbra Hospital and University Center, Epe, Coimbra, Portugal

Introduction: It is not clear if large thyroid nodules citologically benign have a higher malignancy risk than smaller nodules. We evaluated the malignancy rate of thyroid nodules ≥4cm submitted to surgery and its correlation with the pre-surgery ultrasound guided fine-needle aspiration citology (US-FNA).

Methods: We performed a retrospective review of thyroid nodules undergoing US-FNA at our institution during 2017 and were selected those with size ≥4cm.

Results: 1398 thyroid nodules, from 1096 patients (mean age 59.6±14.1 years; 84% female) underwent US-FNA. 94 nodules had ≥4cm (6.7%) corresponding to 89 patients. 39 patients were submitted to surgery (44%). Histological study was available in 37 patients. No differences in Bethesda diagnostic categories or age were seen between nodules ≥4cm or <4cm, however male patients had higher frequency of nodules ≥4cm (25% vs 15%; p = 0.02).

The Bethesda categories in nodules ≥4cm submitted to thyroidectomy were: I-0%, II-86.5%, III-8.1%, IV-5.4%, V-0%, VI-0%). Histological study from patients submitted to thyroidectomy was benign in 81% (n = 30), malignant in 16% (n = 6) and uncertain malignant potential in 3% (n = 1). Of those with reported malignancy, 5 had a previous cytology Bethesda-II and 1 Bethesda-IV. Despite the presence of malignancy in 16% of Bethesda-II category (n = 5), 80% were incidental papillary thyroid microcarcinoma (PTMC) (n = 4) and 20% papillary thyroid carcinoma (n = 1) - malignancy risk in Bethesda-II category was 3.2%.

Conclusion: Almost 50% of patients with large thyroid nodules were submitted to thyroidectomy despite more than 80% had a previous benign cytology. Malignancy risk in nodules ≥4cm with Bethesda-II, excluding incidental PTMC, was similar to that described in literature for this category in general. Most of the malignant tumors were incidental findings. We also didn´t find differences between Bethesda categories according to nodule size. Surgery must be individualized and not just based on nodules size due to unnecessary exposure to complications.

P1-05-46

A COMPUTER-AIDED DIAGNOSTIC SYSTEM FOR THYROID NODULE SONOGRAPHIC EVALUATION IMPROVES THE SPECIFICITY OF LESS EXPERIENCED EXAMINERS

Vito Cantisani[1], Giorgio Grani[2], Maria Luna De Pascali[1], Daniele Fresilli[1], Gregorio Alagna[1], Eleonora Tassone[1], Livia Lamartina[1], Valeria Ramundo[1], Marco Biffoni[1], Marco Bononi[1], Vito D'Andrea[1], Fabrizio Frattaroli[1], Laura Giacomelli[1], Ferdinando D'Ambrosio[1]

[1]University of Rome Sapienza, Rome, Italy; [2]Sapienza University of Rome, Dept. of Translational and Precision Medicine, Rome, Italy

Objectives: Computer-aided diagnosis (CAD) may improve interobserver agreement in the risk-stratification of thyroid nodules. This study aimed to evaluate the performance of the Korean TIRADS classification as estimated by an expert radiologist, senior resident, medical student, and a commercially-available CAD system, as well as the interobserver agreement.

Methods: Between July 2016 and 2018, 107 nodules (size 5-40 mm, 27 malignant) were classified according to the K-TIRADS by an expert radiologist and by CAD software (S-Detect, Samsung Medison). A third-year resident and a medical student with basic imaging training, both blinded to all previous findings, retrospectively estimated the K-TIRADS classification for each nodule.

Results: The CAD system and the expert achieved a sensitivity of 70.37% (95% CI 49.82-86.25%) and 81.48% (61.92-93.7%), and a specificity of 87.50% (78.21-93.84%) and 88.75% (79.72-94.72%), respectively. The specificity of the student was significantly lower (76.25% [65.42-85.05%], p = 0.02).

Conclusions: The CAD system may be useful for less experienced operators as its specificity was significantly higher.

Sensitivity, specificity, predictive values, and area under the receiver operating characteristics curve of the K-TIRADS system evaluated by S-Detect™ and three clinicians (expert attending radiologist, resident, and medical student)

	Sensitivity	*Specificity*	*PPV*	*NPV*	*AUROC*
S-Detect™	70.37% (49.82-86.25%)	87.50%*** (78.21-93.84%)	65.52% (45.67-82.06%)	89.74% (80.79-95.47%)	0.79 (0.69-0.88)
Expert	81.48% (61.92-93.7%)	88.75%** (79.72-94.72%)	70.97% (51.96-85.78%)	93.42% (85.31-97.83%)	0.85 (0.77-0.93)
Resident	74.07% (53.72-88.89%)	85.00%* (75.26-92.0%)	62.50% (43.69-78.9%)	90.67% (81.71-96.16%)	0.80 (0.7-0.89)
Student	70.37% (49.82-86.25%)	76.25% (65.42-85.05%)	50.00% (33.38-66.62%)	88.41% (78.43-94.86%)	0.73 (0.63-0.83)

*The specificity of the student is significantly lower than that of the expert and S-Detect™ (*p = 0.16 vs. the resident; **p = 0.02 vs. the expert; ***p = 0.022 vs. S-Detect™); no significant difference was reported between S-Detect™ and the more experienced examiners.

P1-05-47

ULTRASOUND-GUIDED PERCUTANEOUS TREATMENT FOR CYSTIC THYROID NODULES: SYSTEMATIC REVIEW AND META-ANALYSIS

Sasikan Danviriyakul[1], *Pawin Numthavaj*[2], *Ammarin Thakkinstian*[2]
[1]Department of Otolaryngology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [2]Mahidol University, Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Cystic thyroid nodules are common diseases in thyroid clinics. Ultrasound-guided treatment options have been advocated by some authors. However, treatment regimens vary between institutions and efficacy of each regimen is unknown.

Objective: To systematically review and pool the cure rates for each percutaneous treatment regimen in cystic thyroid nodule.

Method: Studies were identified from Medline, Scopus, and Cochrane database since each database inception to December 18, 2018. Studies which describe or compare outcome of injection agents in patient with predominantly cystic nodule were selected. Cure rate according to the definition in each study were extracted and pooled with prevalence meta-analysis separately for each regimen. (Prospero registration CRD42018081346)

Results: Through database searching, 383 articles were identified. After screening and assess for eligibility, 29 studies with a total of 3,202 nodules were included in quantitative synthesis of cure rate. Regimens used in studies were injection of ethanol (N = 19), tetracycline (N = 5), OK-432 (N = 3), polidocanol (N = 2), saline (N = 2), radiofrequency ablation (N = 5), and simple aspiration (N = 4). Pooling of cure rate revealed the most effective injected regimen as polidocanol (97%, 95%CI: 94-99%), followed by radiofrequency ablation (95%, 95%CI: 86-100%), tetracycline (72%, 95%CI: 53-91%), OK-432 (70.6%, 95%CI 62-79%), and ethanol (67.2, 95%CI: 56-79%). Simple aspiration and saline injection have low cure rate (59%, 95%CI: 4-100% and 32%, 95%CI: 5-60%). Notable systemic side effect was fever (6 cases in ethanol, OK-432, and polidocanol group), and local side effect included transient vocal cord palsy (5 cases in ethanol group) and transient local pain (30 cases in ethanol group). No other systemic side effects reported.

Conclusion: Polidocanol has the best cure rate in the literature followed by radiofrequency ablation. However, this data is from smaller number of studies compared to ethanol which has been studied extensively more than other medication with moderate cure rate. More well-designed comparative studies are needed.

Treatment modality	Number of studies (N)	Cure rate	95% CI
Ethanol injection	19	0.67	0.55-0.79
Tetracycline injection	5	0.73	0.53-0.92
Radiofrequency ablation	3	0.96	0.86-1.00
OK-432 injection	3	0.71	0.62-0.79
Simple aspiration	3	0.59	0.04-1.00
Polidocanol injection	2	0.97	0.94-0.99
Saline injection	2	0.32	0.05-0.59

P1-05-48

THE FEASIBILITY OF EUROPEAN THYROID IMAGING AND REPORTING DATA SYSTEM (EU-TIRADS) SCORE FOR PREDICTING GROWTH OF EUTHYROID NODULAR GOITER IN AN AREA WITH SUFFICIENT IODINE SUPPLY

Katica Bajuk Studen[1], *Edvard Pirnat*[1], *Katja Zaletel*[1], *Simona Gaberšček*[2]
[1]Department of Nuclear Medicine, University Medical Centre Ljubljana, Slovenia; [2]Department of Nuclear Medicine, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Slovenia

Background: Optimal follow-up strategy for benign euthyroid nodular goiter (ENG) has not been determined since few longitudinal data on the natural course of the disease exist. Our aim was to establish the clinical course of ENG considering ultrasound stratification tool European Thyroid Imaging Reporting and Data System (EU-TIRADS).

Methods: Patients diagnosed with ENG were invited for re-evaluation 5 years after the diagnosis. Baseline characteristics of the nodules (volume and EU-TIRADS) were retrospectively collected. At follow-up, thyroid ultrasound including nodule volume measurement was performed. Data are presented as mean ± standard deviation (SD).

Results: One hundred and one patients (92 females and 9 males, mean age 50.4±13.1 years, mean TSH 1.52±0.73 mIU/L) were included in the study. At baseline, 143 nodules were diagnosed with the mean volume 1.2±2.3 ml. Regarding EU-TIRADS, 36.4% of nodules were categorized as EU-TIRADS 2, 37.1% as EU-TIRADS 3, 22.4% as EU-TIRADS 4 and 1.4% as EU-TIRADS 5 (excluded from further analysis due to insufficient sample size). After 5 years, the mean volume of the nodules significantly increased to 1.8±3.8 ml ($p<0.001$). In EU-TIRADS 3, the mean increase of nodule volume was the largest 1.2±1.7 ml, in EU-TIRADS 4, 0.9±3.7 ml, and in EU-TIRADS 2, a decrease in nodule volume of -0.03 ± 2.8 ml was observed. The absolute change in nodule volume differed significantly between EU-TIRADS groups when compared pairwise (between EU-TIRADS 2 and 3, $p<0.001$, between EU-TIRADS 2 and 4, $p<0.05$, and between EU-TIRADS 3 and 4, $p<0.001$, respectively).

Conclusions: Our results show that nodules with ultrasound morphological characteristics classified as EU-TIRADS 3 have the largest growth potential, while nodules classified as EU-TIRADS 2 tend to decrease in size. Further research should evaluate if there is an increased need for clinical management of EU-TIRADS 3 subgroup of ENG patients.

P1-05-49

CHARACTERISTIC AND EARLY OUTCOMES OF ULTRASOUND-GUIDED PERCUTANEOUS ALPHA-CHYMOTRYPSIN INJECTION (PAI) IN THE BENIGN CYSTIC THYROID NODULES

Nguyen Thi Thu Trang[1]
[1]Hanoi Medical University, Taipei Medical University, Taipei, Taiwan

Objective: Thyroid cysts are prevalent and their management remains controversial. Simple aspiration is the treatment of choice, but the recurrence rate is quite high. The aim of this study was to evaluate the characteristic and results of using alpha-chymotrypsin aspiration in benign cystic thyroid nodules in euthyroid patients.

Methods: We conducted the prospective study evaluating the initial results in 75 patients, aged over 20 years old, and euthyroid (based on thyroid hormone profile). The lesion ≤ 40% solid components was classified as thyroid cyst. All patients underwent at least one US-guided fine needle aspiration (US-FNA of relevant thyroid nodules) and there was no malignant or indeterminate biopsy. Lesions ≥ 1 cm^3 were aspirated prior to PAI with the same volume under US guidance. Patients returned each 1 to 3 months after each session for US re-evaluation. Alpha-chymotrypsin was re-injected when there was no significant reduction in the cyst volume. Therapeutic success was defined as cyst volume ≤ 1ml at the end of follow-up.

Results: 50 of the 75 subjects received the treatment and followed consistently. The objects were mean age (43 ± 13.01 y), BMI (21± 1.8), TSH and FT4 in the normal range. There was 8 % entire cyst, 16 % spongiform or multiple small cyst, 76 % partly cystic nodule. The volume and pattern of cys-

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

tic nodule increase with advancing age. More 70% of the large nodule (over 3 cm^3) was presented on the oldest group (age, >45 y), meanwhile, the majority of the medium nodule (1 to 3 cm^3) was displayed on a younger group (age, < 45 y). Simultaneously, the entirely cystic nodules were only reported in the youngest group (age, 20-30 y). We performed a mean of 2.5 ± 1.7 PAI sessions and a 2 years follow-up. There was a reduction of at least 50 % of initial cyst volume in 45 patients (90 %). 37 out of 50 patients was obtained the successful outcome and the treatment was stopped. Percentage of success (volume < 1ml) was higher in pure and mixed cyst compared to the spongiform cyst ($p<0.05$). 16 % of patients had moderate and severe pain. Fever, abscess, hematoma and transient laryngeal nerve damage have not been reported. The average treated time was 9 months. All patients remained euthyroid during follow up (normal TSH, T3, FT4).

Conclusion: Ultrasound-guided PAI seem to be an effective, safe and affordable alternative treatment, particularly in entire and mixed cystic thyroid nodules.

P1-05-50

COULD SERUM TSH LEVELS PREDICT MALIGNANCY IN THYROID NODULES WITH INDETERMINATE CYTOLOGY?

Ilenia Pirola[1], *Elena Gandossi*[1], *Mario Rotondi*[2], *Davide Lombardi*[3], *Claudio Casella*[4], *Fiorella Marini*[1], *Maura Saullo*[1], *Elena Di Lodovico*[1], *Luca Chiovato*[5], *Alberto Ferlin*[1], *Carlo Cappelli*[1]

[1]Department of Clinical and Experimental Sciences, Ssd Medicina Ad Indirizzo Endocrino-Metabolico, University of Brescia, Asst Spedali Civili di Brescia, Brescia, Italy; [2]Unit of Internal Medicine and Endocrinology, Ics Maugeri I.R.C.C.S., Laboratory for Endocrine Disruptors, University of Pavia, Pavia, Italy; [3]Department of Otorhinolaryngology - Head and Neck Surgery, University of Brescia, Brescia, Italy; [4]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; [5]Unit of Internal Medicine and Endocrinology, Ics Maugeri I.R.C.C.S., Laboratory for Endocrine Disruptors, University of Pavia, Pavia, Italy

Objectives: To evaluate the serum thyreotropin (TSH) levels as a possible predictor of malignancy in thyroid nodules with indeterminate cytology.

Methods: We reviewed the medical records of patients who had ultrasound-guided FNA of thyroid nodules at our Department between September 2014 and February 2018. Only patients with indeterminate cytology and TSH values within the normal range obtained one month before FNA were enrolled. All patients had been submitted to hemi or thyroidectomy in our Institute.

Results: Histologic evaluation revealed malignancy in 74/378 (19.6%) nodules. The rate of cancer was significantly lower in TIR 3A (9.8%) than TIR 3B lesions (27.4%), $p<0.0001$. Patients with malignancy evidenced higher serum TSH levels than those with histological proven benign nodules (3.03±1.16 vs. 2.37±1.19 mIU/L, $p<0.001$). To better analyze the role of serum TSH as a predictor of thyroid cancer, we subdivided the sample into 4 quartiles of similar size according to patients' TSH values. The prevalence of malignancy was 12.2% for the first quartile and 50.0% for the last quartile. The ROC curve analysis indicated that a TSH value of ≥2.7 mIU/L identified patients with malignancy with a sensitivity of 61% and a specificity of 65%.

Conclusions: Higher TSH levels are associated with an increasing risk of malignancy in patients affected by thyroid nodules with indeterminate cytology. The use of TSH can represent an easy adjunctive diagnostic test for decision-making in patients with indeterminate cytological findings.

P1-05-51

THE COMBINED CONSIDERATION OF THE NODULE'S PRE-FNA ULTRASOUND AND THE FNA RESULT DURING DECISION MAKING TOWARDS SURGERY REDUCES THE NUMBER OF OPERATIONS IN PATIENTS WITH FOLLICULAR LESION BY CYTOLOGY

Miklós Bodor[1], *Gyula Toth Lukacs*[2], *Szabina Szujo*[3], *Peter Ferencz*[4], *Laszlo Bajnok*[5], *Emese Mezösi*[6], *Eszter Berta*[7], *Endre Nagy*[8], *Tamas Solymosi*[9]

[1]Department of Medicine, Division of Endocrinology, University of Debrecen, Debrecen, Hungary, Division of Clinical Pharmacology, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary; [2]Department of Pathology, Bugat Hospital, Gyongyos, Hungary; [3]Department of Medicine, University of Pecs, Pecs, Hungary; [4]Department of Surgery, Bugat Hospital, Gyongyos, Hungary; [5]Department of Medicine, University of Pecs, Pecs, Hungary; [6]Department of Medicine, University of Pecs, Pecs, Hungary; [7]Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [8]Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, [9]Department of Thyroidology, Bugat Hospital, Gyongyos, Hungary

Objectives: Thyroid nodules with fine needle aspiration cytology (FNA) result of follicular lesion require surgery by present guidelines. However, only less than 25 % of these lesions prove to be malignant, and of these, two third turns out to be papillary cancer in spite of the follicular FNA result. We aimed to evaluate whether re-consideration of the pre-FNA ultrasound characteristics of the nodule during FNA-based decision making may reduce the number of unnecessary thyroid operations.

Methods: Between 1995 and 2004 (Cohort 1, n = 1140), all patients having follicular lesions by FNA were sent to surgery. Between 2005 and 2014 (Cohort 2, n = 1163), if the FNA result was follicular lesion, four additional features were also considered during decision making towards surgery: the presence/absence of a capsule by ultrasound, the presence/absence of ultrasound signs suggesting increased risk for PTC (at least one major and/or two minor signs), presence/absence of atypia by cytology, and presence/absence of nuclear features of papillary cancer in the follicular lesion by cytology. Patients with non-atypical follicular lesions and no ultrasound signs of a capsule, as well as patients with non-atypical follicular lesions with ultrasound signs of a capsule were separately analyzed and were only operated on if the nodule size was larger than 3 cm or the volume increased by ≥30% during follow-up.

Results: In Cohort 1, the risk for malignancy was 3.6%, 9.2% and 1.5% in all, atypical and non-atypical follicular lesions, respectively. In non-atypical lesions, the risk of follicular cancer was not higher in capsule-positive vs. capsule-negative patients (1.8% vs. 0.7%, $p = 0.23$). In Cohort 2, the surgery rate dropped to 64.8% compared to 100 % in Cohort 1. The FNA misdiagnosis of follicular lesion instead of PTC dropped to one-fourth in Cohort 2.

Conclusions: The repeated consideration of pre-FNA ultrasound characteristics in addition to the cytology during decision making markedly reduced both the number of thyroid operations and the misdiagnosis of PTC as follicular lesion. For 'low-risk' patients identified by combined consideration of cytology and pre-FNA ultrasound results, regular follow-up may be a safe approach.

P1-05-52

FOLLOW-UP VISIT FREQUENCY IN BENIGN THYROID NODULES: ARE YEARLY CHECKS SUPERFLUOUS? A STUDY OF 985 NODULES IN 565 PATIENTS

Gábor Tóth-Várady[1], *Annamária Gazdag*[1], *Eszter Berta*[1], *Lívia Síra*[1], *Judit Boda*[1], *Miklós Bodor*[1], *Endre V. Nagy*[1], *Annamária Erdei*[1]

[1]Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Hungary

The incidence of thyroid nodules diagnosed by ultrasound is growing world-wide. Clinical follow-up of these patients pose a financial burden on

health care systems. The aim of the study was to determinate the appropriate frequency of the follow-up visits of patients with benign thyroid nodules >1 cm.

Objectives and methods: We analyzed the data of 565 patients (523 females, 42 males; age 52.2±12.7 years) retrospectively, who were referred to our clinic between 2000 and 2015. A nodule was considered benign if either FNA was C1-C2 or B1-B2 or less, or the nodule was hot on a 99m-Tc gamma camera image. 145 patients had single nodules, while 420 patients had multinodular goiters; the dominant nodules in the right and left lobes were analyzed separately. The mean follow-up time of the 985 nodules was 6.6±3.7 years. Regular checks at least once a year were performed and the largest nodule diameter was recorded. An increase of 5 millimeters or more in the diameter of the nodule was considered clinically relevant and usually indicated a repeated FNA.

Results: Clinically relevant increase of the nodule size was detected in 387 nodules of 242 patients (42.8%). The median follow-up time until clinically relevant diameter increase was 5.94 years after the initial detection of the nodule. Of the 35 patients operated on, thyroid cancer was found in 5 patients (0.51% of the 985 thyroid nodules) by histology, all papillary cancers, 4 of them microcarcinomas.

Conclusions: We assume that yearly size checks during follow up of benign nodules may be superfluous and can be restricted to selected cases, at least in areas which have been, until recently, mildly iodine deficient.

P1-05-53

DIAQNOSTIC ACCURACY IN PARATHYROID ADENOMAS OF PARATHYROID HORMON LEVELS IN WASH OUT SAMPLES AND COMPARISON MIBI PARATHYROID SPECT-CT SCINTIGHRAPHY

Anar Aliyev[1], *Aziz Aliyev*[2], *Rashad Ismayilov*[3], *Sure Novruzova*[3], *Elnur Mehdi*[3]

[1]Department of Nuclear Medicine, Department of Thyroid Center, Baku, Azerbaijan; [2]Head and Neck Surgery Department, Azerbaijan National Center of Oncology, Baku, Azerbaijan; [3]Department of Nuclear Medicine, Azerbaijan National Center of Oncology, Baku, Azerbaijan

Objectives: The most preferred diagnostic methods for the localization of parathyroid adenomas are ultrasonography (USG) and parathyroid scintigraphy. However, in many cases, it is difficult to discriminate parathyroid lesions from thyroid lesions or lymph nodes, even in cytology. The aim of this study was to determine the usefulness of parathyroid hormone (PTH) measurement in fine-needle aspiration (FNA) washout fluid in the diagnosis and compored MIBI parathyroid SPECT/CT scintigraphy of parathyroid adenomas.

Materials and methods: Fifteen patients (2 men and 13 women, mean age was 51.6 ± 10.57 years) with primary hyperparathyroidism (PHP) and parathyroid adenoma with suspicious localization were included in the study. All patients underwent USG-guided PTH measurement in FNA washout fluid. Values above the simultaneous serum PTH level were considered positive for FNA-PTH. Laboratory tests, MIBI scintigraphy and postoperative histopathology results were evaluated.

Results: The mean serum PTH level was 196.8 ± 151.56 pg/ml (normal range: 15-65 pg/ml). FNA-PTH values were positive with 100% sensitivity in all 15 patients (mean was 4497.93 ± 1325.12 pg/ml). Scintigraphy was positive in 8 patients (%53.3) and negative in 7 patients. Histopathological examination revealed parathyroid adenoma in all patients.

Conclusion: The FNA-PTH assay has a higher sensitivity than MIBI SPECT/CT scintigraphy in USG experienced hands. It is particularly useful in the preoperative evaluation of parathyroid adenomas with suspected localization. Further studies with more patients are needed to determine the diagnostic power of the test and the cut-off value.

P1-05-54

MALIGNANCY RATE IN AUS/FLUS THYROID NODULES

Joana Lima Ferreira[1], *Francisco Simões de Carvalho*[2], *Joana dos Santos*[3], *Ana Paula Marques*[4]

[1]Matosinhos Local Health Unit, Endocrinology, Senhora Da Hora, Portugal; [2]Pedro Hispano Hospital, Matosinhos Local Health Unit, Endocrinology, Portugal; [3]Pedro Hispano Hospital, Matosinhos Local Health Unit, Pathology, Portugal; [4]Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Endocrinology, Portugal

Objectives: The meaning of the AUS/FLUS thyroid nodules is unclear. The aim of this study is to assess the approach of AUS/FLUS thyroid nodules and their risk of malignancy.

Methods: A retrospective study was performed with inclusion of thyroid nodules submitted to ultrasound-guided FNA (fine needle aspiration biopsy) between 2011 and 2018 with at least one AUS/FLUS cytology. Patients with active extrathyroidal neoplasm, previous cervical surgery or suspicion of parathyroid nodule were excluded.

Results: 405 nodules corresponding to 402 patients were analyzed (80.6% female; mean age 57 ± 14.7 years). At first AUS/FLUS cytology, immediate surgery was proposed to 16.7% of patients (67/402). 13.7% (55/402) underwent immediate surgery and malignancy was found in 25.45% (14/55). 67.9% of nodules (275/405) were submitted to more 340 FNAs. Considering the cytology guiding the clinical decision for each nodule with more than one FNA, 52% (143/275) were benign, 42.9% (118/275) AUS/FLUS, 3.3% (9/275) suspicious for follicular neoplasm, 0.7% (2/275) suspicious for malignancy and 0.8% (3/275) malignant. Surgery was proposed to 35.7% of patients with repeated FNA (97/272), the majority (67/97) due to recurrent AUS/FLUS. Malignancy was found in 16.42% (11/67) of operated patients.

Among all 402 patients, 30.3% (122/402) underwent surgery. Malignancy was found in 19.7% (24/122) of operated patients.

Of 118 recurrent AUS/FLUS nodules, 13.6% (16/118) had benign cytology later. 39.8% (47/118) were resected and 8.5% (4/47) were malignant. Of 37 benign nodules followed by an AUS/FLUS cytology, 11 underwent surgery and 1 was malignant.

Conclusions: The actual risk of malignancy in nodules surgically excised is quite different in literature: median 14% (6-48%). In our cohort, we found a malignancy rate of 19.7%. Interestingly, we verified that the rate of malignancy of just one AUS/FLUS diagnosis is higher than recurrent AUS/FLUS (25.45% vs 8.5%, p = 0.026), questioning the benefit of repeating FNA.

Orbitopathy

P1-06-55

EVALUATION OF THE INFLUENCE OF GENDER ON THE SEVERITY AND COURSE OF GRAVES' ORBITOPATHY

Michael Oeverhaus[1], *Winkler Luisa*[1], *Anke Schlüter*[2], *Esser Joachim*[1], *Utta Berchner-Pfannschmidt*[3], *Anja Eckstein*[4]

[1]University Eye Hospital, Essen, Germany; [2]Department of Otorhinolaryngology, University Hospital Essen, Essen, Germany; [3]Molekulare Ophthalmologie, Department of Ophthalmology, University Hospital Essen, Essen, Germany; [4]Univ.-Augenklinik, Molecular Ophthalmology, Department of Ophthalmology, University Eye Hospital Essen, Essen, Germany

Objective: Severity and natural course of Graves‘ orbitopathy (GO) show wide individual differences and are influenced, among others, by thyroid situation and smoking habits. For optimal treatment, it is important to be able to predict the natural course of the disease as accurate as possible to counteract with anti-inflammatory and surgical treatment as much as needed and as little as possible. Therefore, we aimed to further elucidate the impact of Gender on GO.

Methods: We collected the clinical and demographic data of all patients of our tertiary referral center from January 2008 till May 2017 and analyzed it with descriptive statistics.

Results: In total, we evaluated the data of 4641 patients. Of these referred patients, 92% (n = 4260) were diagnosed with GO. Most of these were women (83%). The mean age at onset of the disease was 41.8 years. Men were significantly older at onset compared to women (52.9 vs. 39.1; p<0.0001). About one third of patients were smokers in both gender groups. 2203 patients (52%) were treated with intravenous steroids. 1198 patients (28%) were treated with orbital irradiation. Orbital decompression had to be performed in 20% of patients (n = 839). About 18% of patients had to undergo strabismus (n = 795) and oculoplastic surgery. Men presented significantly more often with more severe forms of GO compared to women (p<0.0001) and were therefore treated significantly more often with surgery, steroids and irradiation.

Conclusions: Our retrospective analysis showed once more that women are more often afflicted by GO. In contrast, men seem to be more severely afflicted and in need of anti-inflammatory and surgical treatments. This might be due genetic and hormonal differences, as well as different approaches to the health system. Men seem to be more hesitant to seek medical help, which might be the reason for less frequent mild male GO cases in our specialized center cohort.

P1-06-56

EFFICACY OF INTRAVENOUS METHYLPREDNISOLONE FOLLOWED BY RADIOTHERAPY AND/OR ORAL PREDNISONE FOR ACTIVE AND MODERATE-TO-SEVERE GRAVES' ORBITOPATHY

Gabriela Bluszcz[1], *Anna Jablonska*[2], *Dorota Bialas-Niedziela*[2], *Klaudia Walczak*[1], *Dariusz Kecik*[2], *Piotr Miskiewicz*[1], *Tomasz Bednarczuk*[1]

[1]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Poland; [2]Department of Ophthalmology, Medical University of Warsaw, Poland

Background: Intravenous methylprednisolone pulse therapy (ivMP) remains the first-line treatment for active and moderate to severe Graves' orbitopathy (GO). However its efficacy ranges from 35% to 90% according to different studies. Some of them suggested that adjuvant treatment with oral glucocorticoids and/or orbital radiotherapy (RT) may improve the response and decrease the relapse rate after ivMP treatment.

Methods: A retrospective study was performed in a single, academic tertiary referral centre with a joint thyroid-eye clinic. Patients with active moderate-to-severe GO received ivMP (500 mg once per week for 6 weeks followed by 250 mg per week for 6 weeks) followed oral prednisone (P) at a gradually reduced dose over a three-month period. Additionally, patients with no improvement in diplopia score were referred to RT (Gy in 10 fractions within two weeks). Responses at 12 weeks (after ivMP), 24 weeks (after P ± RT) and 36 weeks (after follow-up) were evaluated using a composite ophthalmic index (CI) and a clinical activity score (CAS). Responses were classified as "improved", "unchanged", "deteriorated", compared to baseline.

Results: A total of 63 patients, with an average age of 53 years (SD = 12.3) were included in the study. At week 12, improvement in CI was observed in 55.6% of patients (35/63) and deterioration in 1.6% (1/63). Improvement in CAS was noted in 63.5% (40/63). Additional treatment with oral P was conducted on 39 patients, whereas 21 patients were referred to RT + P. In the P group, an improvement in CI was registered in 56.4%, 71.8%, and 71.8% of patients at 12, 24 and 36 weeks, respectively, and deterioration was observed in 1 patient (2.6%). Moreover, further significant improvement in CAS was observed (p = 0.03 at week 24; p = 0.02 at week 36). The improvement rates in the RT+P group were 61.9%, 66.7%, and 76.2% at 12, 24 and 36 weeks, respectively, with no deteriorated patients. Adjuvant RT was ineffective in reducing diplopia and no significant improvement in CAS was noted. Serious adverse effects requiring discontinuation of the treatment occurred in 5 patients (7.9%): in 3 during ivMP and in 2 during P treatment.

Conclusions: The results of this study confirm that ivMP is an effective treatment for active, moderate-to-severe GO, especially in reducing CAS. Adjuvant therapy with oral P may further improve the efficacy of ivMP. Careful monitoring of side effects during treatment is advised. Prospective RCT are needed to confirm these finding.

P1-06-57

DOES ATYPICAL GRAVES' ORBITOPATHY HAVE THE WORSE CLINICAL SEVERITY? A SEVEN-YEAR RETROSPECTIVE STUDY

Wino Vrieda Vierlia[1]

[1]Brawijaya University, Saiful Anwar General Hospital, Malang, Indonesia

Objectives: Graves' orbitopathy is an autoimmune inflammatory disorder of the orbit and periorbital tissues that may be presented with atypical and typical forms. The purpose of this study was to evaluate the clinical severity and activity in patients with atypical Graves' orbitopathy compared with typical presentation.

Methods: In a single-center retrospective study, all medical records of patient with Graves' orbitopathy at our hospital from January 2012-December 2018 were collected. Demographics, clinical severity and activity based on Clinical Activity Score and EUGOGO Classification were recorded. The data were further reviewed and classified into atypical and typical Graves' orbitopathy.

Results: Seventy-one medical records of patient with Graves' orbitopathy were evaluated. Atypical presentation was found in 17 patients (23.9%) with unilateral involvement accompanied with thyroid dysfunction or bilateral eyes without evidence of thyroid dysfunction. Statistical analysis showed that the mean age of atypical form (32.71±7.45) was significantly younger than the typical form (40.35±12.2, p = 0.02). There was also a lower Clinical Activity Score in atypical group (3.14±0.69) compared with typical group (3.81±1.48, p = 0.02). Most patients with atypical presentation had been considered as having sight-threatening condition (10/17,58.8%). However, the clinical severity as determined by the increasing number of signs and symptoms did not show significant differences between the two groups (p>0.05).

Conclusions: Atypical presentation of Graves' orbitopathy might be less frequently found in comparison with typical form. Nevertheless, the presentation of atypical form should raise awareness as the majority of cases were classified into sight-threatening condition according to clinical severity assessment and did reveal a lower clinical activity score.

P1-06-58

THYROID-ASSOCIATED ORBITOPATHY AND QUALITY OF LIFE: CORRELATION OF GO-QOL WITH CLINICAL ACTIVITY SCORE AND SEVERITY IN 101 PATIENTS

Borel Marine[1], *Grunenwald Solange*[2], *Philippe Imbert*[3], *Dekeister Céline*[4], *Philippe Caron*[5]

[1]Department of Endocrinology and Metabolic Diseases, Chu Larrey, Toulouse, France; [2]Chu Larrey, Service D' Endocrinologie, Department of Endocrinology and Metabolic Diseases, Chu Larrey, Toulouse, France; [3]Service D'ophtalmologie, Clinique du Parc, Department of Endocrinology and Metabolic Diseases, Chu Larrey, Toulouse, France; [4]Maxillo-Facial Surgery Department, Chu Purpan, Toulouse, France; [5]Department of Endocrinology and Metabolic Diseases, Chu Larrey, Toulouse, France

Thyroid-associated orbitopathy (TAO) is a classic and sometimes severe complication of autoimmune process associated with thyroid diseases, more common in Graves' disease. Due to its functional impairment and disfiguring clinical presentation, TAO affects the quality of life of patients. Few studies have examined the importance of this impact in TOA patients.

The main objective of this retrospective study is to determine if there is a correlation between the deterioration of quality of life in patients seen in a multidisciplinary orbitopathy consultation, the severity and the inflammatory activity of the TAO.

101 patients (75 women, mean age 51 ± 12 years, 93 Graves' diseases) consulting for a TAO between March and November 2017, completed the GO-specific quality of life questionnaire, GO-QOL, validated by EUGOGO. This questionnaire is sub-devised in two subscales, one measuring the consequences of diplopia and decreased visual acuity on visual functioning, and one measuring the psychosocial consequences of a changed appearance. Clinical activity was evaluated using the Clinical Activity Score (CAS) and clinical severity based on three criteria (decrease of visual acuity, oculomotor disorders, proptosis): 9.9% of patients had active TAO (CAS ≥ 3) and 47.5% had severe impairment.

No significant correlation was found between quality of life, both for visual functioning and for appearance, and TAO severity (respectively p = 0.89 and 0.88). However, inflammatory activity was significantly associated with impairment of the quality of life for visual functioning (p = 0.01) and there was a non-significant trend for appearance (p = 0.08). The deterioration of the quality of life in terms of appearance was significantly more important for women (p < 0.001).

This study confirms an alteration of the quality of life in patients with TAO, correlated with inflammatory activity, which is more important in women because of appearance consequences. During TAO treatment, the GO-QoL questionnaire could be useful for early detection of patients requesting psychological support.

P1-06-59

GRAVES' OPHTHALMOPATHY: EARLY RESPONSE TO INTRAVENOUS GLUCOCORTICOIDS IS PREDICTIVE OF THE LONG TERM CLINICAL OUTCOME AND IT IS RELATED TO AGE AND LDL COLESTEROL LEVELS

Diletta Moretti[1], *Adriano Naselli*[1], *Fabrizio Lo Giudice*[2], *Maria Luisa Arpi*[3], *Rosario Le Moli*[4]

[1]University of Catania, Catania, Italy; [2]University of Catania, University of Catania, Catania, Italy; [3]Endocrine Unit, Garibaldi-Nesima Hospital, University of Catania Medical School, Catania, Italy, University of Catania, Catania, Italy; [4]Endocrinology Unit, Clinical and Experimental Medicine, Garibaldi Nesima Hospital - University of Catania, Catania, Italy

Introduction: parenteral glucocorticoid (IGT) are the first choice for active and moderate-to-severe (MS) Graves'orbitopathy (GO).

Aim: 1: GO early clinical response to IGT as predictors of medium and long term clinical outcome, 2: some metabolic and phenotypic features as predictors of early, medium and long term GO clinical outcome (CO).

Methods: MSGO patients treated with IGT from 2013 to 2018 were studied. GO was evaluated at baseline, 6, 12 and 24 weeks after the starting of IGT according to the EUGOGO overall clinical criteria. Metabolic and phenotypic features were also evaluated. Clinical outcomes were categorised as Improved (G1), Unchanged (G2) or Deteriorated (G3) when compared to the baseline assessment. Univariate and multinomial logistic regression analysis were used for statistical analysis.

Results: 58 patients, 32 smokers, 41 females and 17 males, age 45.1±13.3, Body Mass Index 24.2±6.7, Clinical Activity Score 3.8±0.6, LDL colesterol 129.5±42.4, glycemia 98.8±30.4, were treated with IGT at medium dose. At 6 weeks (w) 22 patients improved (G1), 35 patients were unchanged (G2), 1 patient deteriorated (G3). **Table 1** shows the outcomes of G1 and G2 and G3 at 12 and 24 weeks.

G2 and G3 at 6 weeks showed an high chance to remain unchanged at 12 (Odds ratio = 12.0; 95% CI = 3.3-43.57; p<0.0001) and 24 weeks (Odds ratio = 12.96; 95% CI = 3.15-53.29; p<0.0001), respect to G1. G1, G2 and G3 were mached for thyroid function and autoimmunity, age and LDL were reduced in G1 respect to G2 or G3, 38.8±11.1 vs 50.1±14.1 years, p = 0.004 and 108.8±19.6 vs 142.9±47.9 mg/dl, p = 0.003. Age > 50 years and LDL > 130 mg/dl were significantly related to unchanged or deteriorated early (6 weeks) GO clinical outcome: OR (95% C.I.) = 15.4 (1.4 -172.8), Wald 4.9, p = 0.027 and OR (95% C.I.) = 13.9 (1,6- 118.8), Wald 5.8, p = 0.016. Age and LDL were not related to the GO clinical outcome at 12 and 24 weeks.

Conclusions: GO early clinical outcome to IGT predicts the medium and long term clinical outcome and it is related to older age and elevated LDL colesterol levels.

Table 1.

	G1 (n. 22)			G2 (n. 35)			G3 (n. 1)		
	I	U	D	I	U	D	I	U	D
At 12 w (55)	16	6	0	6	26	0	0	0	1
	72.73%	27.27%		18.25%	81.25%				
At 24 w (49)	12	5	0	5	24	2	0	1	0
	70.59%	29.41%		16.13%	77.42%	6.45%			

I = improved, U = unchanged, D = deteriorated, W = weeks, numbers between the brackets

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

P1-06-60

THYROID EYE CLINIC- WHAT CAN BE LEARNED FROM EARLY REFERRAL?

Anabela Martins[1], *Mara Ferreira*[1], *Francisco Sobral do Rosário*[1], *Daniel Macedo*[1], *Jorge Oliveira*[2]
[1]Hospital Da Luz, Lisboa, Portugal; [2]Universidade Lusófona

Introduction: Graves Orbitophaty (GO) needs a correct assessement. Early referral protocol of all cases of Graves Disease (GD) by the Thyroid Clinic to the Thyroide Eye Clinic (TEC) since 2014 aims this goal.

Material and Methods: Retrospective evaluation of TEC data from 2007 to 2018. GO activity assessed using CAS score and severity using EUGOGO score. Statistical analysis done with SPSS 21.

Objectives: Comparing patients with <1 Year (Y) of diagnosed GD vs > 1 Y of diagnosed GD, the referral protocol is evaluated.

Results: 391 patients, 201 <1 Y, 81% women, mean age 46.71 (<1Y) and 50.63 (>1Y). Smoking in 57 patients <1 Y and 73 >1Y. CAS in patients <1 Y: 0, 47.7%; 1, 22.6%; 2, 11.6%; 3.8%; 4, 6%; 5, 2.5%; 6, 1.0%, 7 0.5%. In patients> 1 Y: 0, 58.9%, 1, 22.1%, 2, 11.1%, 3, 2.6%, 4, 3.2%, 5, 2,1% (p>0.05). Severity in total: 52% absent, 36% mild, 5% moderate and 7% moderate-severe. Endocrinology (E) referrals 128 patients> 1 Y vs 165 patients with <1 Y (p <0.05). Early referral is higher in E than in other specialties (p <0.05). Of the <1 Y referred by E, the CAS distribution after 2014: 0, 57.3%; 1, 20.5%; 2, 6.8%; 3, 7.7%; 4.3, 4.3%; 5, 0.9%; 6, 1.7%, 7, 0.9%; before 2014: 0, 29.8%; 1, 27.7%; 2, 19.1%; 3, 6.4%; 4, 12%; 5, 4.3% (p <0.05). Methylprednisolone pulses in 25 cases <1Y, 14 cases >1Y (p <0.05). Tobacco relates to CAS in patients with> 1 Y diagnosis (p <0.05), but not in <1 Y (p = 0.062 total). Tobacco causes greater disease severity in general and activity in the second observation (p <0.05).

Conclusions: Early referral prevents evolution and treat more symptoms. Data suggest that tobacco is relevant mainly in perpetuation/resistance to therapeutic.

P1-06-61

EXTRAOCULAR MUSCLE DYSFUNCTION CAUSED BY THREE CONCOMITANT DISORDERS

Ilaria Muller[1], *Elisa Lazzaroni*[2], *Nicola Currò*[2], *Veronica Resi*[2], *Giacinta Pirola*[2], *Alessia Dolci*[2], *Maura Arosio*[2], *Mario Salvi*[2]
[1]Graves' Orbitopathy Centre, Endocrinology Department, Fondazione IRCCS Ca' Granda, University of Milan, Milan, Italy, Thyroid Research Group, Division of Infection & Immunity, School of Medicine, Cardiff University, Cardiff, UK; [2]Graves' Orbitopathy Centre, Endocrinology Department, Fondazione IRCCS Ca' Granda, University of Milan, Milan, Italy

Introduction: Graves' orbitopathy, a disease associated with thyroid autoimmunity, affects orbital tissues with inflammation and significant muscle impairment. Other diseases can also induce extraocular muscle dysfunction.

Case Report: A 53-year-old woman with metabolic syndrome developed inconstant diplopia in August 2018. After one month (September) the diplopia became constant and she developed right oculomotor nerve palsy; the orbits MRI showed thickening of inferior and medial rectus muscles of the right eye. In October she developed right upper eyelid ptosis; antibodies to acetylcholine receptor (AChR) were only slightly positive (0.80 nmol/l; nv <0.4), while antibodies to muscle-specific kinase (MuSK) were negative. A repeated orbits MRI showed increased thickening of inferior and medial rectus muscles of the right eye, suggestive for thyroid-associated orbitopathy; in December she was treated with iv methylprednisolone (total 2.5 g) followed by oral prednisone (total 500 mg), under metformin treatment to control metabolic adverse effects. After one month (January) she was referred to our Centre; the eyes examination showed bilateral exophthalmos, conjunctival hyperaemia (clinical activity score 1/7) and eye movements impairment. We confirmed the presence of moderate thyroid-associated orbitopathy and diagnosed subclinical autoimmune hypothyroidism: thyroid-stimulating-hormone 5.73 mIU/L (0.28-4.30), free-thyroxine 12.1 ng/L (8.0-17.0), free-triiodothyronine 3.9 ng/L (2.0-5.0), anti-thyroglobulin antibodies 1811 KIU/L (<60), anti-thyrotropin-receptor antibodies 0.25 KIU/L (<0.55). Her right eyelid ptosis had worsened after steroids withdrawal: repeated AChR-antibodies were positive (3.5 pmol/ml; nv <0.5), thus she was diagnosed with concomitant myasthenia gravis and started on pyridostigmine treatment, with significant improvement of eyelid ptosis.

Conclusions: This woman presented extraocular muscles dysfunction due to three concomitant diseases: thyroid-associated orbitopathy, myasthenia gravis and right oculomotor nerve palsy. The cause of the oculomotor palsy is multifactorial, in this patient likely secondary to myasthenia gravis and metabolic syndrome. We advise careful differential diagnosis in the presence of extraocular muscles dysfunction associated with eyelid ptosis.

P1-06-62

A CASE OF GRAVES' OPHTHALMOPATHY AND PRETIBIAL MYXEDEMA TWO YEARS AFTER SUBTOTAL THYROIDECTOMY IN PATIENT WITH GRAVES' DISEASE

Narine Martirosian[1], *Nina Petunina*[1], *Liubov Trukhina*[1]
[1]Sechenov University, Moscow, Russian Federation

Graves' disease, ophthalmopathy and thyroid dermopathy are parts of systemic autoimmune condition commonly associated with thyroid dysfunction and TSH receptor antibodies. Up to 5-15% of patient with Graves' disease have signs of ophthalmopathy and dermopathy that occurs simultaneously or within months of each other. We present a case of ophthalmopathy and pretibial myxedema that manifested two years after subtotal thyroidectomy in patient with Graves' disease.

Case report: A 38 years old man was presented with exophtalmos, orbital pain, eyelids swelling. He has history of subtotal thyroidectomy due to Graves' disease and received levothyroxine. Two years after thyroidectomy appeared double vision, pain, gritty sensation in the eyes, tearing, eyelids redness and swelling, conjunctival redness and chemosis, swollen caruncle. He also had hickening of the skin localized in the pretibial area with nonpitting edema and multiple skin colored nodules. Ophthalmological examination revealed active Graves' ophthalmopathy (CAS 6). Orbital computed tomography showed apical muscle enlargement. Blood test showed TSH – 1,75 ME/ml, FT4 – 11.76 pmol/l (7.86-14.41), TRAb – 11.0 U/L. Thyroid ultrasound revealed 6 ml thyroid remnant. Thyroid dermopathy was confirmed with histological examination. He was treated with iv methylprednisolone with good clinical outcomes, decreased both pretibial and eyelids swelling, improved exophthalmos with no orbital pain and double vision.

Conclusions: This case demonstrate a rare coexistence of Graves' ophthalmopathy and thyroid dermopathy after years of thyrotoxicosis manifestation and subtotal thyroidectomy. The remaining thyroid tissue could be a substrate for maintaining an active autoimmune process in the retrobulbar and pretibial tissues, so total thyroidectomy should be performed for patients with Graves' disease.

P1-06-63

GRAVES ORBITOPATHY WITHOUT GRAVES' DISEASE: QUITE A RARE OF A FINDING!

Nishitha Kotla[1], *Sushma Dugyala*[2], *Ramya Kallur*[3], *Naga Sasidhar Kanaparthy*[4], *Dinesh Voruganti*[5]
[1]Sutter Medical Group, Auburn, USA; [2]University of Alabama Medical Center, USA; [3]Mount Sinai St Luke's Roosevelt, USA; [4]Westchester Medical Center, USA; [5]University of Iowa Hospitals and Clinics, USA

Background: Graves orbitopathy (GO) is an auto-immune disease of the retro-orbital tissues. It is frequently observed in patients with Graves' Disease (GD). Here we describe a case of GO in a patient without any clinical signs or symptoms of GD.

Case: 71-year-old Caucasian female presented to primary care physician with symptoms of prominently looking eyes along with gritty and a foreign object sensation for one year. She denied having any diplopia, color vision changes, headaches, pain with eye movement, recent weight gain, fever, fatigue, tiredness, intolerance to heat or cold, loss or increased appetite, cough, shortness of breath, mental status changes or any recent statin medication use.

Past Medical History:

- Type I Diabetes Mellitus on Insulin pump.
- Essential Hypertension.
- Chronic Kidney Disease Stage III- (Diabetic Nephropathy).
- Anemia of chronic disease.
- Depression
- Overweight BMI 29.3
- Diabetic Neuropathy

Past Social History:
- Former smoker with 12 pack year history quit in 2002
- No history of alcohol or drug use

Family history:
- No family history of GO or inheritable genetic disease.

Medications:
- Insulin pump
- Hydrochlorothiazide
- Lisinopril
- Sertraline
- Gabapentin

Decision Making:
- Complete blood count – Normocytic Anemia.
- Basic metabolic profile – Chronic Kidney Disease stage 3.
- Thyroid function tests – Thyroid stimulating hormone: 3.37, free T4: 0.81.
- Thyroid stimulating immunoglobulin: negative.
- Thyroid peroxidase antibody, TSH receptor antibody: negative.
- MRI orbits (bilateral) without contrast: increased tissue volume of extraocular muscle behind the eye, consistent with fat tissue. No optic nerve compression noted. Radiological findings were consistent with thyroid opthalmopathy.
- Hertel ophthalmometry reading: 24-90-23.
- Optical Coherence Tomography: optic nerve 110, 100.
- Visual acuity: right 20/40, left 20/20.
- Extraocular movement in both the eyes is full; visual field normal.
- Intraocular pressure OD (right) 17, OS (left) 24.

Patient course: The patient was diagnosed with Euthyroid GO. She is serially followed by ophthalmology and neuro-ophthalmology for one year. Given that she does not have any significant visual defects, corticosteroid or immunosuppression therapy or surgical intervention was not pursued.

Conclusions: This case highlights the difficulty and importance of identifying GO in Euthyroid patients. The clinical course though insidious, prompt identification and treatment could prevent grave ophthalmic complications.

Disclosures: The authors have no disclosures.

P1-06-64

GRAVES' ORBITOPATHY AND INCIDENTAL PAPILLARY THYROID MICROCARCINOMA

Mirsala Solak[1], *Tanja Skoric Polovina*[2]
[1]University Hospital Center Zagreb, Croatia; [2]Penta, Croatia

Introduction: Patients with thyroid carcinoma and Graves' orbitopathy are rare.

Case Report: Here we present 28-year old woman examined in our outpatient clinic for hyperthyroidism two years ago. Her symptoms started few months earlier with sweating, weight loss and tremor. Symptoms of Graves' orbitopathy (GO) occurred simultaneously with the onset of hyperthyroidism. She smoked 20 cigarettes per day. The eye evaluation revealed severe active Graves' orbitopathy (CAS 7/7 and intensity 4 according to EUGOGO). We started treatment with thiamazole as well as high doses of methylprednisolone (500 mg iv every 2 weeks) for GO. After 3 months of the treatment eye changes improved and she stopped coming to control examinations. Ten months later she came again with florid hyperthyroidism and worsening of eye symptoms (CAS 6/7, intensity 4). We gave her second course of intravenous glucocorticoids in pulse doses during the next three months (cumulative dose of 6 g of methylprednisolone in two courses). She was referred to total thyroidectomy because of a very large goiter, uncontrolled hyperthyroidism and bad compliance. We also planned orbital radiotherapy after the surgery. An ultrasound of the thyroid, which was performed before the surgery, revealed signs of a diffuse lesion as well as few small hypoechogenic nodules of around 5 mm in diameter in both lobes. Pathohistological examination showed multiple focuses of papillary microcarcinoma in both lobes. The patient was qualified for ^{131}I radioiodine complementary therapy (RAI) because of an intermediate cancer risk. We decided to give her human recombinant TSH (rTSH) before RAI therapy to decrease the possibility of GO worsening. After the RAI orbital radiotherapy will be applied.

Conclusion: Treatment of patients with GO and thyroid carcinoma can be challenging.

Pregnancy, Nutrition, Metabolism

P1-07-65

EFFECTS OF IODINE SUPPLEMENTATION IN PREGNANCY ON IODINE STATUS, THYROGLOBULIN LEVELS AND THYROID FUNCTIONAL PARAMETERS: A RESULT OF A RANDOMIZED CONTROLLED TRIAL

Jacopo Manso[1], *Simona Censi*[2], *Sara Watutantrige-Fernando*[3], *Susi Barollo*[4], *Loris Bertazza*[4], *Caterina Mian*[5]
[1]Endocrinology Unit, Padua University, Padua, Italy; [2]University of Padua, Department of Medicine (Dimed), Endocrinology Unit, Padua, Italy; [3]Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Italy; [4]Dept. Medicine (Dimed), University of Padova, Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Italy; [5]Operative Unit of Endocrinology, Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Dept. of Medicine, Padova, Italy

Background: Iodine (IO) is a micronutrient required for adequate thyroid function, it's taken with diet, and excreted by the kidney. Pregnant women need a higher daily intake of IO. In fact, low IO intake in pregnancy is responsible for induced IO deficiency disorders in pregnant women and fetus.

Patients and methods: In this randomized, placebo-controlled trial, pregnant women in the 1st trimester of pregnancy living in Veneto region, both Italian and foreign, were randomized (3:2) to orally receive 225 µg IO once a day or placebo until delivery. Exclusion criteria: age <16 years, presence of autoimmune or thyroid or malabsorption diseases, treatment with L-thyroxine, twin pregnancy. A total of 90 women were enrolled and double-blind randomized in an intervention group (IG) of 52 subjects and placebo group (PG) of 38 subjects. In every gestational trimester, we measured urinary iodine concentration (UIC), serum thyrotropin (TSH), free thyroxine (fT4), free tri-iodothyronine (fT3) and thyroglobulin (Tg); we also performed a thyroid ultrasonography (US) to evaluate thyroid gland volume. At the baseline (T0) and at 3rd trimester, women were asked to answer a frequency food questionnaire.

Results: The two groups at T0 were homogeneous by age, ethnicity, BMI, consumption of cow's milk and iodized salt, level of education, biochemical (UIC, TSH, Tg, fT3, fT4) and US point of view. In the 2nd and 3rd trimesters, women in IG showed significantly higher UIC values than women in PG (2nd trimester UIC 215 µg/L vs 53,5 µg/L, p<0,0001; 3rd trimester UIC 187,2 µg/L vs 72 µg/L, p<0,0001). A significant difference emerged between the two groups concerning the trend of TSH levels variation in the three trimesters (p<0,001), with a tendency to decrease in the IG. Tg values also showed a significant difference both in the trend of variation in the three trimesters with a tendency to decrease in IG (p = 0.008) and in 3rd trimester levels with lower values in the IG (p = 0,021). Moreover, UIC and Tg values were significantly negatively correlated (p = 0,0027, r = -0,20) and this correlation was even stronger (p = 0,0001, r = -0,35) excluding the 1st trimester (influenced by b-HCG values). fT4, ft3 and US did not differ between the two groups.

Conclusions: These data confirmed a mild-moderate IO-deficiency condition in Veneto. IO supplementation during pregnancy is safe and allows to reach optimal UIC values (>150 µg/L); it seems to reduce the hyperstimulation of the thyroid gland, lowering the TSH and Tg values, in supplemented women without affecting the production of fT4 and fT3. As a result, we recommend IO supplementation from preconceptional age.

P1-07-66

ADEQUACY OF THYROID HORMONE REPLACEMENT IN PREGNANCY AND THE PRECONCEPTION PERIOD IN WOMEN WITH HYPOTHYROIDISM: A UK PRIMARY CARE AUDIT

Anh Tran[1], *Steve Hyer*[2], *Nicola Kirby*[3], *Malcolm Prentice*[4], *Onyebuchi Okosieme*[5]

[1]Shadbolt Park House Surgery, Worcester Park, UK; [2]Epsom and St Helier University Hospital NHS Trust, Carshalton, UK; [3]The Longcroft Clinic, Banstead, UK; [4]Croydon University Hospital, Croydon University Hospital, London, UK; [5]Cardiff University, Prince Charles Hospital, Cardiff, UK

Introduction: Suboptimal thyroid function in pregnancy carries significant risks of poor obstetric outcomes including pregnancy loss and neurodevelopmental impairment in the offspring. Current guidelines recommend pre-conception optimisation of thyroid hormone replacement in women with hypothyroidism who are planning pregnancy.

Aim: To audit the prevalence of suboptimal thyroid function in women of reproductive age with primary hypothyroidism on levothyroxine treatment in primary care.

Methods: Eight UK GP practices with a total population of 118831 patients [practice population range 3,758-33,242] were audited using EMIS Population Reporting Manager. No patient identifiable data was collected. The study population comprised women aged 15-55 years with treated primary hypothyroidism who were potentially still reproductive (not coded with menopause, hysterectomy or sterilization). We analysed the percentage of patients with latest TSH >upper limit of local normal reference range [ULNR] and the percentage of those coded as pregnant or trying to conceive with latest TSH >3 mU/L.

Results: The prevalence of treated primary hypothyroidism in the eight Practices' total population was 3.26% [N = 3872], of whom 375 (10%) had latest TSH>ULNR, and 102 (2.6%) with TSH>10mU/L.

1192 (30%) of the population with primary hypothyroidism on levothyroxine treatment were women aged 15-55 years, of whom 1087 (91%) were identified as being potentially still reproductive (not coded with menopause, hysterectomy or sterilization). In this group, 135 (12%) had latest TSH >ULNR, and 40 (3.3%) had latest TSH>10 mU/L.

63 women were coded as pregnant or trying to conceive in the previous 12 months. In this group, 21 (33%) had latest TSH >3 mU/L.

Conclusions: Suboptimal thyroid hormone replacement is common in women of reproductive age on levothyroxine treatment for hypothyroidism. Further studies are needed to identify strategies (e.g. improving coding to facilitate identification of patients with hypothyroidism who are pregnant or planning pregnancy, patient and GP education to increase awareness of current thyroid guidelines) to ensure thyroid hormone replacement is optimised for this cohort of patients.

P1-07-67

PREGNANCY OUTCOMES ARE NOT ALTERED BY VARIATION IN THYROID FUNCTION WITHIN THE NORMAL RANGE IN WOMEN FREE OF THYROID DISEASE

Veltri Flora[1], *Pierre Kleynen*[1], *Pepersack Thierry*[2], *Serge Rozenberg*[1], *Kris Poppe*[1]

[1]Chu Saint-Pierre (Université Libre de Bruxelles, ULB), Brussels, Belgium; [2]Bordet Institute (Université Libre de Bruxelles, ULB), Belgium

Objective: In the recently revised guidelines on the management of thyroid dysfunction during pregnancy, treatment with thyroid hormone (LT4) is not recommended in women without thyroid autoimmunity (TAI) and TSH levels in the range 2.5-4.0 mIU/L, and in a recent study in that particular group of pregnant women, more complications were observed when a treatment with LT4 was given. The objective of the study was therefore to investigate whether variation in thyroid function within the normal (non-pregnant) range in women free of thyroid disease was associated with altered pregnancy outcomes?

Design: Cross-sectional data analysis of 1321 pregnant women nested within an ongoing prospective collection of pregnant women's data in a single centre in Brussels, Belgium.

Methods: Thyroid peroxidase antibodies (TPO-abs), thyroid-stimulating hormone (TSH), free T4 (FT4) and ferritin levels were measured and baseline characteristics were recorded. Women taking LT4, with TAI and thyroid function outside the normal non-pregnant range were excluded. Pregnancy outcomes and baseline characteristics were correlated with all TSH and FT4 levels within the normal range and compared between two groups (TSH cut-off < and ≥2.5 mIU/L).

Results: Tobacco use was associated with higher serum TSH levels (OR: 1.38; CI 95%: 1.08-1.74); $P = 0.009$. FT4 levels were inversely correlated with age and BMI (rho = -0.096 and -0.089; $P<0.001$ and 0.001 respectively) and positively correlated with ferritin levels (rho = 0.097; $P<0.001$). Postpartum haemorrhage (>500 mL) was inversely associated with serum FT4 levels (OR: 0.35; CI 95%: 0.13-0.96); $P = 0.040$. Also 10% of women free of thyroid disease had serum TSH levels ≥2.5 mIU/L.

Conclusions: Variation in thyroid function during the first trimester within the normal (non-pregnant) range in women free of thyroid disease was not associated with altered pregnancy outcomes. These results add evidence to the recommendation against LT4 treatment in pregnant women with high normal TSH levels and without TPO antibodies.

P1-07-68

IMPACT OF FIRST-TRIMESTER THYROTROPIN LEVEL ON PREGNANCY LOSS AMONG THYROID-ANTIBODY-POSITIVE WOMEN DURING A NATURAL PREGNANACY

Ai Yoshihara[1], *Noh Jaeduk Yoshimura*[1], *Natsuko Watanabe*[1], *Yo Kunii*[1], *Hidemi Ohye*[1], *Miho Suzuki*[1], *Masako Matsumoto*[1], *Nami Suzuki*[1], *Marino Hiruma*[1], *Kenji Iwaku*[1], *Kiminori Sugino*[1], *Koichi Ito*[1]

[1]Ito Hospital, Tokyo, Japan

Objective: To determine the impact of thyrotropin (TSH) level on pregnancy loss among Japanese women who tested thyroid-antibody (TA)-positive during a natural pregnancy.

Subjects and Methods: We retrospectively reviewed the cases of TA-positive women who had conceived naturally and whose serum TSH, FT3, and FT4 levels had been measured during 4 to 8 weeks of pregnancy. Of the 1663 women whose FT3 and FT4 levels were within their reference ranges at our hospital during early pregnancy, 489 women had not being treated with levothyroxine (LT4), 284 women had been started on LT4 during their pregnancy, and 890 women were already on LT4 therapy at the time they conceived. We attempted to identify factors that were associated with early pregnancy loss.

Results: The overall incidence of early pregnancy loss was 8.7%. Stepwise multiple regressions identified age at conception as the strongest predictor of early pregnancy loss, and the incidence of pregnancy loss increased with age group. We then reviewed the cases of the 940 women under 34 years old. The results showed that their incidence of pregnancy loss in this age group was 5.5% and that TSH level, age, and LT4 replacement had no impact on pregnancy loss.

Conclusion: The strongest predictor of early pregnancy loss among TA-positive women was higher age. TSH level during the 1st trimester was not a strong factor that influenced pregnancy loss among TA-positive women regardless of whether they received LT4 replacement therapy or not.

P1-07-69

THE ASSOCIATION OF THERAPY-ADHERENCE, IODINE STATUS AND THYROID FUNCTION IN ADULT PATIENTS WITH PHENYLKETONURIA

Csaba Sumánszki[1], *Erika Kiss*[2], *Erika Simon*[2], *Erika Galgóczi*[3], *Áron Soós*[4], *Attila Patócs*[5], *Béla Kovács*[4], *Endre V. Nagy*[3], *Péter Reismann*[6]

[1]2nd Dep of Med, Semmelweis Univ, Budapest, Hungary; [2]1st Department of Pediatrics, Semmelweis University, Budapest, Hungary; [3]Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [4]Institute of Food Science, Faculty of Agricultural and Food Science and Environmental Management, University of Debrecen, Debrecen, Hungary; [5]Department of Laboratory Medicine, Semmelweis University, "Lendület" Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary; [6]2nd Department of Medicine, Semmelweis University, Budapest, Hungary

Background: To avoid the development micronutrient deficiencies the lifelong natural protein-restricted diet in phenylketonuria (PKU) is completed Phenylalanine (Phe)-free L-amino acid mixtures that provide the daily necessary micronutrients, such as iodine and selenium.

Objectives: Our main objective in this study was to assess the iodine and selenium status of patients with PKU, based on their adherence to the low-Phe diet, compared to a healthy control group.

Methods: A single-center, case-control study was conducted with seventy-seven PKU patients (age 18–41 years) and 50 matched healthy controls. Thyroid hormones, serum thyroglobulin (Tg), thyroid antibodies (TgAb, TPOAb), urinary iodine (UIC) and selenium concentrations (USeC) were measured, and thyroid ultrasound was performed.

Results: Although optimal iodine status was found in the entire PKU population, by dividing the patients according to their therapy compliance significantly higher median urinary iodine concentration was found in the control and good adherence group compared to the low adherence group (control: 145 µg/l good adherence: 165 µg/L vs. low adherence: 61 µg/l, $p = 0.001$, and $p < 0.001$, respectively). Median urinary selenium concentration was comparable between control and good adherence groups (21 vs 21 µg/g), whereas low adherence group had significantly lower USeC levels (16 µg/g, $p = 0.019$, and $p = 0.017$, respectively). The incidence of thyroid dysfunction in the PKU group was infrequent (5%). Median serum TSH was significantly higher in the control the ($p = 0.018$) and good adherence ($p < 0.001$) groups compared to low adherence group, without any free thyroid hormones changes. TSH levels in PKU group showed a negative correlation with Phe levels ($rs = -0.34$, $p = 0.005$).

Conclusions: The results of this study suggest that iodine status is strongly influenced by the adherence to therapy in early-treated adult PKU patients. Protein-restricted diet combined with Phe-free L-amino acid mixtures provide adequate iodine intake.

P1-07-70

SELENIUM AND SELENOPROTEIN P LEVELS IN PREGNANT WOMEN WITH THYROIDITIS AND ADVERSE PREGNANCY OUTCOME

Anastasia Katsaka[1], *Anastasios Boutsiadis*[2], *Maria Mavrouli*[3], *Ioannis E Grammatikakis*[4], *Leonidas Duntas*[5]

[1]Third Department of Obstetrics and Gynecology, School of Medicine, Attikon Hospital, National and Kapodistrian University of Athens, Athens, Greece; [2]Evgenidion Hospital, Unit of Endocrinology, Diabetes and Metabolism, Athens, Greece; [3]National and Kapodistrian University of Athens, Institute of Biopathology, Unit of Immunology and Infection, Evgenideion Hospital, Department of Microbiology, Athens, Greece; [4]3rd Department of Obstetrics and Gynecology, Medical School University of Athens, Attikon Hospital, Athens, Greece; [5]Evgenideion Hospital, University of Athens, Unit of Endocrinology, Diabetes and Metabolism, Thyroid Section, Athens, Greece

Background: Se deficiency during pregnancy has been associated with adverse outcomes, including preterm delivery, neonatal low weight, impaired intrauterine growth, and preeclampsia. The aim was to investigate Se and selenoprotein P (SEPP) levels in 3rd trimester pregnant women, with and without autoimmune thyroiditis (AIT), and the risk for adverse pregnancy outcomes.

Methods: Thirty-five 2nd trimester pregnant women were recruited and followed until delivery due to low serum Se (<80 µg/l) levels. 16/35 patients had AIT (G1/G2, respectively). Another group of 34 patients with higher Se levels (>80 µg/l) in the 2nd trimester, 19/34 had AIT (G3/G4, respectively) and served as controls. TSH, Se, SEPP, T4, T3, TPOAB, and TgAB were determined in pregnancy weeks 32-36.

Results: Se levels decreased from 73 ± 11 µg/l (mean ± SD) to 65 ± 17 µg/l in Gr1/G2, while in Gr3/G4, Se dropped from 85 ± 19 µg/l to 79 ±18 µg/l (n.s), and SEPP from 4.7 ± 1.7 mg/l to 4.5 ± 1.6 mg/l in the 3rd trimester (G2/G3). A positive correlation, s.s at 0.01 level (Pearson 2-tailed), was found between SEPP and Se throughout the study. No associations between SEPP and TSH and thyroid antibodies were recorded. Preeclampsia (n = 3), preterm deliveries (n = 4), and gestational diabetes (n = 1), were more frequently observed among Gr1 (n = 6) and Gr2 (n = 2) and less in Gr3/Gr4, eclampsia (n = 1) and preterm delivery (n = 1). There was no clear evidence of differences between groups regarding infant birthweight or neonatal death. There were no differences in T4 and T3 concentrations. None of the groups exhibited congenital anomalies. After adjusting for covariates, women with lower serum Se levels (<75 µg/l) in 2nd trimester had a higher risk for adverse pregnancy outcomes compared to women with higher Se levels. A SEPP threshold reflecting a higher risk was difficult to determine due to the small number of samples, although it could be tentatively estimated at about 3.5-3.0 mg/l.

Conclusions: In this observational study, low Se levels were associated with a high risk for pregnancy complications, also probably when in combination with AIT. The presence of AIT per se was not associated with adverse events in the 3rd trimester. Nevertheless, caution is recommended until more studies have been conducted. SEPP levels were positively correlated with Se levels, offering a reliable assessment of Se availability in the human body. As SEPP does not reflect only serum Se levels, it may represent a more robust biomarker of Se status than Se itself.

P1-07-71

THYROID HORMONE REFERENCE RANGES IN PREGNANT WOMEN BASED ON INDIGENOUS POPULATION: A MULTI CENTRIC STUDY FROM IODINE-DEFICIENT ENDEMIC ZONES IN THREE STATE OF INDIA

Snehlata Tendi[1], *Nikku Yadav*[2], *Atul Kathait*[3], *Shruti Mishra*[4], *Jayanti Semwal*[5], *Asha Chandola-Saklani*[6]

[1]Apeejay Stya University, Gurgaon, India; [2]Department of Community Medicine, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, India; [3]Centre for Biosciences and Clinical Research, School of Biosciences, Apeejay Stya University, Apeejay Stya University, Sohna Gurgava, Gurgaon, India; [4]Apeejay Stya University, Sohna Gurgava, Haryana, India; [5]Department of Community Medicine, Himalayan Institute of Medical Science, Swami Rama Himalayan University, Jolly Grant, Dehradun, India; [6]Dept Biosciences & Clinical Research, School of Biosciences, Apeejay Stya University, Sohna-Gurgaon, Ncr India-122103, Sohna- Gurgaon, India

Background and Rationale: Given the developmental role of thyroid hormones it is critical to monitor the level of thyroid hormones during pregnancy to ensure maternal/child health. International standards have been prescribed for TSH, and to some extent FT4, which serve as the diagnostic tools to detect thyroid dysfunction. These international guidelines recommend that the standard cut-offs be applied strictly for populations only with optimal iodine intake. We do not know till date how iodine deficiency impacts normal reference ranges. But majority of countries all over the world use these standard cut-offs as references to define the thyroid status of their populations irrespective of whether iodine-sufficient or iodine-deficient (ID). In India international guidelines have been imported by the Regulatory bodies and physicians mandated to use themforthyroid dysfunction diagnosis despite differences of iodine-status, ethnicity, genetics, life style etc. This may lead to misclassification errors and have serious impact considering that even minor variations in thyroid hormone levels can have clinical implications.

Objective: To examine TSH/FT4 profiles of populations drawn from ID-endemic zones and match the cut-offs based on indigenous normal population versus that of international standards

To assess the impact of iodine-deficiency on reference range of thyroid hormones.

Methods: Epidemiological observational survey conducted in three states viz.,Haryana, Bihar,Uttarakhand. 960rural pregnant women fulfilling inclusion criteria enrolled at Government Primary Health Centers. TSH & FT4 were measured in DBS_ELISA. UIC was measured spectrophotometrically. BMI was recorded.IEC approval & informed consent weretaken.

Results: Summarized in table. The overall median of UICindicated mild iodine deficiency. 63-67% women had normal BMI as per WHO which is comparable with world figures.

63-67% women had cut offs above the International standard range currently mandated by Indian Regulatory Bodies. Judging from the International cut-offs 33, 38 and 63% were likely to be over-diagnosed and considered for treatment, whereas according to population outliers they were apparently normal (within 2.5 -97.5 percentile).

Conclusion: Results indicate that in Iodine-deficient zones high TSH may be a norm which is able to maintain a normal FT4 and BMI. Population specific reference ranges should be developed to avoid misclassification errors.

Financial assistance from Apeejay Education Society and Himalayan Hospital Trust is gratefully acknowledged.

State	Thyroid Hormone Range					
	TSH(mIU/L)			FT4(Pmol/L)		
	I	II	III	I	II	III
Haryana	1.02-3.70	1.54-4.83	2.20-5.74	10.38-18.63	9.00-17.60	8.20-16.09
Bihar	1.31-4.73	1.65-5.74	2.58-6.41	7.82-18.46	7.43-17.00	7.30-16.30
Uttarakhand	0.15-5.16	0.46-5.24	1.03-6.21	6.12-24.45	8.20-19.82	7.06-16.52

P1-07-72

THE INCIDENCE OF HASHIMOTO'S THYROIDITIS IS UNDERESTIMATED IN PREGNANCY

Simona Gaberscek[1], *Tina Ušaj*[2], *Katja Tuta*[2], *Katica Bajuk Studen*[3], *Nataša Bedernjak Bajuk*[3], *Miha Jesenko*[3], *Nina Ostaševski Fernandez*[3], *Edvard Pirnat*[3], *Katja Zaletel*[3]

[1]Department of Nuclear Medicine, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Slovenia, Ljubljana, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Slovenia; [3]Department of Nuclear Medicine, University Medical Centre Ljubljana, Slovenia

Objectives: Thyroid dysfunction is associated with the increased likelihood of menstrual irregularities and ovulatory disturbances as well as with the harmful effects on the course of pregnancy and on fetal development. Hashimoto's thyroiditis is the most frequent cause of thyroid dysfunction. In some reports, even euthyroid Hashimoto's thyroiditis with the increased level of thyroid peroxidase antibodies (antiTPO) and/or thyroglobulin antibodies (antiTg) was shown to be associated with the increased risk of pregnancy loss. Currently there is no consensus on universal screening for thyroid disorders in women of reproductive age. The aim of our study was to establish the incidence of Hashimoto's thyroiditis in pregnant and non-pregnant women of reproductive age.

Methods: In this prospective clinical study we included 142 pregnant and 306 non-pregnant female volunteers of reproductive age. Women with the known thyroid disease were not included in the study. In every volunteer, the level of antiTPO and antiTg antibodies was measured.

Results: Pregnant women were significantly older than non-pregnant women (32.9±5.1 and 29.8±7.1 years, respectively, $p<0.001$). Increased level of antiTPO and/or antiTg antibodies (Hashimoto's thyroiditis) was detected in significantly lower portion of pregnant than non-pregnant women (6.3% and 16.9%, respectively, $p = 0.035$). In the first trimester, 3/13 (23.1%), in the second trimester 2/56 (3.6%) and in the third trimester 4/73 (5.5%) pregnant women had increased level of antiTPO and/or antiTg antibodies. The incidence of positive antibodies was significantly higher in the first as compared to the second and to the third trimester ($p = 0.015$ and $p = 0.033$, respectively).

Conclusions: In spite of older age, pregnant women had a lower incidence of Hashimoto's thyroiditis than non-pregnant women. An immune suppression in pregnancy causing false negative measurements of antiTPO and antiTg antibodies seems to be responsible for our findings. Screening for Hashimoto's thyroiditis in pregnancy can result in an underestimation of the incidence.

P1-07-73

IODINE STATUS EVALUATED BY MEDIAN URINARY IODINE CONCENTRATION IN PREGNANT WOMEN AND NEONATAL TSH LEVELS IN 5 ROMANIAN COUNTIES

Monica Livia Gheorghiu[1], *Horea Ursu*[1], *Corina Elena Delia*[2], *Geanina Mirela Toma*[3], *Andreea Suta*[4], *Ramona Aldea*[5], *Corina Raducanu Lichiardopol*[6], *Mihai Popescu*[7], *Ionela Pascanu*[8], *Michaela Nanu*[3], *Mariana Purice*[9]

[1]"C.I. Parhon" National Institute of Endocrinology, "C. Davila" University of Medicine and Pharmacy, Bucharest, Romania; [2]"Alessandrescu Rusescu" National Institute for Mother and Child Care, Bucharest, Romania; [3]"Alessandrescu Rusescu" National Institute for Mother and Child Care, Bucharest, Romania; [4]Bucharest University, Faculty of Biology, Bucharest, Romania; [5]Campulung Hospital, Arges, Romania; [6]Craiova University of Medicine and Pharmacy, Craiova, Romania; [7]Ramnicu Sarat Hospital, Buzau, Ramnicu Sarat, Romania; [8]University of Medicine and Pharmacy Targu Mures, Targu Mures, Romania; [9]"C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania

Introduction: Universal Salt Iodization and neonatal screening for congenital hypothyroidism are implemented in Romania.

Objective: To evaluate the iodine status as reflected by median urinary iodine concentration (UIC) in pregnant women and neonatal TSH (nTSH) in 5 Romanian counties: 4 endemic iodine deficient regions (Arges, Dolj, Buzau, Covasna) and one iodine-sufficient area (Bucharest-Ilfov).

Subjects and methods: Median urinary iodine concentration (UIC), urinary creatinine and UIC/creatinine ratio were evaluated by spectrophotometry (Sandell – Koltoff method) in the morning urine collected between Feb 2016-Apr 2017 from 252 pregnant women (46 in early pregnancy and 206 in late pregnancy). Neonatal TSH, measured by fluorescence enzymatic immunoassay from blood spot, was analyzed in 2909 children born in January 2016 and in 3156 children born in January 2017.

Results are shown in the table. Normal UIC for pregnant women is > 150 mcg/L; nTSH >5 mIU/L in 3-19.9% of the newborns reflects mild iodine deficiency, 20 – 39.9% reflects moderate iodine deficiency.

Conclusions: In counties with geographical iodine deficiency, mild iodine deficiency is still prevalent in pregnant women after more than 10 years since the universal salt iodization in Romania. The percentage of neonatal TSH > 5 mIU/L suggests mild to moderate iodine deficiency in the same counties, but also in an area with normal UIC in pregnant women, a paradoxical result which warrants further studies.

	Arges	Dolj	Buzau	Covasna	Bucuresti
Pregnant women	74	52	29	15	82
mUIC (mcg/L)	89.6	121.8	110.6	143.9	205.1
mIUC/gCreatinine	99.8	118	95	147.3	Not available
2016 newborns	300	347	204	122	1936
Median nTSH	3.43	2.77	3.92	3.65	3.72
nTSH > 5 mIU/L	16.67%	4.03%	32.84%	20.49%	24.64%
2017 newborns	260	400	269	188	2039
Median nTSH	2.32	2.55	2.56	3.17	3.00
nTSH > 5 mIU/L	6.92%	8.25%	13.75%	22.87%	16.92%

P1-07-74

SELENIUM LEVELS IN PREGNANT WOMEN IN RELATION WITH DIETARY SELENIUM INTAKE HABITS IN LATVIA

Ieva Kalere[1], *Tatjana Zake*[2], *Vija Veisa*[2], *Andrejs Skesters*[2], *Sabine Upmale*[2], *Ieva Strele*[2], *Ilze Konrade*[2]

[1]Riga Stradins University, Riga Stradins University, Department of Human Physiology and Biochemistry, Riga, Latvia; [2]Riga Stradins University

Objectives: The main food groups contributing to selenium intake are milk and dairy products, meat and meat products, grains and grain-based products and fish. Absorbed selenium compounds are available for the synthesis of selenoproteins. Selenoproteins have a variety of functions, including antioxidant effects, T-cell immunity and thyroid hormone metabolism. Pregnant women are a special interest group due to increased risk of autoimmune thyroid disease in the postpartum period. The aim of this study was to describe selenium intake and serum selenium levels.

Methods: The study used data from the Health Behaviour among Latvian Adult Population survey (aged 15 to 64 years) for the period 2000-2016. Pregnant women (N = 40) in the first trimester were sampled for serum selenium levels. Consumption prevalence and median selenium, % and 95% confidence interval is shown.

Results: The percentage of participants eating one slice of rye bread/day decreased from 80.6% (78.9, 82.1) to 70.1% (68.5, 71.5), p = 0.016. The percentage of participants drinking at least 1 glass of milk daily decreased from 61.2% (59.1, 63.1) to 47.3% (45.6, 48.9), p = 0.001. The percentage of participants consuming fish weekly decreased from 69.6% (67.5, 71.5) to 58.7% (57.0, 60.2), p = 0.003. The percentage of participants consuming meat weekly decreased from 90.1% (88.3, 91.5) in 2006 to 85.0% (83.7, 86.1) in 2016, p = 0.007, similar trend was observed with meat products (p = 0.015). Median serum selenium level in pregnant women of 83.1 mcg/L (60.1, 127.2) was adequate, but substantial proportion of pregnant women had selenium levels below 70 mcg/L: 30% (N = 12).

Conclusions: The consumption of selenium rich products, i.e., bread, milk, fish and milk, has decreased significantly 2000-2016. Insufficient dietary intake may lead to decreased serum selenium levels, which is particularly important in thyroid disease risk groups, e.g. pregnant women. The trends in dietary habits should be considered when recommending a selenium sufficient diet.

P1-07-75

TREATMENT IN A PATIENT WITH HYPERTHYROIDISM IN THE FIRST TRIMESTER OF PREGNANCY AND PROPYCIL INDUCED HEPATITIS

Emma Anda Apiñariz[1], *Maria Huarte Ziganda*[2], *Juan Zubiria Gortazar*[3], *M Dolores Ollero*[3], *Ana Irigaray*[3], *Joaquin De Carlos Artajo*[3]
[1]Endocrinology and Nutrition Service, Complejo Hospitalario de Navarra, Pamplona, Spain; [2]S. Obstetricia Y Ginecología. Complejo Hospitalario de Navarra, Pamplona, Spain; [3]Complejo Hospitalario Navarra, Pamplona, Spain

Introduction: Hyperthyroidism during pregnancy is rare and can lead to major maternal-fetal complications. The indicated treatment is pharmacological, being propylthiouracil (PTU) the drug of choice during the first trimester. One of the most severe side effect is liver failure. We present the case of a patient who developed acute hepatitis due to propylthiouracil.

Clinical report: A 30-year-old patient was diagnosed with Graves' disease at week 5 of pregnancy (T4l 2.6, TSH 0.01, TSI 26). Treatment with propylthiouracil 200mg daily is initiated. Three weeks later she developed pruritus and jaundice. The blood tests confirmed a hepatic alteration: ALT 850 (0-55), AST 393 (5-34), bilirubin 1.6 (0.3-1.2), prothrombin time 15 (17-23) and biliary acid 106 (0-6). PTU was immediately suspended and studies were performed to consider viral and autoimmune hepatitis, but they were discarded. After two weeks without treatment (week 10 of pregnancy) improvement in liver function was observed but also a worsening of the hyperthyroidism. The treatment to perform would be a thyroidectomy on the second trimester. At the moment, it was decided to restart pharmacological treatment with methimazole prior to surgery with strict control of liver function, inasmuch as cross-reaction is described and the new treatment could also cause liver alteration. The initial dose was 15mg/day, achieving good control of thyroid function, with progressive reduction of TSI (negative in week 20) and normalization of liver function. It was maintained with a dose of 2.5mg/day during the third trimester and thyroidectomy was not performed due to good progression. The patient presented normal delivery of a 2,700 g girl at week 40.

Conclusion: During pregnancy, propylthiouracil liver disease can have a favorable clinical course after the immediate suspension of the drug. Treatment with methimazole after hepatopathy due to propylthiouracil may be an adequate therapeutic option to control hyperthyroidism in these cases.

Thyroid Hormone Action and HPT Axis

P1-08-76

EARLY POSTNATAL HYPERTHYROIDISM RESULTS IN INHIBITED HYPOTHALAMIC-PITUITARY-THYROID AXIS AND EUTHYROIDAL PERIPHERAL TISSUES IN ADULT MICE

Dóra Kővári[1], *Anett Stiftné Szilvásy-Szabó*[2], *Fekete Csaba*[3]
[1]Institute of Experimental Medicine Hungarian Academy of Sciences, Semmelweis University, Károly Rácz School of PhD Studies, Budapest, Hungary; [2]Institute of Experimental Medicine Hungarian Academy of Sciences, Budapest, Hungary; [3]Institute of Experimental Medicine, Hungarian Academy of Sciences, Institute of Experimental Medicines Hungarian Academy of Sciences, Budapest, Hungary

The hypothalamic-pituitary-thyroid (HPT)-axis is responsible for maintaining relatively steady circulating levels of thyroid hormones (THs). This function of the HPT axis is primarily regulated by the TH negative feedback regulation of the hypophysiotropic thyrotropin-releasing hormone (TRH) synthesizing neurons and the pituitary thyrotrops. The TH feedback regulation develops in distinct developmental stages in different species. We have observed that the inhibitory effect of THs on the thyroid-stimulating hormone synthesis in the pituitary is continuously increased in mice during the first postnatal week indicating the maturation of the feedback regulatory mechanism in this period of life.

To understand, how the TH status influences the development of the HPT axis and the peripheral TH signaling, mouse pups were treated subcutaneously with daily 1 µg/bwg T4 or with vehicle from the 2nd postnatal day for 5 days and were sacrificed 2 months later.

In adult mice, the early postnatal T4 treatment caused a marked reduction of TRH mRNA level in the hypothalamic paraventricular nucleus where the hypophysiotropic TRH neurons reside and an approximately 50% reduction of the circulating free T4 levels. The observed central hypothyroidism suggests that the perturbation of TH status in early postnatal life causes a lifelong alteration of the feedback set point in mice.

The early postnatal T4-treatment affected body composition of adult mice: The treated animals had decreased lean body mass and decreased body weight, but the treatment had no effect on the fat mass.

Despite these changes, the adult mice had normal free T3 level, increased locomotor activity, energy expenditure and also increased resting energy expenditure, while the food intake of the mice was not influenced. Since the locomotor activity and the measured metabolic parameters highly depend on the thyroid status of tissues, these data suggest that the peripheral TH metabolism can compensate the developmental inhibition of the HPT axis activity.

Our data indicate that alteration of TH levels during the development of the TH negative feedback regulation of the HPT axis results in a lifelong alteration of the feedback set point. The resulted inhibition of the HPT axis is, however, compensated by the peripheral TH metabolism and/or signaling.

P1-08-77

THYROTROPIN-RELEASING HORMONE-SYNTHESIZING NEURONS OF THE HYPOTHALAMIC PARAVENTRICULAR NUCLEUS ARE INHIBITED BY GLYCINERGIC INPUTS

Edina Varga[1], *Györgyi Zséli*[1], *Andrea Kádár*[1], *Zoltán Máté*[1], *Ferenc Erdélyi*[1], *Masahiko Watanabe*[2], *Hans Ulrich Zeilhofer*[3], *Ronald M. Lechan*[4], *Balazs Gereben*[5], *Csaba Fekete*[1]
[1]Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; [2]Hokkaido University School of Medicine, Japan; [3]University of Zurich, Zurich, Switzerland; [4]Tupper Research Institute, Tufts Medical Center, USA; [5]Institute of Experimental Medicine, Hungarian Academy of Sciences, Lab Molecular Cell Metabolism, Budapest, Hungary

Glycine is a classical neurotransmitter that has role in both inhibitory and excitatory synapses. To understand whether glycinergic inputs are involved in the regulation of the hypophysiotropic thyrotropin-releasing hormone (TRH) neurons, the central controllers of the hypothalamic-pituitary-thyroid (HPT) axis, the glycinergic innervation of the TRH neurons was studied in the hypothalamic paraventricular nucleus (PVN).

Double-labeling immunocytochemistry for demonstrated that GlyT2, a marker of glycinergic neurons, is present in axons establishing symmetric type of synapses on TRH neurons in the PVN. Presence of glycine receptor-immunoreactivity were also observed in the TRH neurons.

Using anterograde and retrograde tract tracing, the raphe magnus (RMg) and the ventrolateral periaqueductal gray (VLPAG) were found to be the exclusive sources of the glycinergic innervation of the TRH neurons within the PVN.

Using patch clamp electrophysiology, glycine was found to hyperpolarize the TRH neurons and completely blocked the firing of the these neurons. Glycine also markedly hyperpolarized the TRH neurons in the presence of tetrodotoxin demonstrating that can directly inhibit the TRH neurons. In more than 60% of TRH neurons, spontaneous inhibitory postsynaptic currents (sIPSC) were observed even after the pharmacological inhibition of the glutamatergic and GABAergic neuronal transmission. The glycine antagonist strychnine almost completely abolished these sIPSCs demonstrating the inhibitory nature of the glycinergic input of TRH neurons.

Our data demonstrate that the TRH neurons in the PVN receive glycinergic inputs from the RMg and the VLPAG. The symmetric type synaptic connection and the results of electrophysiological experiments demonstrate the inhibitory nature of these inputs.

P1-08-78

IS25, A NOVEL HALOGEN FREE TRBETA SELECTIVE AGONIST, AND ITS PRODRUG TG46 SIGNIFICANTLY DECREASE LIPID ACCUMULATION IN HUMAN HEPATOMA CELLS (HEPG2) WHILE STIMULATING AMPK ACTIVATION

Grazia Chiellini[1], *Massimiliano Runfola*[2], *Lorenza Bellusci*[2], *Simona Sestito*[2], *Lavinia Bandini*[2], *Riccardo Zucchi*[2], *Simona Rapposelli*[2]

[1]Dept. of Pathology, University of Pisa, Pisa, Italy; [2]University of Pisa, Italy

Recent studies revealed that administration of T3 to rats activates liver AMPK, supporting hepatoprotection against ischemia-reperfusion (IR) injury. Hence, thyromimetics may find clinical application in human liver transplantation and hepatic resections.

In the present work we evaluated the *in vitro* effect of newly developed TRb selective agonist IS25 and its prodrug TG46 on AMPK activation and its possible repercussion on lipid metabolism in HepG2 cells.

Methods: HepG2 cells, cultured in DMEM supplemented with 10 % FBS and 10 mg/ml penicillin/streptomycin, were seeded in 24-well plates and treated for 24 h with IS25, TG46, or T3 at 1 and 10 mM doses, to assess total lipid accumulation. Cloroquine (25 mM) was used as positive control. The growth media was then collected to perform glycerol level measurements, whereas cells were stained with Oil Red O (ORO) solution to perform spectrophotometric (510 nm) quantitative analysis of cellular lipids.

In parallel experiments, cells were seeded in 6-well plates and exposed to the same treatment with test compounds for 24h. Cells were lysed and exposed to WB analysis to assess AMPK, p-AMPK, ACC and p-ACC expression.

Results: Novel thyromimetic IS25 and its prodrug TG-46 significantly decreased lipid accumulation in HepG2 cells, while stimulating AMPK phosphorylation ($p < 0.05$) with an efficacy comparable or even higher than equimolar doses of T3. AMPK stimulation led to the phosphorylation and consequent inactivation of acetyl coenzyme A carboxylase (ACC), the major regulator of fatty acids synthesis ($p < 0.05$). ORO staining revealed a significant reduction of total lipid accumulation into lipid droplets compared to the control ($p < 0.01$). Increased level of glycerol in the cell medium after 24 h treatment with test compounds, suggests that the decreased accumulation of lipids observed after ORO staining was caused by increased lipolysis.

Conclusion: Novel TRβ selective thyromimetics can be explored *in vivo* for hepatic pathologies.

P1-08-79

ANALYSIS OF IODOTYROSINES IN PLASMA AND URINE BY LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY

Marco Borsò[1], *Cristian Gonzaléz-Guerrero*[2], *Simone Codini*[1], *Lavinia Bandini*[1], *Alireza Mani*[3], *José C. Moreno*[4], *Riccardo Zucchi*[5], *Alessandro Saba*[1]

[1]University of Pisa, Pisa, Italy; [2]Thyroid Molecular Laboratory, Institute for Medical and Molecular Genetics, La Paz Universitary Hospital, Madrid, Spain; [3]Division of Medicine, University College London, London, UK; [4]Thyroid Molecular Laboratory, Institute for Medical and Molecular Genetics, La Paz Universitary Hospital, Autonomus University of Madrid, Madrid, Spain; [5]University of Pisa, Dept. of Pathology, University of Pisa, Pisa, Italy

Objectives: Deiodination of 3-iodotyrosine (MIT) and 3,5-diiodotyrosine (DIT) by iodothyronine dehalogenase (DEHAL-1) in crucial for iodine recycling after thyroglobulin endocytosis and proteolysis. Reduced activity of DEAHL-1, either primary or caused by endocrine disruptors, might be an important cause of iodine deficiency. Evaluating this possibility in the clinical setting requires sensitive analytical methods for MIT and DIT. To this purpose, we developed and validated an HPLC-MS-MS method to detect MIT and DIT in plasma and urine samples.

Methods: 100 µL of plasma/urine were used. After the addition of appropriate amounts of stable isotope-labeled internal standards, proteins were precipitated using cold acetone. The supernatants were dried under N_2 and incubated for 45 min at 60°C with 200 µL of butanol - HCl 3.0 N to form the corresponding butyl esters of the analytes. The samples were dried again and submitted to solid phase extraction (SPE). The eluates were evaporated and reconstituted with 100µL of 0.1 M acetonitrile-HCl 0.1 M (50:50 by volume) before the injection in the HPLC-MS-MS system.

Results: The described method showed good linearity ($r = 0.998$ and $r = 0.999$ for MIT and DIT, respectively), with accuracy in the range of 84-113%. Instrumental lower limit of detections (LOD) were 50 and 25 pg/mL, while lower limit of quantification (LOQ) was 100 pg/mL for MIT and DIT, respectively. Recovery averaged 74-86%, if corrected for derivatization, while matrix effect was in the range of 66-81%. In representative mouse urine and plasma samples MIT and DIT signals were apparent, but did not reach LOQ, while both analytes were clearly detectable in urine samples from DEHAL-1 knock out mice.

Conclusions: We developed a method able to simultaneously quantify MIT, DIT – and potentially T3 and T4 - in plasma and urine samples, which could be applied to investigate the relationship between iodotyrosines and thyroid hormones in pathological conditions.

P1-08-80

NON-FUNCTIONAL TRACE AMINE-ASSOCIATED RECEPTOR 1 (TAAR1) VARIANTS IN PATIENTS WITH MENTAL DISORDERS

Grazia Rutigliano[1], *Julia Bräunig*[2], *Claudia Del Grande*[3], *Vittoria Carnicelli*[3], *Isabella Masci*[3], *Sergio Merlino*[3], *Kleinau Gunnar*[4], *Luca Tessieri*[5], *Simone Pardossi*[5], *Sarah Paisdzior*[6], *Liliana Dell'Osso*[7], *Heike Biebermann*[8], *Riccardo Zucchi*[9]

[1]Scuola Superiore Sant'anna, National Research Council (Cnr), University of Pisa, Pisa, Italy; [2]Institut für Experimentelle Pädiatrische Endokrinologie, Charité Universitätsmedizin Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany; [3]University of Pisa, Italy; [4]Charité - Universitätsmedizin Berlin, Institut für Experimentelle Pädiatrische Endokrinologie, Institut für Experimentelle Pädiatrische Endokrinologie, Berlin, Germany; [5]Scuola Superiore Sant'anna, Italy; [6]Institut für Experimentelle Pädiartrische Endokrinologie, Berlin, Germany; [7]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [8]Inst F Exp Päd Endokrinologie, Charité Universitätsmedizin Berlin, Berlin, Germany; [9]University of Pisa, Dept. of Pathology, University of Pisa, Pisa, Italy

The G protein-coupled receptor (GPCR) trace amine associated receptor 1 (TAAR1) is widely expressed across brain areas involved in emotions, reward and cognition, and modulates monoaminergic and glutamatergic neurotransmission. TAARs own their name to their first-described ligands, namely trace amines, such as β-phenylethylamine (PEA) and p-tyramine (TYR), which modulate the effects of other neurotransmitters in the synaptic cleft in the mammalian central nervous system (CNS). TAAR1 is also activated by thyronamines, in particular by 3-iodothyronamine (T1AM), an endogenous messenger thought to derive from thyroid hormone. The human gene for TAAR1 maps to locus 6q23, within a region associated with major mental disorders. Here, we screened a cohort of patients with major mental disorders (n = 104) and a group of healthy controls (n = 130) for TAAR1 variants. We detected 13 missense variants in TAAR1 coding region, with a significant enrichment in patients as compared to healthy controls (11 vs 1, 1 variant in both groups, $p < 0.01$). *In silico* analysis identified 4 potentially dysfunctional variants, all found in patients. Three of these – R23C, Y131C, C263R – were further functionally characterized. In cells co-transfected with wild type and mutated TAAR1 we observed a significant reduction of cell surface expression using the Nano-Glo® HiBiT extracellular detection system. Gs/adenylyl cyclase activation was monitored using a real-time live-cell cAMP Assay (GloSensorTM Technology), upon stimulation with 3-iodothyronamine (T1AM 10^{-5} M), β-phenylethylamine (PEA 10^{-5} M), or a high-affinity high-selectivity synthetic TAAR1 agonist, RO5166017 (10^{-5} M). In heterozygosity, the 3 TAAR1 variants substantially dampened Gs signaling in response to PEA, and, more robustly, to T1AM. Co-stimulation with PEA and RO5166017 did not yield any improvement in Gs signaling. R23C, Y131C, and C263R are rare in the general population and map in functionally important highly conserved positions across TAAR1 orthologous and paralogous genes, consistently with their detrimental effect. Our 3D TAAR1 molecular homology model indicates that the tested TAAR1 variants are spatially located at essential hot spots for receptor functions. Our findings suggest that disruptions of TAAR1 activity may be relevant to the pathophysiology of mental disorders, thereby providing a promising target for novel psychopharmacological interventions.

P1-08-81

MENDELIAN RANDOMIZATION ANALYSES REVEAL A CAUSAL EFFECT OF THYROID FUNCTION ON STROKE RISK VIA ATRIAL FIBRILLATION

Eirini Marouli[1], *Aleksander Kus*[2], *Fabiola Del Greco M.*[3], *Layal Chaker*[2], *Robin Peeters*[2], *Alexander Teumer*[4], *Panos Deloukas*[5], *Marco Medici*[2]

[1]Smd, Smd, London, UK; [2]Academic Center for Thyroid Diseases, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Institute for Biomedicine, Eurac Research, Affiliated Institute of the University of Lubeck, Bolzano, Italy; [4]Institute for Community Medicine, University Medicine Greifswald, Germany; [5]William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Objective: Despite progress in prevention and treatment in the past two decades, cardiovascular disorders remain the leading cause of mortality worldwide. Several observational studies suggest that variations in thyroid function, even within the normal range, are a risk factor for cardiovascular diseases, but it remains to be determined if these associations are causal or not. This poses the question as to whether common forms of mild thyroid dysfunction should be treated to prevent these complications. This study investigates whether the relationship between variation in normal range thyroid function, as well as hypothyroidism and hyperthyroidism, and the risk of stroke and Coronary Artery Disease (CAD) are causal and via which pathways these relations are mediated.

Methods: Mendelian randomization (MR) study using genetic instruments associated with TSH and FT4 levels within the normal range, hypothyroidism or hyperthyroidism. The potential mediatory role of known risk factors for stroke and CAD was also examined.

Results: A one standard deviation increase in TSH within the normal range was associated with a 5% decrease in the risk of stroke (OR = 0.95, 95% CI = 0.91 to 0.99). Multivariable MR analyses indicate that this effect is mediated through atrial fibrillation (AF). While normal range thyroid function was not associated with CAD, Hashimoto's Disease (HD) was associated with a 7% increased risk of CAD (OR = 1.07, 95% CI = 1.01 to 1.13). The effect of Hashimoto's Disease (HD) on CAD risk appears to be mediated via body mass index. There was no evidence for a causal association between normal range FT4 levels and the risk of stroke or CAD.

Conclusions: These results provide important new insights into the causal relationships and mediating pathways between thyroid function, stroke and CAD. These findings suggest minor variation in normal range thyroid function as a novel modifiable risk factor for stroke and pave the way to consider future adjustment of thyroid function within the normal range in managing patients' risk of stroke.

P1-08-82

3-IODOTHYRONAMINE (T1AM) INDUCES CHANGES ON GLUTAMATERGIC POSTSYNAPTIC SIGNALING PATHWAY

Lavinia Bandini[1], *Ginevra Sacripanti*[2], *Emanuele Matteo Figuccia*[3], *Sara Verlotta*[3], *Riccardo Zucchi*[3], *Sandra Ghelardoni*[3]

[1]University of Pisa, Pisa, Italy; [2]University of Pisa, Livorno, Italy; [3]University of Pisa, Dept. of Pathology, Pisa, Italy

Objective: Exogenous 3-iodothyronamine (T_1AM), a derivative of thyroid hormone, produces antiamnestic and prolearning effects in mice. Glutamatergic neurotransmission, the major excitatory system in brain, plays a key role in regulating neuroplasticity, learning and memory, and it is often compromised in neurological disorders. In the present work, we characterized the gene expression profile of two different neuronal cell lines and we evaluated the effects of T_1AM on the expression of proteins involved in glutamatergic signaling pathway.

Methods: A hybrid line of cancer cells of mouse neuroblastoma and rat glioma (NG108-15) and a human glioblastoma cell line (U-87 MG) were used. We first characterized the *in vitro* model by analyzing gene expression of several proteins involved in the glutamatergic postsynaptic cascade by real time PCR. Cell lines were then treated with T_1AM for 24h, ranging from 0.1 to 10 μM, alone or in combination with 10 μM resveratrol (RSV) and/or 10 μM amyloid β peptide (25-35). Cell viability, glucose consumption, protein expression, and cAMP production were assessed.

Results: NG108-15 and U-87 MG cell lines expressed receptors and other proteins belonging to the glutamatergic postsynaptic signaling pathway, while only U-87 MG cells expressed TAAR1, one of the putative T_1AM receptors. In NG 108-15 cells, T_1AM in combination with RSV upregulated PKC protein expression vs the baseline ($p<0.05$). Furthermore, in the same cell line, T_1AM decreased glucose consumption ($p<0.01$ vs control), without affecting cell viability. In U-87 MG cells, T_1AM improved pCREB/CREB ratio ($p<0.01$) without altering glucose consumption. Cell viability and cAMP concentration were significantly increased at 0.1 mM T1AM ($p<0.01$ vs control).

Conclusions: Our results show that in *in vitro* models of neuronal cells T_1AM may produce changes in the postsynaptic signaling cascade of the glutamatergic system.

P1-08-83

EFFECT OF THYROXINE TREATMENT DURING LACTATION ON THYROID STRUCTURE AND FUNCTION IN NEWBORN RATS

Zohra Hamouli-Said[1], *Souhila Dahmani*[1], *Assia Kamel*[1]

[1]Lbpo/Section Endocrinology, Faculty of Biological Sciences, Usthb, Algiers, Algeria

Aims: LT4, precursor of thyroid hormone used in therapeutic applications, has been detected in milk. We studied the effects of LT4 exposure during lactation on body weight (BW), hormonal levels and thyroid histology of young Wistar rat offspring.

Methods: Female rats were divided into: control (T), LT10 (LT4: 10 μg/100g BW/day) and LT20 (LT4: 20 μg/100g BW/day). LT4 was administered in drinking water to dams from postnatal days (PN) 1 to 21. Euthanasia occurred on PN 20. Plasma free thyroxin (FT4) and free triiodothyronine (FT3) levels were measured in duplicate using the radio-immunoassay (RIA) method and thyroid structure was analyzed on five micrometers thick sections after Masson's trichrome staining.

Results: At PN 7, the average body weights of the three groups of pups were similar. At PN 14 and 20, no difference was observed between body weight values of LT10 and controls male pups while LT20 male pups showed significantly lower body weight. LT10 and LT20 male pups had higher plasma FT4 and FT3. The thyroid of control and LT10 pups was characterized by numerous follicles with a strongly colored colloid and many resorption vesicles suggesting a significant internalization of thyroglobulin and thus an active synthesis of thyroid hormones. Thyroid sections of LT20 pups showed fewer follicles with high epithelium and retracted colloid.

Conclusion: Thyroxin treatment during lactation, mainly at high dose, induces changes in body mass and hormonal levels and affects the regulation of thyroid function of the progeny.

P1-08-84

WITHDRAWN

P1-08-85
FACTORS DETERMINING THE RISK OF THYROTOXIC ATRIAL FIBRILLATION DEVELOPMENT

Daria Savitskaya[1], *Alina Babenko*[2], *Ilia Derevitskii*[3], *Anastasiia Hushkina*[4]
[1]Federal Almazov North-West Medical Research Centre, Institute of Endocrinology, St. Petersburg, Russian Federation; [2]Federal Almazov Medical Centre, Almazov National Medical Research Centre, Institute Endocrinology, Saint-Petersburg, Russian Federation; [3]Itmo University, Saint-Petersburg, Russian Federation; [4]Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation

Objectives: To identify the most significant predictors of thyrotoxic atrial fibrillation (TAF) development and to investigate the predictive impact of each. To develop a model for the risk of the TAF calculating.

Methods: The study included 420 patients with overt thyrotoxicosis, associated with Graves disease, toxic adenoma or multinodular toxic goiter. Among them: 127 (30.2%) individuals with and 293 (69.8%) without AF.

Using a retrospective analysis of medical records and patient interviews, the following potential AF risk factors were assessed: physical data and parameters of the cardiovascular system, characteristics of thyrotoxicosis, comorbid conditions, treatment modality. In addition, the association of TAF with rs2200733 and rs10033464 SNPs from chromosome 4q25 was determined. Genotyping of was carried out by the method of real time polymerase chain reaction.

Results: The factors that make the greatest contribution to the risk of TAF development include: the duration of thyrotoxicosis, age, heart rate and body mass index. TAF was also more common: in men than in women: 47,1% vs 25,8%, p<0,001, in patients with non-immune thyrotoxicosis than in patients with Graves disease: 52% vs 28,7%, p = 0,014, and in those with atrial hypertension (independently with predominantly target blood pressure ranges or no): 16% vs 38,4%, 46,9%, respectively, p<0,001.

The genotyping of rs2200733 (G/T) and rs10033464 (C/T) SNPs revealed a statistically significant prevalence of TT genotype (17.2% vs 0.8%, p<0.001 and 7.1% vs 0.8%, p = 0.03, respectively) in the group of patients with TAF when compared with the group without AF.

Conclusion: On the basis of the data obtained a model was development that, with 84% accuracy, determines who will have and who won't have AF, associated with thyrotoxicosis. The TT genotype of SNPs rs2200733 and rs10033464 from chromosome 4q25 may serve as an additional predictor of TAF development.

Cancer Clinical 2

P2-01-86
EPIDEMIOLOGICAL, RETROSPECTIVE, LONGITUDINAL STUDY TO CHARACTERIZE THE NATURAL HISTORY OF PATIENTS WITH ADVANCED DIFFERENTIATED THYROID CARCINOMA IN SPAIN AND PORTUGAL: ERUDIT STUDY

Rita Joana Santos[1], *Cintia González*[2], *Marta Llanos*[3], *Virginia Pubul*[4], *Elena Navarro*[5], *Sonsoles Guadalix*[6], *Carlos Zafón*[7], *Guillermo Crespo Herrero*[8], *Javier Santamaria*[9], *Miguel Navarro*[10], *Marcelino Gómez*[11], *Manel Puig*[12], *Pablo Gajate*[13], *Javier Valdivia Bautista*[14], *María José Villanueva*[15], *Juan Carlos Galofré*[16], *Beatriz Castelo*[17], *Iñaki Arguelles*[18], *Ángel Segura*[19], *Javier Aller*[20], *Carlos López López*[21], *Marcel Sambo*[22], *Juan Antonio Vallejo*[23]
[1]Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [2]Hospital Sant Pau, Barcelona, Spain; [3]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [4]Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain; [5]Hospital Virgen del Rocío, Sevilla, Spain; [6]Hospital 12 de Octubre, Madrid, Spain; [7]Hospital Vall D' Hebrón, Barcelona, Spain; [8]Complejo Asistencial de Burgos, Burgos, Spain; [9]Hospital Universitario de Cruces, Vizcaya, Spain; [10]Hospital Universitario de Salamanca, Salamanca, Spain; [11]Hospital Universitario Doctor Peset, Valencia, Spain; [12]Hospital Universitari Germans Trias I Pujol, Barcelona, Spain; [13]Hospital Ramón Y Cajal, Madrid, Spain; [14]Hospital Virgen de Las Nieves, Granada, Spain; [15]Complejo Hospitalario Universitario de Vigo, Vigo, Spain; [16]Clínica Universidad de Navarra, Navarra, Spain; [17]Hospital La Paz, Madrid, Spain; [18]Hospital Son Espases, Palma de Mallorca, Spain; [19]Hospital La Fe, Valencia, Spain; [20]Hospital Puerta de Hierro, Madrid, Spain; [21]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [22]Hospital Gregorio Marañón, Madrid, Spain; [23]Hospital Reina Sofia, Córdoba, Spain

Objective: Differentiated thyroid carcinoma (DTC) is the most frequent histologic subtype of thyroid cancer (TC). However, available data about its natural history in Europe, namely in Spain and Portugal is limited. This study is aimed at characterizing the natural history of the DTC since the diagnosis of the advanced disease, the clinical and temporal patterns of RAI refractoriness, and the potential predictive clinical and/or analytical markers of progression. This study also addresses the contribution of the different medical specialties involved in the management of RAI-refractory DTC patients.

Methods: ERUDIT is a multicenter, observational, longitudinal, retrospective study of patients diagnosed with advanced DTC (aDTC) in Spain and Portugal between January 2007 and December 2012. Patients ≥18 y-o, diagnosed with DTC (papillary, follicular, Hürthle´s cells, mixed, poorly differentiated), with first evidence of locally unresectable or metastatic disease with documented follow-up until 31st August 2017, death, or lost to follow-up were enrolled. Patients with anaplastic or medullary TC, or without the minimum follow-up data for assessment were excluded. Variables analyzed included: patient demographics at aDTC diagnosis, treatment patterns of relapsed and RAI-refractory DTC, and clinical status at the time of data collection.

Results: 240 patients were enrolled in 22 centers in Spain and 1 center in Portugal. Enrolled patients were divided into 4 groups according to their baseline characteristics: de novo metastatic, de novo loco-regional unresectable, recurrent/relapsed metastatic, and recurrent/relapsed loco-regional unresectable disease. Also, an alternative grouping was made based on whether patients became or not RAI refractory during the study period.

Conclusion: By the time of the ETA Congress, initial results of the ERUDIT study will be presented.

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

P2-01-87

AGGRESSIVE RARE SUBTYPES OF THYROID CARCINOMA: CLINICOPATHOLOGY AND PROGNOSIS ANALYSIS OF SEER DATABASE

Qiuyang Zhao[1], *Tao Huang*[1], *Shuntao Wang*[1], *Yiquan Xiong*[1], *Zhi Li*[1], *Zhi Li*[1]

[1]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Objectives: Columnar cell, diffuse sclerosing and insular carcinomas are rare subtypes of thyroid cancer. Published researches focus more on cytology features while their clinical characteristics and prognosis remain incompletely explicit. This study aimed at revealing these by analyzing large amount of patients' information from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: We collected clinical and survival information of 96066 patients, the histology including papillary thyroid carcinoma (PTC), anaplastic thyroid carcinoma (ATC), columnar cell, diffuse sclerosing and insular carcinomas. The clinicopathologic features are listed in the Table. Hazard ratios for thyroid cancer specific mortality of different subtypes were estimated by multivariate cox proportional hazards regression analysis.

Results: We collected 92963 PTC, 1433 ATC, 1104 columnar cell carcinoma, 364 diffuse sclerosing carcinoma and 202 insular carcinomas patients from the SEER database during 2003-2014. Compared to PTC patients, these rare subtypes patients were generally older in age at diagnosis, the tumor size were larger, more likely to occur lymph node and distant metastasis, had significant higher rate of extrathyroidal extension. Rare subtypes patients had higher rate of thyroid cancer specific deaths even though their average survival time were not significant shorter than PTC patients. The multivariate Cox regression indicated that all these subtypes were risk factors for thyroid cancer-specific mortality compared to PTC. Whereas, these aggressive subtypes still held better prognosis than ATC.

Conclusions: The results indicated that these uncommon subtypes indeed tended to present with higher risk factors like large tumor size, extrathyroidal extension, lymph node and distant metastasis, also be associated with worse prognosis than PTC. Therefore, clinical treatment should not be conservative, total thyroidectomy and central lymph node dissection as well as radioactive iodine therapy should be conducted for these patients, other necessary examination for distant metastasis should also be taken into consideration.

P2-01-88

ASSOCIATION OF PREOPERATIVE NEUTROPHIL-TO-LYMPHOCYTE AND PLATELET-TO-LYMPHOCYTE RATIOS WITH MEDULLARY THYROID CANCER CLINICOPATHOLOGICAL FEATURES - RETROSPECTIVE ANALYSIS OF 76 CASES

Ana Figueiredo[1], *Susana Esteves*[2], *Margarida M. Moura*[3], *Joana Simões-Pereira*[4], *Valeriano Leite*[5]

[1]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [2]Unidade de Investigação Clínica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [3]Unidade de Investigação Em Patobiologia Molecular (Uipm), Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisboa, Portugal; [4]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Unidade de Investigação Patobiologia Molecular, Instituto Português de Oncologia de Lisboa Francisco Gentil, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal; [5]Servico de Endocrinologia, Instituto Português de Oncologia de Lisboa, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal

Introduction: Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are two well-established prognostic factors in several types of tumours. However, there are only a few studies analysing their prognostic value in medullary thyroid cancer (MTC), with discordant results. Aims: to evaluate the association of preoperative NLR and PLR with MTC clinicopathological features at diagnosis and to determine if they represent independent predictive factors of lymph-node metastases (LNM).

Methods: Retrospective analysis of all MTC patients submitted to surgery at our institution, between 1990-2016. Statistical analysis was performed using Spearman and Mann-Whitney tests; to evaluate if LNR/PLR represent independent risk factors of LNM we used logistic regression model.

Results: We included 76 patients: mean age at MTC diagnosis was 54.8±17.5 years and 42(56%) were women. Median preoperative calcitonin was 1699 (IQR = 7231.5)pg/mL. Regarding clinicopathological characteristics: median tumor diameter was 25 (IQR = 3.46)mm; 16(21.3%) were multifocal and 26(34.7%) had extrathyroidal extension; *RET* somatic status was analysed in 35(46.7%) patients: 13(37%) harboured a mutation in codons 918/883. LNM was observed in 48(64%). Biochemical cure after surgery was observed in 28(37.3%) patients. The association of NLR and PLR with MTC clinicopathological features are presented in table 1.

	Papillary thyroid carcinoma n = 92963	Anaplastic thyroid carcinoma n = 1433	Columnar cell carcinoma n = 1104	Diffuse sclerosing carcinoma n = 364	Insular carcinoma n = 202
Age	49.36±15.29	61.92±18.24	54.39±16.42	45.07±18.16	61.46±16.37
Tumor size ≤ 20mm	55606 (62.3%)	220 (16.9%)	284 (28.1%)	128 (40.0%)	6 (3.6%)
Lymph node metastasis	18460 (21.0%)	505 (42.5%)	429 (44.7%)	159 (50.8%)	38 (24.4%)
Distant metastasis	1132 (1.2%)	397 (29.5%)	42 (4.2%)	8 (2.5%)	37 (21.4%)
extrathyroidal extension	14847 (16.3%)	806 (61.6%)	536 (53.0%)	145 (44.1%)	73 (43.7%)
Survival time (months)	49.09±33.76	26.41±34.08	46.04±33.74	51.18±36.15	46.95±33.23
Thyroid cancer specific deaths	966 (1.0%)	661 (46.1%)	92 (8.3%)	14 (3.8%)	47 (23.3%)
Hazard ratio for thyroid cancer specific mortality (95% CI)	ref	12.36 (10.65-14.34) p<0.001	1.95 (1.45-2.60) p<0.001	2.18 (1.03-4.60) P = 0.041	2.43 (1.58-3.75) p<0.001

Table 1

	NLR	PLR
Serum calcitonin levels at diagnosis (pg/mL)	ρ = 0.3;p = 0.03	NS
Largest tumor size (mm)	NS	NS
Multifocality	NS	NS
Angioinvasion*	2.7 *vs* 2.1;p = 0.02	NS
Extrathyroidal extension*	2.8 *vs* 2.1;p = 0.02	156.4 vs 134.2; p = 0.04
Somatic *RET* 918/883 codon mutation	NS	NS

*Presence *vs* absence of the characteristic

In the univariate analysis, LNR but not PLR was associated with LNM (OR = 2.69/IC95%:1.50-5.84;p = 0.004); however in multivariate model, when adjusted for other variables, LNR was no longer a predictive factor of LNM (OR = 1.14/IC 95%: 0.65-2.01;p = 0.649).

Conclusion: We present further evidence that NLR is associated with calcitonin at diagnosis and also with aggressive histological characteristics, such as angioinvasion and extrathyroidal extension. However, neither NLR nor PLR represent an independent predictive factor of LNM.

P2-01-89

FACTORS RELATED TO DTC OUTCOME IN ELDERLY PATIENTS

Aleksandra Ledwon[1], *Ewa Paliczka-Cieślik*[1], *Aleksandra Kropinska*[1], *Tomasz Olczyk*[1], *Aleksandra Sygula*[1], *Aneta Kluczewska*[1], *Jozef Roszkosz*[1], *Dorota Kula*[1], *Daria Handkiewicz-Junak*[2]
[1]Maria Sklodowska-Curie Institute – Oncology Center, Gliwice Branch, Gliwice, Poland; [2]Gliwice, Poland

Although age is recognized as poor prognostic factor in thyroid cancer (TC) its influence on diagnostic and therapeutic strategy is still a matter of debate. This is especially true in elderly patients and incidentally diagnosed DTC.

Material and methods: Patients > 65 years of age (n = 365, median age 70) with the diagnosis of non-medullary TC were enrolled into this retrospective study. Median follow-up was 5,4 years. In 57 (15,6%) TC was diagnosed as incidentaloma after surgery due to goiter.

Results: Majority of patients (85%) were diagnosed with differentiated thyroid cancer (DTC). Anaplastic TC (ATC) and unfavorable DTC histopathology were diagnosed in 2% and 13% of patients respectively. Number of incidentaloma was decreasing with increasing age. Surgery was feasible in 98% of DTC and only one ATC. Although age did not influence extent of thyroid surgery with increasing age there was a slight increase in hypoparathyroidism (p = 0.06).

When excluding ATC mean DTC diameter was 20±18 mm. Extrathyroidal extension (ETE) and lymph nodes metastases (LNM) were diagnosed respectively in 35% and 16% patients. There was no difference in tumor diameter between incidentaloma and other tumors but incidentaloma less frequently had ETE and LNM (p< 0.05). With increasing age there was an increased number of patients with unfavorable DTC histopathology, but there was no correlation with ETE or LNM.

During the follow-up 39 (11%) patients were diagnosed with disease recurrence. Histopathology, extrathyroidal extension and lymph nodes metastases correlated with increased risk of recurrence. There was no significant correlation between age or incidentaloma diagnosis and risk of recurrence.

Distant metastases were diagnosed in 50 (14%) of patients and 28 (56%) were radioiodine avid. Radioidine avidity did not correlate with patients age.

Conclusions: If surgery feasible tumor related factors rather than age influence DTC outcome in elderly patients.

P2-01-90

CLINICAL FEATURES AND SURVIVAL ANALYSIS OF 80 ANAPLASTIC THYROID CARCINOMAS FOLLOWED-UP AT A SINGLE CENTRE

Joana Simões-Pereira[1], *Ricardo Capitão*[2], *Edward Limbert*[3], *Valeriano Leite*[4]
[1]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Unidade de Investigação Patobiologia Molecular, Instituto Português de Oncologia de Lisboa Francisco Gentil, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal; [2]Hospital Egas Moniz, Hospital Egas Moniz, Hospital Egas Moniz, Lisboa, Portugal; [3]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa, Francisco Gentil, Portugal; [4]Servico de Endocrinologia, Instituto Português de Oncologia de Lisboa, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal

Introduction: Anaplastic thyroid cancer (ATC) is a rare neoplasm, but presents one of the poorest survival rates among all solid tumours. Aims: to describe ATCs' clinical presentation and therapy modalities and to determinate the prognostic factors associated with disease-specific survival (DSS).

Methods: Retrospective analysis of patients' clinical files with cytological or histological diagnosis of ATC established between 2000 and 2018. Cox regression model was used in the multivariate analysis of DSS.

Results: We included 80 patients in this study. Median follow-up was 80 (IQR 162) days and mean age at ATC diagnosis was 70.6±11.6 years. Tumour diagnosis was primarily retrieved by cytology in 37(46.3%) patients and by histology in the remaining. The most frequent complaints were dysphagia [32(40%)] and dyspnoea [30(37.5%)], and almost half of the population reported a personal history of nodular goitre [37(46.3%)]. A high leucocyte count (>20,000x10^3/μL) was identified in 20(25%) cases. At diagnosis, the majority of the patients were at stage IVC [47(58.8%)]; the disease was confined to the gland only in 5(6.3%) patients. Considering the therapeutic approaches, 33(41.3%) were submitted to surgery, 28(35%) to radiotherapy and 19(23.8%) to chemotherapy [including tyrosine-kinase inhibitors (ITK)]. DSS rates at 1 and 6 months were 71.3% and 23.1%, respectively. Sex, stage at diagnosis, age ≥70, tumour dimension ≥60 mm, surgery, radiotherapy and chemo/TKI therapy were included in the multivariate analysis. Stage at diagnosis – IVB (HR = 4.73, 1.32–17.02/p = 0.017), IVC (HR = 5.67, 1.66–19.34/p = 0.006) –, surgery (HR = 0.25, 0.13–0.48/p<0.001), radiotherapy (HR = 0.18, 0.09–0.38/p<0.001) and chemotherapy/ITK (HR = 0.35, 0.17–0.70/p = 0.003) were significantly associated with DSS.

Conclusion: Although poor, DSS rates may be improved if a multimodality approach is adopted. However, ATCs are still diagnosed at very advanced stages of disease, frequently in older patients, which may lead to a less aggressive therapeutic strategy than the required by these tumours. Furthermore, there's still a lack of effective ATC-directed target treatments.

P2-01-91

CANCER-SPECIFIC SURVIVAL AND CAUSES OF MORTALITY IN DIFFERENTIATED THYROID CANCER PATIENTS: EXPERIENCE OF A SINGLE CENTER

Pei Ing Lee[1], *Yu Yi Huang*[1], *Bor Tau Hung*[1], *Li Ying Juan*[1], *Ya Ling Hsu*[1], *Sing Lian Lee*[1]
[1]Koo Foundation Sun-Yat Sen Cancer Center, Taiwan

Objectives: Most patients with differentiated thyroid cancer (DTC) have a favorable outcome. However, there are still deaths related to DTC. The aim of this study was to analyze the survival rates of DTC patients at our center, and to evaluate the causes of mortality.

Methods: A retrospective review was performed in 1197 DTC patients treated at our center between 1992 and 2015. Cancer-specific survival rates were assessed using Kaplan-Meier method. Causes of death were documented.

Results: After a median follow-up of 7.9 years (range 0.4-26 years), there were 54 mortality cases (4.5%). Among them, 11 patients (0.92%, 6 female and 5 male) died of DTC. According to AJCC TNM 8th edition staging system, there was 1 patient with Stage I disease, 4 with Stage II, 2 with Stage 3, and 4 with Stage 4. Cancer-specific survival rates at 10-years for AJCC stage I to IV were 99.9%, 92.8%, 93.6% and 50% respectively. Five patients had papillary thyroid carcinoma, 5 had follicular type and 1 had insular type. At

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

the time of diagnosis, 4 patients had distant metastasis. However, all patients developed distant metastasis at the time of death, with lung as the commonest site (72%). Also, tumor dedifferentiation was found in 2 patients with papillary histology. The majority of death was due to pulmonary complications related to lung metastasis (7 patients, 63.6%), followed by cord compression by bone metastasis (3 patients, 27.3%) and brain metastasis (1 patient, 9.1%). Thyroglobulin doubling time < 6 months (log rank test, p = 1478), distant metastasis at time of diagnosis or death (log rank test, p = 0.3134) was not associated with shorter disease-specific survival.

Conclusion: Although rare (less than 1%), death-related to DTC occurs. As expected, Stage IV patients had the worst prognosis. The main cause of death was respiratory failure due to lung metastasis.

Keywords: Differentiated thyroid cancer, cancer-specific death

---

P2-01-92

DIETARY IODINE INTAKE, THERAPY WITH RADIOIODINE AND INCIDENCE OF ANAPLASTIC THYROID CARCINOMA

Nikola Besic[1], *Barbara Gazic*[1]
[1]Institute of Oncology, Ljubljana, Slovenia

Background: Anaplastic thyroid cancer (ATC) is one of the most aggressive tumors. The aim of the study was to determine the correlation between a higher dietary intake of iodine and the characteristics of ATC, and to find out how often patients had a history of RAI therapy.

Methods: This retrospective study included 220 patients (152 females, 68 males; mean age 68 years) with ATC who were treated in our country from 1972 to 2017. The salt was iodinated with 10 mg of potassium iodide/kg before 1999, and with 25 mg of potassium iodide/kg thereafter. The patients were assorted into 15-year periods: 1972–1986, 1987–2001, and 2002–2017.

Results: The incidence of ATC (Table 1) decreased after a higher iodination of salt (p = 0.04). Patients are nowadays older (p = 0.013) and have less frequent lymph node metastases (p = 0.012). The frequency of distant metastases did not change over time. The median survival of patients in the first, second, and third periods was 3, 4, and 3 months, respectively (p < 0.05). The history of RAI therapy was present in 7.7 % of patients. The number of patients with a history of RAI therapy did not change over time.

Conclusion: The incidence of ATC in Slovenia decreased because of higher salt iodination.

P2-01-93

THE RISK FACTORS OF RECURRENCE OF PAPILLARY THYROID CARCINOMA AFTER MODIFIED RADICAL NECK DISSECTION

Sungjun Han[1], *Jung Hae Cho*[2]
[1]Catholic University of Korea, Department of Otorhinolaryngology-Head and Neck Surgery, Rep. of South Korea; [2]St. Vincent's Hospital, Catholic University of Korea, College of Medicine, Rep. of South Korea

Objective: Biopsy-proven metastatic lymph node of lateral neck (N1b) is an indication of modified radical neck dissection (MRND) for the management of papillary thyroid carcinoma (PTC). The purpose of this study is to identify the risk factors that can predict the recurrence of N1b PTC after MRND.

Material & Methods: The medical records of 62 PTC patients who underwent total thyroidectomy with central and modified radical neck dissection from 2009 March to 2017 February were retrospectively reviewed.

Table 1. Mean incidence of anaplastic thyroid carcinoma during 15-year periods.

Period	All patients	Mean incidence (range)
1972–1986	95	6.3 (range 2–12)
1987–2001	87	5.8 (range 3-10)
2002–2017	38	2.5 (range 1–10)

Results: Of total 62 patients with follow-up of mean 75 month (21-111 months), 21 patients had a recurrence during follow-up. In multivariate analysis, tumor size > 2cm (HR 1.63; 95% CI, 1.39-1.91; p = 0.02), gross ETE (HR 1.26; 95% CI, 1.07-1.47; p = 0.04), and ratio of positive neck node > 0.50 (HR 2.44; 95% CI, 2.14-2.79; p = 0.01) were risk factors of recurrence of PTC.

Conclusion: Tumor size > 2cm, gross ETE, and ratio of positive neck node > 0.50 are associated with recurrence of PTC after MRND. Following-up patients with these factors after MRND should be more careful with more frequent imagings.

P2-01-94

PROGNOSIS OF CHILDHOOD THYROID CANCER IN A SINGLE CENTER STUDY

Chelghoum Lydia Imane[1], *Baz Ouidad*[1], *Hasbellaoui Fella*[1], *S. Mimouni*[1]
[1]Cancer Center: Pierre and Marie Curie, Algiers, Algeria

Introduction: With a standardized incidence of 0.54 cases per 100,000 persons, differentiated thyroid cancer (DTC) is a rare disease in children and adolescents; it nonetheless concerns ~1.4% of all pediatric malignancies. Furthermore, its incidence is rising. In children and adolescents, DTC almost exclusively manifests in the form of papillary thyroid cancer (PTC).

Objective: The aim of the study is to evaluate clinical aspects of pediatrics patients with thyroid cancer, their treatment and their fellow up.

Material and method: In this retrospective study is based on patients who had been diagnosed with thyroid cancer between 2004 -2018 in our clinic. We included 43 children (10 boys, 33 girls) aged between 05-16 years with no history of exposure to external irradiation. The follow up after surgery consists in a post-operative radioiodine administration with a whole body scintigraphie and TSH-stimulated with Tg (thyroglobuline) measurement.

Results: In this research the used diagnostic procedure has shown mainly a common complaint with growing thyroidal nodule or a persistent lymph node in the neck. Goiter has been found in the 43 patients whereas lymph-adenopathy is observed in 12 patients and only one patient had miliary (lung metastases). In the same context, 35 patients underwent total thyroidectomy surgery and 08 patients went through two times surgery. 28 patients were treated by lymph-node surgery (bilateral or central neck compartment), 42 patients received radioactive iodine treatment except one patient with a micro-carcinoma.

In our study 26 patients have an excellent response whereas 13 patients have biochemical incomplete response and 04 patients present structural incomplete response (recurrence disease).

Conclusion: Compared to adults thyroid cancer in children is more often present with lymph node. However if appropriate treatment is given excellent prognosis is obtained for these young patients.

P2-01-95

DISTRIBUTION OF HISTOPATHOLOGICAL TYPES AND PROGNOSTIC FACTORS FOR THYROID CARCINOMAS: NATIONAL SURVEY (1999-2015)

Tanja Makazlieva[1], *Olivija Vaskova*[1], *Sinisha Stojanoski*[1], *Nevena Manevska*[1], *Vesna Velikj Stefanovska*[2]
[1]Institute of Pathophysiology and Nuclear Medicine, Medical Faculty, University "Ss Cyril and Methodius", Skopje, Macedonia; [2]Institute of Epidemiology and Biostatistics With Medical Informatics, University "Ss Cyril and Methodius", Skopje, Macedonia

Objectives: To present distribution of histhopathological types, survival rate and prognostic influence of four features: age, gender, initial lymph node involvement and histopathological type for survival rate in thyroid carcinomas (TC) diagnosed in Republic of North Macedonia during the period of 17 years (1999 – 2015).

Material and methods: The retrospective analysis of medical data for TC diagnosed at national level from two main state thyroid departments during 1999 – 2015 was performed. The survival rate of all types of TC using Kaplan Meier method was estimated. Univariate Cox - proportional model was applied for evaluation of the predictors for survival rate.

Results: A total number of 422 TC cases were diagnosed, with female/male ratio 3.5/1. Histopathology was available for 386 cases showing distribu-

tion of papillary TC in 79.5%, follicular TC in 10.9%, medullary TC in 4.2% and anaplastic TC in 3.1%. The mean survival time of all TC patients was 212.99 [95% CI (204.6 – 221,4)] months, with longest mean survival time for papillary TC – 223.07 [95% CI (218.6 – 227,5)] months; for follicular TC – 161 [95% CI (138.8 – 184.7)] months; medullary TC – 179 [95% CI (155.5 – 203.3)] months and for anaplastic TC 22.3 [95% CI (10.2 – 34.4)] months. Age, initial lymph node involvement and histopathology were selected by Cox - proportional model as independent significant predictors for survival.

Conclusion: During a survey period, our study revealed continuous increase in TC cases, with papillary TC as most common type. There was an excellent overall prognosis of TC at national level. Age, histopathological type and initial lymph node involvement were found as significant independent prognostic predictive features for survival rate in the evaluated patients. Further evaluation of prognostic influence of different therapy protocols used during analyzed period should be performed.

Cancer Diagnosis

P2-02-96

CLINICAL IMPORTANCE OF THYROGLOBULIN DOUBLING TIME IN PATIENTS WITH PAPILLARY THYROID CARICINOMA TREATED WITH THYROID LOBECTOMY

Ken-ichi Matsuzu[1], *Kiminori Sugino*[1], *Mitsuji Nagahama*[1], *Chie Masaki*[1], *Jyunko Akaishi*[1], *Kiyomi Hames*[1], *Chisato Tomoda*[1], *Akifumi Suzuki*[1], *Takashi Uruno*[1], *Keiko Ohkuwa*[1], *Wataru Kitagawa*[1], *Koichi Ito*[1]
[1]Ito Hospital, Tokyo, Japan

Objective: Thyroglobulin (Tg) doubling time (DT) is recognized as a strong prognostic predictor in patients with papillary thyroid carcinoma (PTC) who undergo total thyroidectomy, although its significance in patients treated with lobectomy remains unknown. The purpose of this study was to evaluate the prognostic impact of Tg-DT on recurrence in PTC patients who underwent thyroid lobectomy.

Methods: Among 1088 consecutive PTC patients who underwent thyroid lobectomy at Ito Hospital between 1986 and 1995, 73 patients developed recurrences in the remnant thyroid gland (n = 6), thyroid bed (n = 2), local lymph node (n = 62), and distant organ (n = 8). These 73 patients with recurrence (Group-R) and another 73 patients without any recurrence (Group-C) were adopted as the study subjects. There were 28 males and 118 females, with a median age of 51 years. Tg-DT (years) was calculated using four serial serum Tg measurements, just before the detection of the recurrence in Group-R and any time during follow up in Group-C. Cases in whom Tg were below the detectable level or showed gradual decreases were expressed as Tg-DT negative. The ratio of Tg-DT positive and negative cases was compared using the chi square test. ROC curve analysis was performed to determine the optimal cutoff point of Tg-DT for prediction of recurrence. Sensitivity and specificity of the predictive ability of Tg-DT were calculated at the optimal cutoff point.

Results: Tg-DT negative cases were significantly more common in Group-C (n = 46) than in Group-R (n = 18) ($p<0.0001$). Tg-DTs in Group-R were: ≤1 (n = 16), >1 and ≤3 (n = 20), and >3 (n = 19), with a median time of 1.8 (0.3-17.8) years. Those in Group-C were: ≤1 (n = 1), >1 and ≤3 (n = 3), and >3 (n = 23), with a median time of 10.2 (0.7-91.2) years. ROC analysis revealed 2.4 years as the optimal cutoff point of Tg-DT. Sensitivity and specificity at the cutoff point of 2.4 years were 47.9% and 97.2%, respectively.

Conclusion: Tg-DT has some role to play in detecting recurrence even in PTC patients treated with lobectomy. The lower sensitivity suggests that although Tg-DT alone is not enough to survey recurrence, a shorter Tg-DT of less than 2.4 years might strongly imply the possibility of recurrence.

P2-02-97

PROSPECTIVE EVALUATION OF THE EUROPEAN THYROID IMAGING AND REPORTING DATA SYSTEM (EU-TIRADS) FOR MALIGNANCY RISK STRATIFICATION OF THYROID NODULES BASED ON HISTOLOGICAL RESULT

Inna Dimitrova[1], *Alexander Shinkov*[1], *Roussanka Kovatcheva*[1], *Radina Ivanova*[2]
[1]Department of Endocrinology, Medical University of Sofia, Bulgaria; [2]Department of Pathology, Medical University of Sofia, Bulgaria

Objectives: To evaluate prospectively the diagnostic accuracy of the Thyroid Imaging Reporting and Data System established by ETA (EU-TIRADS) based on the final histological result.

Methods: For a period of one year, 211 nodules in 157 patients were prospectively classified according to EU-TIRADS and consecutively submitted to ultrasound-guided fine-needle biopsy and to surgery. In patients with cytologically benign nodules, the indications for surgery were nodule size (≥3 cm), multinodularity and compressive symptoms. Thyroid nodules were finally classified as benign and malignant according to the histological result. We evaluated the malignancy rate in each EU-TIRADS category based on histology. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and diagnostic accuracy were calculated using EU-TIRADS 5 as a cut off category.

Results: According to histological result, 99 (46.9%) nodules were malignant and 112 (53.1%) were benign. The mean nodule diameter was 18.94±15.9 mm. The malignancy rate in EU-TIRADS category 2 to 5 was 0%, 0%, 18.2%, 66%, respectively. The difference in malignancy rate between EU-TIRADS category 4 and 5 was statistically significant ($p<0.001$). Sensitivity, specificity, NPV, PPV and diagnostic accuracy were 93.9%, 57.1%, 91.4%, 65.9% and 74.4%, respectively.

Conclusions: EU-TIRADS has high sensitivity and NPV, providing effective malignancy risk stratification of thyroid nodules. EU-TIRADS is a valuable tool in the daily clinical practice.

P2-02-98

STUDY OF LYMPH NODE METASTATIC LOAD USING ONE STEP NUCLEIC-ACID AMPLIFICATION (OSNA) IN PATIENTS WITH PAPILLARY THYROID CARCINOMA. CORRELATION WITH THE PROGNOSTIC CRITERIA FOR LYMPH NODE INVOLVEMENT OF THE AMERICAN THYROID ASSOCIATION (ATA)

Zafon Carles[1], *Temprana Jordi*[2], *Oscar Gonzalez*[3], *Garcia-Burillo Amparo*[4], *Iglesias Carmela*[5]
[1]Hospital Vall D'Hebron, on Behalf of the Consortium for the Study of Thyroid Cancer (Cecat), Diabetes and Metabolism Research Unit (VHIR), Barcelona, Spain; [2]Hospital Vall D'Hebron, Department of Pathology, H. Universitari Vall D'Hebron. UAB, Barcelona, Spain; [3]Deparment of Surgery, Hospìtal Universitari Vall D'Hebron. UAB, Barcelona, Spain; [4]Hospital Vall D'Hebron, Deparment of Nuclear Medicine, Hospital Universitari Vall D'Hebron. UAB, Barcelona, Spain; [5]University Hospital Vall D'Hebron, Department of Pathology, Department of Pathology, Hospital Universitari Vall D'Hebron. UAB, Barcelona, Spain

Introduction: Attempts have been made to characterize the metastatic tumor load (MTL) of lymphatic metastases (LM) to define those patients with papillary thyroid carcinoma (PTC) of higher risk of recurrence. The ATA guidelines define criteria related to the number of lymph nodes affected and their size (ATA-criteria). One Step Nucleic-Acid Amplification (OSNA) is a molecular technique that allows defining the MTL in LM quantitatively by determining the number of mRNA copies of cytokeratin 19 (CK19).

Objective: To analyze by means of OSNA the MTL in patients with LM undergoing to surgical procedure for PTC, and to correlate the result with the ATA-criteria.

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

Material And Methods: All the positive lymph nodes from 42 lymphadenectomies were included. Measurements: weight, diameter, MTL, total number of LM per patient and the total MTL of the lymphadenectomy (TMTL).

Results: 187 of 573 lymph nodes were positive. The median (IQR) of weight and diameter was 0.11 (0.06-0.19) g and 0.5 (0.4–0.8) cm respectively. The median copy of mRNA of CK19 was 4400 (1100-120000). There was a significant correlation between the weight and diameter and the MTL. Significant differences were found in the MTL between the nodes of <0.2 cm and those of >3 cm, and between those of 0.2-3 cm and those of >3 cm, but there were none between those <0.2 cm and those of 0.2-3 cm. There were no differences in the TMTL according to whether there were <5 affected nodes or >5. Finally, the TMTL was at the limit of significance in relation to the presence or absence of at least one node >3 cm.

Conclusions: The presence of metastatic lymph nodes >3 cm is clearly associated with a greater lymph node MTL analyzed by OSNA, while the rest of the ATA-criteria do not show a clear relationship with this parameter.

P2-02-99

ROLE OF REAL TIME ELASTOGRAPHY, STRAIN RATIO AND TIRADS SCORE IN PREDICTING THYROID NODULE

Maha Hussein[1], *Hussein Okasha*[1], *Mona Mansor*[1], *Nermine Sheriba*[2], *Mervat Essam*[1], *Abeer Awad*[1], *Omar Ashoush*[1], *Yasmine Abd El Fatah*[1], *Dalia Abd El Ftah*[1], *Shereen El Saway*[1]
[1]Cairo University, Cairo, Egypt; [2]Ain Shams University

Introduction: Ultrasonography is the most accurate and cost- effective method in diagnosis of thyroid nodules. A practical thyroid imaging reporting and data system (TIRADS) for thyroid nodules have been proposed to classify nodules of the thyroid gland to solve the problem of nodule selection for FNAC. Real time elastography is a method being used in the evaluation of thyroid nodules.

Aim of the work: To assess the role of the strain elastography and TIRADS scoring system in discriminating malignant from benign thyroid nodules.

Material and Methods: a series of 409 patients with thyroid nodules was referred to undergo thyroid ultrasound from 2015 to 2018. Categorization of each nodule according to TIRADS score was from 1 to 5. Strain Ratio (SR) of nodules were semi quantitatively evaluated. Final diagnosis was done either by post thyroidectomy histopathological examination or US guided FNAC.

Results: Our study included 409 patients with thyroid nodules, their mean age was 39± 10 SD, 36 were males and 373 were females. There were 22 malignant nodules and 387 benign nodules. There was statistical significant difference between benign and malignant nodules regarding TIRADS classification, SR, anteroposterior/transverse diameter, the degree of echogenicity, irregularity of the border, presence of calcification and absence of halo sign ($P<0.001$). SR of thyroid nodules showed to be a good discriminator between malignant and benign nodules ($P<0.001$) with 95.2% sensitivity and 86.5% specificity at a cutoff value of > 2.32. For every unit increase in strain ratio the risk of malignancy increase by nearly 2 times. Patients with irregular border have nearly 17 times increased risk of malignancy than those with regular border.

Conclusion: SR proved to be of high significant value in discriminating between benign and malignant nodules in addition to TIRADS classification.

P2-02-100

TRUCUT VERSUS FINE NEEDLE ASPIRATION (FNAC) IN THE DIAGNOSIS OF ANAPLASTIC THYROID CANCER (ATC): WHICH IS THE BEST?

Luigi De Napoli[1], *Aleksandr Aghababyan*[2], *Antonio Matrone*[3], *Piermarco Papini*[1], *Carlo Enrico Ambrosini*[4], *Liborio Torregrossa*[5], *Fulvio Basolo*[6], *Rossella Elisei*[7], *Gabriele Materazzi*[8]
[1]Department of Surgical, Medical, Molecular Pathology and Critical Area, Unit of Endocrine Surgery, University Hospital of Pisa, Department of Surgery, Pisa, Italy; [2]Department of Surgical, Medical, Molecular Pathology and Critical Area, Unit of Endocrine Surgery, University Hospital of Pisa, Italy; [3]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [4]Department of Surgical, Medical, Molecular Pathology and Critical Area, Unit of Endocrine Surgery, University Hospital of Pisa, Pisa, Italy; [5]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [6]Department of Surgical, Medical, Molecular Pathology and Critical Area, Anatomic Pathology Section, University Hospital of Pisa, Italy; [7]Endocrine Unit, Dept of Clin and Exp Medicine, University Pisa, Pisa, Italy; [8]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, University Hospital of Pisa, Pisa, San Giuiano Terme, Italy

Background: ATC is a rare but extremely aggressive thyroid cancer. Preoperative identification of ATC is extremely important to better plan patient management and to avoid useless and potentially dangerous surgical procedures. High-grade histological features (necrosis and mitoses) and cellularity for a definitive diagnosis of ATC can be difficultly recognised only in FNAC sample. Trucut needle biopsy is already used as an alternative to FNAC and mainly to surgical biopsy for preoperative diagnosis of other tumors. The aim of the study is to compare the diagnostic efficacy of trucut biopsy vs FNAC in a large series of locally advanced neck cancers suspicious for ATC from a single centre.

Patients and Methods: between April 2014 and February 2019 69 cases of locally advanced neck cancers suspicious for ATC were collected. All cases simultaneously underwent FNAC and trucut biopsy. Thyroglobulin, TTF-1 and other immunohistochemical citokeratins were analysed in all trucut samples. The epidemiological, clinical and pathological data were collected.

Results: 98.5% (68/69) of trucut samples were diagnostic (27/69, 39.1% for ATC; 23/69, 33.3% for poorly differentiated thyroid cancer, PDTC; 18/69, 26.1% for lymphoma or metastases from other primary tumor). No complications were reported. In FNAC series the cytological diagnosis was ATC in 5/69 (7.2%), PDTC in 26/69 (37.7%), thyroid cancer (Thyr 5) or lymphoma in 23/69 (33.3%) and insufficient for a diagnosis (Thyr 1) in 15/69 (21.8%). Only 19/69 (27.5%) patients underwent a surgical procedure as there was no preoperative evidence of cervical bundle, oesophageal and/or tracheal massive infiltration. In all these 19 cases preoperative trucut diagnosis was confirmed by final histological examination while FNAC was positive for ATC only in 7/19 (36.8%).

Conclusions: Trucut resulted to be a safe and effective procedure to preoperatively diagnose ATC so as to immediately plan the most appropriate treatment for the patient and to avoid surgical biopsy.

P2-02-101

PREDICTORS OF RECURRENT DISEASE IN PATIENTS WITH PAPILLARY THYROID CANCER AND NECK LYMPH NODE METASTASES CURED AFTER INITIAL TREATMENT

Gabriella Pellegriti[1], *Martina Tavarelli*[2], *Rosario Le Moli*[2], *Pasqualino Malandrino*[1], *Maria Ausilia Giusti*[2], *Maria Luisa Arpi*[1], *Giulia Sapuppo*[2]
[1]Endocrinology, Garibaldi Nesima Hospital, Catania; [2]Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Center, Catania, Catania, Italy

Context: Papillary thyroid carcinoma (PTC) has a good prognosis even when spread to the neck lymphnode (LN). However patients with central (N1a) or laterocervical (N1b) LN metastases have more frequently persistent

or recurrent disease. Identifying predictors of disease events is essential to personalize follow-up.

Objective: Assess the role of N1a and N1b in recurrent disease in a series of PTC patients cured after initial therapy.

Design and patients: We retrospectively reviewed a series of 1,084 PTC N1a or N1b patients underwent to total thyroidectomy plus lymphadenectomy: 644 (59.4%) had N1a and 440 (40.6%) N1b metastases; median follow-up was 4.9 yrs. After surgery almost all patients were treated with I131 and later, according to dinamic risk, evaluated to detect patients cured and patients with persistent disease. These latter were excluded from the analysis (53 N1a and 89 N1b patients).

Results: Among N1a patients, 571/591 (96.6%) were disease free after initial treatment for at least one year and 20 (3.4%) showed a recurrence. In N1b patients, 335/351 (95.4%) patients were cured at the beginning and 16 (4.6%) showed recurrent disease. In both group recurrence occurred after a median of about 40 months. Average age was significantly lower in patients with recurrent disease in both N1a and N1b vs disease free patients (35.2 vs 44.7 yrs and 36.5 vs 39.7). In N1a group, minimal extrathyroid extension (mETE) and tumor > 4 cm (T3 category TNM VII ed) were significantly more frequent in recurrence group. These factors were not significant in N1b patients (probably due to the low number of cases). N1a patients had more frequently biochemical recurrence (55%) instead N1b patients structural disease (87.5%).

Conclusions: The risk of recurrence in PTC patients with nodal involvement, cured after initial treatment, is lower than 5%. This risk is slightly higher in N1b patients and is also related to young age and others clinicopathological characteristics of aggressiveness as multifocality and mETE. Identifying more specific predictors of recurrence could help to detect patients really needs more caution.

P2-02-102

ASSESSMENT OF SERUM MIDKINE LEVEL IN BENIGN AND MALIGNANT THYROID NODULES: CAN MIDKINE BE USED AS A MARKER OF THYROID MALIGNANCY?

Maram Aboromia[1], *Nermin Shereba*[2], *Rana Hashem*[2], *Maha Mohamed*[3]

[1]Ain Shams University Hospitals, Internal Medicine, Diabetes, Endocrinology, Cairo, Egypt; [2]Ain Shams University; [3]National Institue of Diabetes and Endocrinology

Background: Thyroid nodules are a common clinical problem. The prevalence of malignancy in thyroid nodules is currently about 5–15%. Fine needle aspiration biopsy (FNAB) has improved preoperative prediction of malignancy but still has disadvantages including operator variability and non-diagnostic reports .Midkine (MK), {a novel heparin-binding growth factor} have been proposed as indicative of malignancy in numerous tumors. Midkine overexpression in thyroid cancer has been reported to be in correlation with clinicopathological features of the tumor, hypothesizing that Midkine might play a role as a biomarker for malignant thyroid nodules.

Aim: The aim of this study is to evaluate the value of serum Midkine as a marker of Malignancy in Patients with Nodular Thyroid Disease.

Methods: The current study included 75 subjects with age ranging from 25-80 divided into 25 with malignant thyroid nodule (group A) and 25 with benign thyroid nodule (group B) and 25 healthy subjects as a control group (group C). fT3,fT4, TSH and Serum Midkine levels were assessed. Subj ects were submitted to Neck Ultrasonography and Fine needle aspiration biopsy.

Results: On comparing the three studied groups, threre was a high statistical significant difference regarding plasma Midkine levels ($p < 0.001$), being higher in Group A (malignant nodule), Mean (1.127±0.527) than Group B (Benign nodule) Mean (0.536±0.301) and than Group C (Control) Mean (0.366±0.230) Midkine level was significantly higher among patients with papillary carcinoma mean (1.208±0.525). Midkine level was also higher in those nodules with irregular borders and those with microcalcifications ($p<0.001$). Midkine level showed a significant positive correlation with age ($r = 0.317$), and with nodular size ($r = 0.306$) $p < 0.05$.

Conclusions: Our results suggests that Serum Midkine could potentially be used as a useful marker of thyroid malignancy in patients with thyroid nodular disease

Keywords: Serum Midkine, benign/malignant thyroid nodules, thyroid malignancy.

P2-02-103

THE DIAGNOSTIC VALUE OF FNAB CYTOLOGY AND THYROGLOBULIN MEASURMENT IN WASHOUT FLUID IN THE INVESTIGATION OF LYMPH NODE METASTASIS OF DIFFERENTIATED THYROID CANCERS

Anar Aliyev[1], *Aziz Aliyev*[2], *Rashad Ismayilov*[3], *Elnur Mehdi*[3], *Aysel Salmanova*[4], *Mehmet Akif Ciftcioglu*[4]

[1]Department of Nuclear Medicine, Department of Thyroid Center, Baku, Azerbaijan; [2]Head and Neck Surgery Department, Azerbaijan National Center of Oncology, Baku, Azerbaijan, Baku, Azerbaijan; [3]Department of Nuclear Medicine, Azerbaijan National Center of Oncology, Baku, Azerbaijan; [4]Department of Patology, Azerbaijan National Center of Oncology, Baku, Azerbaijan

Objectives: In addition to fine-needle aspiration biopsy (FNAB), thyroglobulin measurement in washout fluid (FNA-Tg) has been shown to be useful to investigate lymph node metastases of differentiated thyroid cancers (DTC), in recent years. However, the cut off value for the test is not exactly clear yet. The aim of this study was to evaluate the diagnostic utility of cytology and Tg measurement in the lymph node, and also to determine the threshold value of the FNA-Tg test.

Materials and methods: A total of 78 patients with suspected metastatic lymph nodes who admitted to our department in 2018 were included in this study. 31 patients were excluded from the study for various reasons. Twelve out of 47 patients were diagnosed with DTC after thyroidectomy and suspected of metastatic lymphadenopathy in their follow-up. 35 patients were the first to present with suspicion of metastatic DTC. The cytology, Tg washout and post-operative pathology results of these patients were evaluated and the cut-off value was taken by the receiver operating characteristic (ROC) analysis.

Table 1 Clinical and histopathological characteristics of N1a and N1b patients

	N1a patients			N1b patients		
	All	Disease free	Recurrent disease	All	Disease free	Recurrent disease
	591	571	20	351	335	16
Age at diagnosis (median)	40,0	44,7	35,2	39,6	39,7	36,6
Gender F/M	480/111	406/109	18/2	243/108	232/103	11/5
Histotypes	551/40	531/40	20/0	332/19	318/17	14/2
T1a	201	197	4	123	118	5
T1b	151	147	4	78	74	4
T2	61	59	2	26	23	3
T3	178	168	10	120	116	4
T4	0	0	0	4	4	0
Multifocality	119	118	1	80	77	3

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

Results: After pathology examination, 41 patients were malignant and 6 patients had benign results. Median FNA-Tg value obtained from malignant patients was 10643 ng/ml and in benign patients was 4.4 ng/ml. When FNA-Tg was 35.9 ng/ml, sensitivity was 95% and specificity was 83% for malignant and benign differentiation ($p<0.0001$). When we compared the results of FNAB cytology with the pathology, the sensitivity of the cytology was calculated as 62% and the specificity was 100% ($p<0.01$). When FNA-Tg values and FNAB cytology results were evaluated together, sensitivity and negative predictive value (NPV) were calculated as 100% ($p<0.0001$).

Conclusions: Although FNA-Tg is a fast, easy, inexpensive and safe method, it helps the FNAB cytology especially in the evaluation of cystic necrotic metastatic lymph node. It also provides additional information for the clinician to map a roadmap to patients scheduled for surgery.

P2-02-104

ATYPIA OF UNDETERMINED SIGNIFICANCE/ FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE AND RISK OF MALIGNANCY: A CYTOLOGICAL APPROACH

Eugénia Silva[1], *Rute Ferreira*[1], *Clara Cunha*[1], *Catarina Saraiva*[1], *Clotilde Limbert*[1], *Ricardo Capitao*[1], *Catarina Roque*[1], *Cátia Ferrinho*[1], *Manuela Oliveira*[1]

[1]Endocrinology Department, Hospital Egas Moniz, Lisboa, Portugal

Introduction: The atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) from the Bethesda classification for fine needle aspiration of thyroid nodules (FNA) remains a challenging category. Some studies report an association between the presence of certain cytological characteristics and the risk of malignancy.

Objective: Analyze cytological characteristics in AUS and its association with malignancy.

Methods: We performed a retrospective analysis at our institution, between January 2015 and December 2018. Clinical records of patients submitted to FNA with AUS diagnosis, and subsequently undergoing thyroid surgery, were investigated for the presence of nuclear atypia, architectural atypia, and Hurthle cells atypia in the cytological study. The diagnosis of benignity or malignancy in the histological result was also investigated. In the statistical analysis, the variables were compared using the chi-square test and the t-student test. Statistical significance was accepted at $p<0.05$.

Results: 124 thyroid nodules were obtained in 123 patients, 84,6% of which were women, with a mean age of 58.6±11.3 years. Approximately 37.4% of patients underwent right lobectomy, 35% a total thyroidectomy and 27.6% a left lobectomy. The mean nodule size was 2.9 ± 1,1 cm. From the 124 surgically resected nodules, 29 % were malignant and 71% were benign. Refering to cytological characteristics, we found that nuclear atypia was present in 94.4% of the malignant nodules and in 75% of the benign ones. We identified follicular aggregates in 100% of the malignant nodules and in 89.8% of the benign ones. Hurthle cell atypia was present in 55.6% of the malignant nodules and in 45.5% of the benign ones. The prevalence of nuclear atypia was statistically significant ($p = 0.012$) in malignant nodules.

Conclusion: In our sample, nuclear atypia was a significant indicator of malignancy in cytologically indeterminate thyroid nodules, suggesting that it might be useful in the therapeutic decision.

P2-02-105

BIOCHEMICAL DETECTING OF RECCURENCE OF DIFFERENTIATED TYHROID CANCER (DTC)

Aleksandra Kropinska[1], *Daria Handkiewicz- Junak*[1], *Aleksandra Ledwon*[1], *Ewa Paliczka- Cieślik*[1], *Tomasz Olczyk*[1]

[1]M. Sklodowska- Curie Institute Oncology Centre, Gliwice Branch, Gliwice, Poland

In patients with DTC, the assessment of thyroglobulin (Tg) concentration is one of the basic elements of follow up. The relapse of DTC occurs only in about 5% of cases. This implies the need for a sensitive and specific marker to avoid unnecessary diagnostic procedures in the majority of patients and to indicate a small group with the highest risk of relapse. Thyroglobulin testing is the gold standard, but the result may be false negative in the presence of antithyroglobulin antibodies (TgAb).

The aim of the study was to analyze Tg and TgAb levels in DTC patients preceding clinical diagnosis of relapse and to estimate significance of TgAb elevation.

Material and methods: 96 patients with DTC with recurrence of cancer in 2007-2009. 76% diagnosed with papillary, 7% follicular, 15% oxyphilic, 2% poorly differentiated cancer. 86,5% of patients underwent total thyroidectomy, 88,5% received 131I treatment. 54% had lymph node metastases,11% had distant metastases at the diagnosis. There were 2 cancer related deaths.

Results: The recurrence occurred after 1,1-185,1 months (median 42,6). In 40,6% of patients had more than one relapse.In 76% the locoregional relapse, in 24% distant metastases occured.

In 73% the relapse was preceded by an increase in serum thyroglobulin level.

In 12,5% of patients TgAb were present. In this group 60% of the patients maintained indetectable Tg level and high titre of TgAb. In 40% of this group the relapse was preceded by an increase in both Tg and TgAb. Only in one case DTC progression was connected with elevation of TgAb without increasing of Tg level.

Conclusions: Elevation of Tg level were the first signal of relapse in 73% of examined group, 12% of relapses was diagnosed only in neck US, without elevation of Tg level. Elevation of anti-Tg titre may be a rare first symptom of reccurence.

Cancer Risk Stratification

P2-03-106

RISK STRATIFICATION IN PEDIATRIC DIFFERENTIATED THYROID CANCER: IS TOTAL THYROIDECTOMY NECESSARY AT ANY RISK?

Kiminori Sugino[1], *Mitsuji Nagahama*[1], *Wataru Kitagawa*[1], *Keiko Ohkuwa*[1], *Takashi Uruno*[1], *Ken-ichi Matsuzu*[1], *Akifumi Suzuki*[1], *Chisato Tomoda*[1], *Kiyomi Hames Yamada*[1], *Junko Akaishi*[1], *Chie Masaki*[1], *Koichi Ito*[1]

[1]Ito Hospital, Tokyo, Japan

Objective: In the recent American Thyroid Association (ATA) guideline for adult differentiated thyroid carcinoma (DTC) patients, risk stratification is clearly defined and hemithyroidectomy is acceptable for low risk DTC. However, risk stratification for pediatric DTC patients in ATA guideline is not very practical and total thyroidectomy is recommended for all patients with any risk. The aim of this study was to attempt risk stratification based on our experience and to consider the appropriate extent of thyroidectomy, especially for low-risk DTC in the pediatric population.

Methods: Subjects comprised 171 patients with DTC ≤ 18 years old, including 70 patients < 16 years old and 150 females, who underwent initial surgery in our hospital between 1979 and 2014. Underlying pathology was papillary carcinoma in 147 patients and follicular carcinoma in 24. Risk factors related to survival were analyzed and risk stratification was performed.

Results: Two patients died of the disease and 34 patients (20%) experienced disease recurrence. At initial surgery, 45 patients (26.3%) had apparent lymph node metastases (cN1) and 18 (10.5%) showed distant metastases (M1). Because a small number of patients died of the disease, risk factors related to disease-free survival (DFS) were analyzed in 153 patients after excluding M1. Significant factors according to multivariate analyses were cN1, extrathyroidal invasion and number of metastatic lymph nodes. According to the risk factors, subjects were divided into 3 categories: low risk (no risk factors, n = 89): intermediate risk (1 risk factor, n = 37) and high risk (³ 2 risk factors, n = 27). Ten-year DFS in the low-, intermediate-, and high-risk groups were 96.1%, 82.6%, and 48%, respectively. Only 12% of low-risk patients underwent total thyroidectomy.

Conclusion: Low-risk patients showed excellent DFS, although most did not undergo total thyroidectomy.

P2-03-107

IMPACT OF EXTRANODAL EXTENSION ON RISK STRATIFICATION IN PAPILLARY THYROID CARCINOMA

Hye In Kim[1], *Jun Park*[2], *So Young Park*[3], *Sun Wook Kim*[4], *Jae Hoon Chung*[5], *Tae Hyuk Kim*[6], *Young Lyun Oh*[6]
[1]Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon-Si, Rep. of South Korea; [2]Samsung Medical Center, Seoul, Rep. of South Korea; [3]Samsung Medical Center, Internal Medicine, Seoul, Rep. of South Korea; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Rep. of South Korea; [5]Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Seoul, Rep. of South Korea; [6]Samsung Medical Center

Background: The current American Thyroid Association (ATA) risk stratification system for papillary thyroid carcinoma (PTC) incorporates the number and size of positive lymph nodes (LNs), but places less weight on extranodal extension (ENE). We investigated how to incorporate ENE into the current system to predict recurrence better in PTC N1 patients.

Methods: A total of 369 N1 PTC patients without distant metastasis were enrolled. We identified the combination of number of positive LNs and LNs with ENE that had the highest C-index in multivariable Cox proportional hazard models. ENE number was incorporated into the current system considering the recurrence rate and unadjusted and adjusted hazard ratios of subgroups. Kaplan-Meier curves for recurrence based on current and alternative systems were compared by log-rank test.

Results: Recurrence rate for the subgroup with ≤5 positive LNs and 1-3 ENEs (7/61, 11.5%) was higher than that of the subgroup with ≤5 positive LNs without ENE [(5/129, 3.9%), adjusted HR 3.42 (0.99-11.75), P = 0.050]. In contrast, adjusted HRs of the subgroup with >5 positive LNs and 1-3 ENEs [2.33 (0.52-10.35)] or with ≥4 ENEs [3.86 (1.05-14.17)] were not higher than those of subgroup with >5 LNs without ENE [4.47 (1.16-17.19)]. Incorporating ENE into the current system as an intermediate risk group yielded a lower log-rank P-value (0.05 vs. 0.01) than current system.

Conclusions: The presence of ENE in low volume LN metastasis confers an intermediate risk of recurrence. Incorporating ENE into the current system allows more accurate decisions regarding further management of PTC N1 patients.

P2-03-108

HISTOLOGY FEATURES ARE MORE IMPORTANT THAN PERSISTENTLY ELEVATED ANTI-TG ANTIBODIES FOR DISEASE COURSE IN PATIENTS WITH DIFFERENTIATED THYROID CANCER (DTC)

Olga Karapanou[1], *George Simeakis*[2], *Katerina Saltiki*[3], *Stylianos Tsagarakis*[4], *Maria Alevizaki*[5], *Barbara Vlassopoulou*[6]
[1]Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece; [2]Endocrine Unit, Dept Clinical Therapeutics, Medical School National Kapodistrian University, Athens, Greece; [3]Clinical Therapeutics, Athens, Endocrine Unit, Dept Clinical Therapeutics, Medical School National Kapodistrian University, Athens, Greece; [4]Endocrinology, Evangelismos Hospital, Department of Endocrinology Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece; [5]Alexandra Hospital, Kapodistrian University of Athens, Endocrine Unit, Dept Clinical Therapeutics, Medical School National Kapodistrian University, Athens, Greece; [6]Evangelismos Hospital, Dept of Endocrinology, Diabetes, Psychico, Athens, Greece

Objectives: Anti-thyroglobulin (anti-Tg) antibodies, present in 20-25% of DTC patients, interfere with Thyroglobulin measurements posing a challenge in the follow-up. Aim of this study was to identify the role of clinical-histological factors that may affect anti-Tg persistence and factors that influence the disease outcome in patients with positive anti-Tg.

Methods: We retrospectively studied 234 thyroidectomized DTC patients, with positive anti-Tg at diagnosis(males17.9%,n = 42). Age at diagnosis was 46.0±14.4yrs (range:14-82yrs). 38/234 (16.2%) underwent lymph-node dissection, 221/234 (94.4%) received radioiodine (RAI) ablation. Median follow-up was 5yrs (range: 1.5-32yrs). Patients were divided into two subgroups according to the anti-Tg state at the end of the follow-up period; those whose anti-Tg became undetectable (anti-Tg-NEG) and those whose anti-Tg remained positive (anti-Tg-POS).

Results: Anti-Tg-POS patients(n = 80, 34.5%) compared to anti-Tg-NEG had more frequently lymph-node infiltration (36.3%vs19.1%, p = 0.006), soft-tissue invasion (35.0%vs21.7%, p = 0.03), classical or poorly-differentiated DTC and increased tumor size (p = 0.001). Sex, multifocality, capsular invasion, stage and distant metastases at diagnosis, previous thyroid disease history did not differ. Anti-Tg-POS patients received higher ablative (85±33vs76±20 mCi, p = 0.017) and total RAI dose (198±295vs86±56 mCi, p<0.001). RAI-ablation after the first surgery, additional lymph-node dissections and/or further RAI-administration did not lead to anti-Tg elimination (p<0.001). They had more frequently structural disease persistence/progression compared to anti-Tg-NEG (remission 78.8%vs96.1%, persistence 13.8%vs3.3%, progression 7.5%vs0.7%,p<0.001). In Cox-proportional-hazard analysis when age, size, lymph-node infiltration, soft-tissue invasion, histological type and anti-Tg positivity were taken into account, the only predictors of lack of disease progression were tumor size and soft-tissue invasion (p≤0.003).

Conclusions: Lymph-node involvement as well as classic and poorly-differentiated DTC adversely affect anti-Tg decline in anti-Tg-POS DTC patients. Further lymph-node dissection and/or additional RAI-administration do not seem to affect anti-Tg elimination. Anti-Tg positivity during follow-up seems to correlate with disease persistence although tumor size and extrathyroidal extension are the main predictors of disease progression.

P2-03-109

PREVIOUS TNM T3 CATEGORY OF PAPILLARY THYROID CANCER: TUMORS WITH MINIMAL EXTRATHYROID EXTENSION VS TUMOR > 4 CM HAVE A DIFFERENT OUTCOME?

Giulia Sapuppo[1], *Martina Tavarelli*[2], *Ilenia Marturano*[3], *Romilda Masucci*[4], *Giacomo Lucio La Rosa*[2], *Gabriella Pellegriti*[3]
[1]Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Center, Catania, Italy; [2]Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Center, Catania, Italy; [3]Endocrinology, Garibaldi Nesima Hospital, Catania; [4]Department of Surgical Oncology, Garibaldi-Nesima Medical Center, Catania, Italy

Context: PTCs are generally associated with an excellent prognosis but some anatomopathological characteristics increase the risk of disease events, often with no impact on mortality. In the VII TNM ed T3 category included both tumors with minimal extrathyroid extension (mETE) and tumors>4 cm (LT). In the VIII ed TNM mETE has no impact in determining T category instead LT fall in T3a. Conversely in ATA risk stratification mETE fall in intermediate risk and LT without aggressive characteristics in low risk. This issue still needs further validation by prospective studies evaluating the risk of disease events in these categories of patients.

Objective: To assess the risk factors and the impact of mETE and LT on PTC patients' outcome.

Design and patients: Retrospective consecutive series of 930 patients (median f-up 4.9 yrs) undergone thyroidectomy for PTC and included in T3 category with TNM VII ed. Patients were subdivided into mETE and LT.

Results: Of 930 patients,835 (89.8%) showed mETE and 95 (10.2%) were LT. Average age was similar (47.4 yrs in mETE vs 47.9 in LT). The male gender was more prevalent in LT vs mETE (F/M = 1.9/1 vs 3.6/1). Multifocality was more frequent in mETE category. Regarding N status, N0 and N1a were significantly more frequent in mETE category, Nx in LT and no difference were in N1b. 95% of mETE and 84% LT were treated with I^{131}. At last follow-up visit 656/835 (78.6%) mETE patients were disease free vs 39/56 (69.6%) in LT (p<0.001). In mETE 68/179 (37.9%) had biochemical and 111 (62.3%) structural disease (64 distant metastases);in LT 10/39 (25.6%) had biochemical and 29 (74.4%) structural disease (23 distant metastases).

Conclusions: Our data confirm that the previous T3 category was heterogeneous for histopathological and clinical aggressiveness and worse long-term clinical evolution in LT (more frequent in male patients and N1b). Furthermore (even if in the new TNM mETE has no impact on T and stage), it is associated with a significant percentage of disease events (30% in our series). Therefore this remains a topic that needs further investigation.

Table 1 Clinical and histopathological characteristics of 2,814 patients operated for papillary thyroid cancer

	mETE	>4 cm
Patients (n.)	835	95
Age (y)		
median	47.4	47.9
Gender		
F/M ratio	3.6/1.0	1.9/1*
N status (N)		
N0	147	13*
Nx	322	54*
N1a	204	13*
N1b	162	15
Multifocality	561	10*
Disease free	656	56*

*P<0.05

P2-03-110

THE PRESENCE OF TALL CELLS > 10% IN A CLASSICAL VARIANT OF PAPILLARY THYROID CARCINOMA (CV-PTC) MAKES ITS AGGRESSIVENESS SIMILAR TO THAT OF TALL CELL VARIANT (TCV-PTC)

Antonio Matrone[1], *Carla Gambale*[1], *Liborio Torregrossa*[2], *Laura Valerio*[1], *Laura Agate*[1], *David Viola*[1], *Eleonora Molinaro*[1], *Fulvio Basolo*[2], *Paolo Vitti*[1], *Rossella Elisei*[1]

[1]Department of Clinical and Experimental Medicine, Endocrine Unit, University of Pisa, Italy; [2]Department of Surgical, Medical, Molecular Pathology and Critical Area, Anatomic Pathology Section, University Hospital of Pisa

Background: The recent WHO classification (2017) reports that the definition of TCV-PTC requires >30% of tall cells (TC), differently from the previous definition of >50% (2004 WHO classification). However, a Japanese study showed that PTC with >50% TC had a worse outcome than PTC with 30–49% TC. Recently, an Italian consensus recommends 10% TC as cut-off for TCV-PTC definition. Therefore, the diagnostic criteria for TCV-PTC definition need further verifications.

Aim: 1) To evaluate the difference of presentation and outcome among CV-PTC, TCV-PTC (with ≥50% TC) and CV/TC-PTC (with <50% TC); 2) To identify the % of TC that impacts on the prognosis.

Methods: We evaluated 610 patients with PTC, divided in: group-A (CV-PTC; 417/610–68.4%), group-B (CV/TC-PTC; 64/610–10.5%) and group-C (TCV-PTC; 129/610–21.1%).

Results: No difference were found in the majority of epidemiological and clinical features with the exception of an older age in group-C (p = 0.02). At variance, neoplastic emboli were more frequent in group-B (23.4%) vs C (13.2%) and A (9.8%). Similarly microscopic extra-thyroidal-extension (ETE) was more present in group-C (73.6%) vs B (57.8%) and A (39.6%) (p<0.01). Stage-I was less frequent in group-C (82.2%) vs B (96.9%) and A (94.7%) (p<0.01). Lower activities of ^{131}I were used in group-A (87.1%), vs B (79.7%) and C (74.4%) (p<0.01).

After 6 years, we found more structural persistent disease (StR) in group-B (13.1%) vs C (8.9%) and A (4.9%) (p<0.01). Regarding the impact of %TC on the prognosis, only CV/TC-PTC with <10% TC had no StR at the end of follow-up while no major differences in StR was found among cases with a 20-40% of TC (all together 14.5% of StR).

Conclusions: the presence of TC, also if <50% but >10% identifies a subgroup of PTC with a biological behavior more similar to TCV-PTC than CV-PTC. Our findings are in line with the indications of the Italian consensus that 10% of TC is enough to define the TCV-PTC.

P2-03-111

THE UTILITY OF HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY IN PROGNOSIS OF POORLY DIFFERENTIATED THYROID CANCER BASED ON A SERIES OF POLISH PATIENTS

Agnieszka Walczyk[1], *Janusz Kopczyński*[2], *Danuta Gasior-Perczak*[3], *IWONA PALYGA*[1], *Artur Kowalik*[4], *Magdalena Chrapek*[5], *Maria Hejnold*[2], *Stanisław Góźdź*[6], *Aldona Kowalska*[7]

[1]Department of Endocrinology, Holycross Cancer Centre, Kielce, Poland; [2]Department of Surgical Pathology, Holycross Cancer Cantre, Kielce, Poland; [3]Holycross Cancer Centre, Department of Endocrinology, Holycross Cancer Centre, Kielce, Poland; [4]Department of Molecular Diagnostics, Holycross Cancer Centre, Kielce, Poland; [5]Faculty of Mathematics and Natural Sciences, Jan Kochanowski University, Kielce, Poland; [6]Department of Clinical Oncology, Holycross Cancer Centre, The Faculty of Health Sciences, Jan Kochanowski University, Kielce, Poland; [7]Holycross Cancer Centre, Jan Kochanowski University, Kielce, Poland

Background: Poorly differentiated thyroid cancer (PDTC) is a rare, but aggressive thyroid cancer (TC) and a main cause of death from non-anaplastic follicular cell-derived TC. The Turin criteria for PDTC are well defined, but it is still debatable which features reported by surgical pathologists could be useful not only as diagnostic, but also as prognostic factors. It is crucial for clinicians to assess the risk of PDTC-death, because it provides the optimal therapeutic approach.

Material and Methods: The retrospective analysis of 49 consecutive PDTC patients treated in a single oncological centre, 2000-2018. We analysed numerous histopathological (HP) features, and the expression of conventional markers by immunohistochemistry (IHC) which are reported routinely in surgical reports, and some pathological parameters such us the presence of atypical mitoses, amount of necrosis, or IMP3 immunostaining, which are not usually determined in surgical reports. The relationship between HP/IHC features of PDTC and the survival of PDTC-patients was evaluated. Overall survival (OS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier method.

Results: Of 49 PDTC-cases, 34 (69%) were insular with the median of PD-area of 95% (range 1-100) and 30 (61.2%) presented the predominant (>50%) insular pattern of growth. During a median follow-up time of 57 months (range 1-187), 23 (46.9%) died, but 20 (40.8%) died of PDTC. The 5-,10-year OS, and 5-,10-year DSS were 60.6%, 53%, and 64.3%, 56.3%, respectively. In a univariate analysis, the risk of PDTC-death was significantly higher in the patients with a tumor size>4cm, presence of atypical mitoses, Ki67>5%, and thyroglobulin (Tg) negative immunostaining. In a multivariate analysis, the only patients with atypical mitoses and Tg-negative IHC were at a higher risk of death.

Conclusions: In PDTC-patients, especially with a prominent insular pattern of growth, an additional HP feature such as a presence of atypical mitoses could be considered to be included in a surgical report for a better assessment of the risk of PDTC-death.

P2-03-112

RESPONSE TO TREATMENT AND SURVIVAL IN A DIFFERENTIATED THYROID CARCINOMA COHORT AFTER TNM MODIFICATION

Emma Anda Apiñariz[1], *Patricia Munarriz*[2], *Javier Pineda Arribas*[2], *Marta Toni Garcia*[2], *Ana Irigaray*[2], *Juan Manuel Zubiría*[2]

[1]Endocrinology and Nutrition Service, Complejo Hospitalario de Navarra, Pamplona, Spain; [2]Complejo Hospitalario de Navarra, Pamplona, Spain

Objective: The new 8th edition of the TNM classification implies reclassifying a third of patients with differentiated thyroid carcinoma (DTC). In our study we want to evaluate how this change impacts the classification based on risk of recurrence and response to treatment.

Methods: Retrospective cohort review of patients with DTC treated in the Complejo Hospitalario de Navarra.

Results: A total of 913 patients who were diagnosed and followed in our hospital were included (79.1% women, average age of 45.8 years). Following the TNM 8th edition, 30.8% of the patients were reclassified. When we

compared it with the TNM 7th edition, stage I increased from 64.3% to 85%, and the rest of stages decreased (stage II decreased from 15.5% to 11.8%, stage III from 12.1% to 0.7% and stage IV from 7.8 to 2.5%).

After a mean follow-up of 127 months, comparing the TNM 7th classification with the 8th, survival of patients in stage I remained on 97-99%, decreased from 91% to 62.5% in stage III and decreased from 65% to 58.3% in stage IV.

The response to treatment showed a percentage of patients with incomplete structural or biochemical response that went from 19.3% to 43.3% in stage II, from 23.9% to 83.7% in stage III, and from 71% to 100% in stage IV.

Conclusions: In our cohort, 30.8% of patients were reclassified when using the 8th edition of the TNM. This had an impact on both 10-year survival and the response to long-term treatment in stages II, III and IV.

P2-03-113

DIFFERENCE BETWEEN STIMULATED AND SUPPRESSED THYROGLOBULIN IN RESPONSE TO THERAPY RECLASSIFICATION

Chae Moon Hong[1], *Ju Hye Jeong*[1], *Sang-Woo Lee*[1], *Shin Young Jeong*[1], *Byeong-Cheol Ahn*[1], *Jaetae Lee*[2]

[1]Kyungpook National University, Kyungpook National University Hospital, Daegu, Rep. of South Korea; [2]Kyungpook National University Hospital, Daegu, Rep. of South Korea

Purpose: Dynamic risk stratification (DRS), response to therapy reclassification, is widely used for follow-up of thyroid cancer patients. However, there is only few studies about difference between DRS using stimulated thyroglobulin (off-Tg) and suppressed thyroglobulin (on-Tg).

Methods: We retrospectively reviewed DTC patients who underwent total thyroidectomy and radioactive iodine (RAI) ablation between Jan-2000 and Feb-2002. ATA risk stratification and TNM staging (AJCC 8th) were performed. And initial DRS using both off-Tg and on-Tg were performed 6-15 months after high-dose RAI therapy. All the patients were under TSH suppression. Median follow-up period after RAI ablation was 15.6 ± 5.4 years.

Results: Finally, 411 patients were included in this study. 80 patients were low risk, 165 were intermediate and 166 were high-risk according to ATA risk stratification. At initial DRS (off-Tg/on-Tg), 176/156 patients were excellent response (ER), 130/159 were indeterminate response (IR), 62/53 were biochemical incomplete (BI), and 43/43 were structural incomplete (SI) and. Progression rates of DRS using off-Tg/on-Tg were 1.7%/5.8% in ER, 15.4%/12.6% in IR, 43.5%/39.6% in BI, 69.8%/69.8% in SI. Progression rate of patients with ER using both off-Tg and on-Tg is 2.6% (3/115), that of patients with ER using off-Tg and IR using on-Tg is 0% (0/60), IR using off-Tg and ER using on Tg is 10.8% (4/38), IR using both off-Tg and on-Tg is 16.3% (14/86). These four groups showed significant difference of progression free survival (PFS) (p<0.001). During the follow-up, 41 patients were down-staged to ER (from IR/BI) or IR (from BI) using off-Tg without any kind of procedures, and only 1 patient (2.4%) showed progression. And 30 patients were down-staged using on-Tg during follow-up and only 1 patient (3.3%) showed progression.

Conclusion: Off-Tg shows better prognostic value than on-Tg on DRS. The patients who down-staged without any procedure showed excellent prognosis.

P2-03-114

THE IMPACT OF HISTOLOGIC VASCULAR INVASION IN PAPILLARY THYROID CARCINOMA

Liliana Fonseca[1], *Diana Borges Duarte*[1], *Catarina Pereira*[1], *Ana Amado*[1], *Patrícia Gouveia*[2], *Rita Ribeiro*[3], *André Carvalho*[1], *Fátima Borges*[1], *Cláudia Freitas*[1], *Helena Cardoso*[1]

[1]Endocrinology Department, Centro Hospitalar Universitário Do Porto, Portugal; [2]Nuclear Medicine Department, Centro Hospitalar Universitário Do Porto, Portugal; [3]Centro Hospital e Universitário Do Porto, Portugal

Background and aims: Papillary thyroid carcinoma prognosis comprises several clinicopathological features such as sex, age, tumor diameter, capsule invasion and regional and distant metastasis at initial diagnosis. However, vascular invasion can also be very important. This study aims to assess the impact of histologic vascular invasion in papillary thyroid carcinoma prognosis.

Methods: Retrospective observational study of patients with papillary thyroid carcinoma admitted in our Thyroid Cancer Unit, between January 1960 and December 2016. We evaluated 905 patients with papillary thyroid carcinoma; only 275 of them had information about histologic vascular invasion on their pathological reports. We compared the outcomes of both groups with and without vascular invasion.

Results: Of the 275 patients, 18.5% (n = 51) had vascular invasion; they were younger (mean age = 49.3y vs 51.3y, p = 0.004), had larger tumors (median: 19mm vs 12 mm, p < 0.001) and more frequent extraglandular invasion (54.0% vs 17.1%, p<0.001), regional lymph node (29.8% vs 12.6%, p = 0.003), distant metastasis (10.9% vs 1.9%, p = 0.003) and extrathyroidal invasion (54.0% vs 17.1%, p< 0.001) at diagnosis.

Patients without vascular invasion had most favourable cancer staging (TNM system): 92.4% had stage I versus 78.4% in patients with vascular invasion (p = 0.003).

Vascular invasion was associated in univariate analysis with a significant increase of regional lymph node [OR 3.0 (IC95% 1.4 – 6.2, p = 0.04)] and distant metastasis [OR 6.3 (IC95% 1.6 – 24.6, p = 0.008)].

Conclusion: Vascular invasion was associated with poorer outcomes. This feature should be included in the initial evaluation of papillary thyroid carcinoma's stratification risk concerning postoperative treatment.

P2-03-115

THE INTEGRATIVE PREDICTIVE MODEL FOR THYROID CANCER RISK STRATIFICATION

Sophia Novosad[1], *Narine Martirosyan*[1], *Larisa Minushkina*[2], *Nina Petunina*[1]

[1]Sechenov University, Moscow, Russian Federation; [2]Central State Medical Academy

Over the past decade, there has been a significant increase in the incidence of thyroid cancer with increase in unwarranted surgical interventions in patients with bening thyroid nodules.

Aim: to develop a predictive model for thyroid cancer risk stratification.

Methods and results: We conducted the retrospective data analysis of 89 patients undergon thyroidectomy from 2010 to 2018. There were 66 female (74,2%) and 23 male (25,8%). The diagnosis was proven histologically. The average age was 54,5±10,9. Of these, 2 patients (2,2%) had follicular carcinoma, 37 (41,6%) – papillar carcinoma, 16 (18,0%) – follicular adenoma and 34 (38,2%) – benign nodules. Patients with thyroid cancer were younger (50,4±11,7 years vs 57,4±9,2 years, p = 0,002), had a higher level of triglycerides (1,3±0,6 mmol/l vs 1,0±0,52 mmol/l, p = 0,031), glucose (5,53±0,86 mmol/l vs 5,49±0,44 mmol/l, p = 0,003), LDL (3,54±0,88 vs 2,98±0,99), and TSH (2,02±1,04 vs 1,68±1,19, p = 0,046) compared with patients having benign nodules. There were more patients undergone radiotherapy among those with thyroid cancer (13,5% vs. 1,9%, p = 0,032). Basing on ultrasonography thyroid cancer was mostly located in the upper part or the isthmus of the thyroid (40,5% vs 19,3%, p = 0,037); hypoechogenicity (62,2% vs 26,9%, p = 0,001), irregular margins (25,0% vs 6,0%), p = 0,012), microcalcification (66,7% vs 9,6%, p = 0,0001), mixed vascularity (73,0% vs 42,3%, p = 0,004) were more common. Basing on regression analysis, following criteria are independently associated with thyroid cancer: TSH above 1,17 (p = 0,025 OR 2,881 [95% CI 1,140-7,282]), triglycerides more than 0,94 (p = 0,021,OR 3,222[1,197-8,670]), localization of nodules in the upper part or the isthmus of the thyroid (p = 0,046 OR 1,735[1,011-2,979]), hypoechogenicity (p = 0,00 1OR 4,459[1,806-11,010]), microcalcification (p = 0,0001, OR 18,800 [5,933-59,573]), mixed vascularity (p = 0,005 OR 3,682 [1,481-9,152]).

The following risk scale was obtained:

Factor	score
microcalcification	5
hypoechogenicity	2
mixed vascularity	2
localization of nodules: upper part	1
localization of nodules in isthmus	2
TSH >1,17	1
triglycerides >0,94	1

The risk of malignancy diagnosis is high if the score sum is 6 and more.

The model demonstrates high diagnostic value AUC (c-criterion) = 0,938 [0,859 - 0,980], sensibility 96,43%, specificity 83,67% p<0,001. Hosmer & Lemeshow test revealed that risk classification according to the scale is appropriate.

Conclusions: Our results suggest that this predictive risk model can be applied in clinical practice for thyroid nodule risk stratification and reducing the number of unwarranted surgical interventions

Cancer Translational

P2-04-116

THYROID FOLLICULAR ADENOMAS AND CARCINOMAS: MOLECULAR PROFILING PROVIDES EVIDENCE FOR A CONTINUOUS EVOLUTION

Geneviève Dom[1], *Sandra Frank*[1], *Sebastien Floor*[1], *Pashalina Kehagias*[1], *Guy Andry*[2], *Frederick Libert*[1], *Ligia Craciun*[2], *Nicolas de Saint Aubin*[2], *Jacques E Dumont*[1], *Carine Maenhaut*[1]
[1]Université Libre de Bruxelles, Belgium; [2]Institut Jules Bordet, Belgium

Introduction and aim: Thyroid nodules are very common in the population, and some are found to be cancer. A key feature is to be able to distinguish the malignant thyroid follicular carcinoma FTC from the benign adenoma FA which are preoperatively indistinguishable and share most of the genetic alterations encountered in follicular thyroid neoplasms.

Material and Method: 20 FA and 8 FTC were hybridized onto double channel microarrays (HEEBO), with their normal adjacent tissues, and 10 FA and 9 FTC and their normal adjacent tissues were hybridized onto miRNA microarrays. Expression data were analyzed, validated by qRT-PCR and immunohistochemistry and compared to the literature.

Results and discussion: Most deregulated mRNA are common between FA and FTC and are downregulated, but there are additional deregulated mRNA in FTC. The two classes of tumors share also deregulated pathways, molecular functions and biological processes, although there are additional ones in FTC, and the lipid transport might play a role in tumor progression. 3 differentially expressed genes that could potentially discriminate follicular adenomas and carcinomas show globally the same modulations at the protein level by immunohistochemistry. Our expression data support the idea of a continuum of tumors, and even a combination of the 3 best markers identified in our data is not able to classify correctly all FTC and FA. Concerning miRNA, they are few deregulations in FTC and even less in FA suggesting that miRNA have minor impact on this tumor progression.

Conclusion: FA and FTC appear to be the same tumor at different level of malignity.

P2-04-117

CA 19.9 POSITIVITY AND DOUBLING TIME ARE PROGNOSTIC FACTORS OF MORTALITY IN PATIENTS WITH ADVANCED MEDULLARY THYROID CANCER (AMTC) WITH NO EVIDENCE OF STRUCTURAL DISEASE PROGRESSION (PD)

Loredana Lorusso[1], *Chiara Fustini*[2], *Cristina Romei*[2], *Paolo Piaggi*[2], *Giovanni Pellegrini*[3], *Eleonora Molinaro*[2], *Laura Agate*[2], *Valeria Bottici*[2], *David Viola*[2], *Paolo Vitti*[2], *Rossella Elisei*[2]
[1]Endocrine Unit, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy; [2]Endocrine Unit, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa, Italy; [3]Uo Analisi Chimico-Cliniche, University Hospital of Pisa, Italy

Serum Ca19.9 positivity represents a prognostic factor of mortality in patients with aMTC, independently from calcitonin (Ct) doubling time (dt). However, it is unknown whether aMTC patients who become positive for Ca19.9 also have a PD.

Aims: to evaluate whether in aMTC, when serum Ca19.9 become positive, a PD according to RECIST is present and to determine the role of Ca19.9 dt in predicting mortality and PD.

Patients and methods: serum Ca19.9, Ct and carcinoembryonic antigen (CEA) were measured (mean number of measurements:5,2±2) in 107 aCMT patients, and their dts were calculated. Restaging of the disease was radiologically performed in 104/107 and the PD was evaluated according to RECIST.

Results: at the end of follow-up, 25/107 patients were Ca19.9 positive and PD was identified in 30/104. No significant correlation was found between Ca19.9 positivity and PD while the correlation between Ca19.9 positivity and mortality was confirmed (p = 0,0002). Ca 19.9 dts <6 months and <1year were not related with PD but with mortality (p<0,0001 and p<0,0001, respectively). PD was related with Ct (p = 0,0009) and CEA (p = 0,002) dts <1year, but not with Ct and CEA dts <6 months. Both Ct and CEA dts <6 months and <1 year were related to mortality (p = 0,01 and p = 0,03 for Ct; p = 0,002 and p<0,0001 for CEA). Multivariate analysis showed that, among dts <6 months, only Ca 19.9 dt was independently able to predict mortality, while, among dts <1 year, both Ca 19.9 and CEA dts were able to predict mortality.

Conclusions: serum Ca19.9 positivity and dts are prognostic factors of mortality but not of PD according to RECIST. The most likely explanation of this observation is that in these cases the PD is microscopic and not detected by CT scan.

P2-04-118

AGE-RELATED DISTRIBUTION OF SOMATIC MUTATIONS IN PATIENTS WITH PAPILLARY THYYROID CARCINOMA

Eliska Vaclavikova[1], *Vlasta Sykorova*[1], *Sarka Dvorakova*[1], *Barbora Pekova*[1], *Jitka Moravcová*[1], *Josef Vcelak*[1], *Petr Vlcek*[2], *Rami Katra*[3], *Jan Betka*[4], *Jan Plzák*[4], *Petr Lastuvka*[5], *Daniela Kodetova*[6], *Bela Bendlova*[1]
[1]Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic; [2]2nd Faculty of Medicine, Charles University, Department of Nuclear Medicine and Endocrinology, Department of Nuclear Medicine and Endocrinology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [3]Dept. of Etn, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Department of Ear, Nose and Throat, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [4]Department of Otorhinolaryngology and Head and Neck Surgery, First Faculty of Medicine, Charles University, Motol University Hospital, Prague, Czech Republic; [5]Department of Otorhinolaryngology and Head and Neck Surgery, 1st Faculty of Medicine in Charles University and University Hospital Motol, Prague, Czech Republic; [6]Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague 5, Czech Republic

Objectives: Papillary thyroid carcinoma (PTC) can occur at any age. Molecular genetic analysis revealed various genetic alterations associated with tumor development. Main genetic changes are somatic mutations in the *BRAF* gene and *TERT* promoter, chromosomal rearrangements (particularly *RET/PTC*) and mutations in *HRAS*, *KRAS* a *NRAS* with not completely clear role of pathogenicity. It is assumed that certain mutations are specific for certain age. The aim of study was to determine distribution of somatic mutations in patients' age groups.

Methods: The study was conducted with the cohort of 588 patients with histologically proven PTC. The patients (median age 44 years) were divided into 7 age groups. Young patients aged <20 years represent one age group and adults were stratified into 10-year age groups. Using molecular genetic methods (NGS, real-time PCR), rearrangements and somatic mutations in the *BRAF*, *TERT*, *HRAS*, *KRAS*, and *NRAS* genes were identified.

Results: Distribution of mutations in age groups significantly differed between the cohort of children and other age groups (p<0.00001). Also patients aged >60 years significantly differed (p<0.00001) from other patients. The most frequent mutation was *BRAF* p.Val600Glu. Whereas in older patients it was often detected together with *TERT* mutation, in younger patients *TERT* mutation was not found. The youngest patient with *TERT* mutation was 40 years old. Its detection rises with increasing patient's age. Children were the only group where *BRAF* mutation was not predominant, but rearrangements

were. Beside *RET/PTC* (21%), other rearrangements (37%) were revealed in children.

Conclusions: The evaluation defined three different age groups with cut-off age 20 and 55 years and representative genetic profile for PTC. Chromosomal rearrangements are specific mainly for patients aged <20 years, *BRAF* mutation is typical for patients aged between 20 and 54 years, and in patients aged >55 years, the *BRAF* mutation is accompanied with *TERT* mutation.

The study was supported by AZV 16-32665A and MHCR–RVO (00023761).

P2-04-119

CORRELATION BETWEEN MOLECULAR, HISTOPATHOLOGICAL, AND CLINICAL DATA IN A SERIES OF 66 PATIENTS WITH MEDULLARY THYROID CARCINOMA

Margarida M. Moura[1], *Rafael Adame Cabrera*[2], *Alexandra Mayer da Silva*[3], *Branca M. Cavaco*[1], *Paula Soares*[4], *Valeriano Leite*[5]

[1]Unidade de Investigação Em Patobiologia Molecular (Uipm), Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisboa, Portugal; [2]Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisboa, Portugal; [3]Registo Oncológico, Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisboa, Portugal; [4]I3s - Instituto de Investigação e Inovação Em Saúde, Universidade Do Porto, Ipatimup - Instituto de Patologia e Imunologia, Universidade Do Porto, Departamento de Patologia, Faculdade de Medicina, Universidade Do Porto, Porto, Portugal; [5]Unidade de Investigação Em Patobiologia Molecular (Uipm), Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Nova Medical School | Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal

Many histological variants of medullary thyroid carcinoma (MTC) have been described in the literature. However, most of them are rarely found and have no proven prognostic significance. In follicular cell-derived thyroid carcinomas, there is a good correlation between genotype, histotype, and phenotype. In this study, we investigated whether such an association occurs in MTC. The histopathological features were evaluated in a series of 66 molecularly characterised tumours in terms of somatic *RET* and *RAS* mutations and correlated with clinical characteristics. Most MTC exhibited the classical variant (55/66, 83.3%). Other histological variants were rarely observed, with spindle cell variant being present in 4/66 (6.1%) cases. Tumours were classified into four groups: group 1, with somatic p.Met918Thr and p.Ala883Phe *RET* mutations; group 2, with other *RET* mutations; group 3, with *RAS* but no *RET* mutations; and group 4, without *RET* or *RAS* mutations. Tumours from groups 1 and 4 were typically associated with the classical variant, with abundant fibrosis, lymphovascular and extrathyroidal invasion, and more advanced stages of disease, whereas group 2 cases included histological variants besides the classical variant, with tumours that were highly cellular, less invasive, and with a better overall prognosis. In tumours from group 4, amyloid deposition was characteristically absent or low. The spindle cell variant was present only in tumours from group 3, which had a high cell content, and a degree of invasion and prognosis intermediate between groups 1 and 2, but better than group 4. The grade of fibrosis was positively correlated with clinical outcome, since prevalence of worse prognosis increased progressively from absent fibrosis < low fibrosis < moderate fibrosis < intense fibrosis. Our results support the idea that a genotype-histotype-phenotype correlation is present in MTC.

P2-04-120

GERMLINE MET-T1010I MAY PREDISPOSE TO SOMATIC GENE ALTERATIONS IN MEDULLARY THYROID CANCER

Alessandro Prete[1], *Cristina Romei*[1], *Alessia Tacito*[1], *Teresa Ramone*[1], *Valeria Bottici*[1], *Rossella Elisei*[1], *Raffaele Ciampi*[1]

[1]University of Pisa, Unit of Endocrinology, Department of Clinical and Experimental Medicine, Pisa, Italy

Background: Virtually all familial cases of Medullary Thyroid Cancer (MTC) harbor germline RET mutations. So far, only one family with hereditary MTC has shown to carry the germline mutation of ESR2 gene. However, oncogenesis of some familial MTCs still needs to be clarified. MET proto-oncogene was found mutated in many cancers and may have a role in MTC oncogenesis.

Methods: We studied a family characterized by 2 brothers with MTC and 14 negative controls. We performed Sanger sequencing (SS) to identify germline mutations of RET and ESR2, Whole Exome Sequencing (WES) (Illumina) to identify other germline mutations, and Target Sequencing (Ion Torrent) to identify somatic mutations of most relevant thyroid cancer oncogenes.

Results: The 2 MTC patients did not harbor RET and ESR2 germline mutations, according to SS analysis. We performed WES in blood samples of MTC patients and 2 negative controls and we identified 22 potential germline variants (*ADGVR1, AFTPH, ANKRD26, BCR, BMP2, COL4A5, CRIM1, CAPN13, CYP2C9, KIA1217, KRTAP15-1F, LRP1, MAD2L1, MET, PRSS36, RAPGEF6, RFX7, SPTBN1, USP34, VWA2, ZFAND4, ZMYM2, ZNF789)*. According to SS, intriguingly, one specific *MET* mutation (MET-T1010I) was present in the two MTC brothers and in the apparently unaffected mother, but not in the other relatives. Furthermore, we performed Target Sequencing of the MTC tissue samples of the two brothers and we identified the MET-T1010I mutation in association with a somatic RET-M918T mutation.

Discussion & conclusion: We demonstrated by WES that this family is not harboring any RET or ESR2 germline mutations. However, we found a germline MET-T1010I mutation associated with a somatic RET-M918T mutation in both MTC cases. We can hypothesize that MET-T1010I mutation may represent an early driver oncogene mutation, which might predispose to the development of a late mutation such as RET-M918T.

P2-04-121

COMPREHENSIVE ROUTINE MOLECULAR GENETIC ANALYSIS OF PAPILLARY THYROID CANCER TISSUES

Jitka Moravcová[1], *Sarka Dvorakova*[2], *Vlasta Sykorova*[2], *Eliska Vaclavikova*[2], *Barbora Pekova*[2], *Jan Plzak*[3], *Martin Chovanec*[4], *Jiri Hoch*[5], *Petr Lastuvka*[3], *Josef Vcelak*[2], *Bela Bendlova*[2]

[1]Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic; [2]Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic; [3]Ent Clinic and Head and Neck Surgery, First Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic; [4]Ent Clinic, Royal Vinohrady Teaching Hospital, Prague, Czech Republic; [5]Department of Surgery, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

Objectives: Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. The aim of this study was to introduce a routine molecular genetic analysis of PTC samples.

Methods: DNA and RNA were isolated from 73 fresh frozen PTC samples. Samples were analyzed by next generation sequencing using Thyro-ID kit (4bases) based on targeted amplification of 14 genes and sequencing on Miseq (Illumina). Samples without detected mutations by Thyro-ID kit were consequently analyzed by Real-Time PCR (LC480, Roche) for detection of fusion genes.

Results: The somatic mutations were detected by Thyro-ID kit in 43 of 73 (59%) patients. The most frequent was V600E mutation in the *BRAF* gene in 39 of 73 (54%) patients, of which in 5 patients co-existed with C228T mutation in the *TERT* promoter, in 2 patients with C250T mutation in the *TERT* promoter and in 1 patient with I251N mutation in the *TP53* gene. Only C228T mutation in the *TERT* promoter in 1 patient was found. VK600-1E mutation in the *BRAF* gene in 1 patient was detected. Two mutations in *RAS*

genes (Q61K+G60G in *KRAS*, Q61K in *HRAS*) in two patients were revealed. No somatic mutation in 30 patients (41%) was found, of them in 14 patients the fusion genes were detected. The fusion genes were – 5x *ETV6/NTRK3*, 4x *RET/PTC1*, 3x *RET/PTC3*, 1x *STRN/ALK* and 1x *SQSTM1/NTRK3*.

Conclusion: Our routine analysis in thyroid cancer includes the detection of somatic mutations using the Thyro-ID genetic panel followed by the detection of fusion genes. In summary, the detection rate of genetic changes increased from 59% to 78%. The most prevalent mutation was V600E in the *BRAF* gene and the most common rearrangement was *ETV6/NTRK3*.

This work was supported AZV 16-32665A and MH CR RVO 00023761.

P2-04-122

CLINICAL AND MOLECULAR CHARACTERISTICS OF HIGH RISK DIFFERENTIATED THYROID CANCERS: RESULTS OF A MONOCENTRIC EXPERIENCE

Simona Censi[1], *Sara Watutantrige-Fernando*[2], *Federica Vianello*[3], *Yi Hang Zhu*[1], *Loris Bertazza*[4], *Elisabetta Cavedon*[5], *Jacopo Manso*[6], *Clara Benna*[7], *Maurizio Iacobone*[8], *Francesca Galuppini*[9], *Gianmaria Pennelli*[9], *Susi Barollo*[1], *Caterina Mian*[10]

[1]University of Padua, Department of Medicine (Dimed), Endocrinology Unit, Padua, Italy; [2]Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Italy; [3]Department of Radiotherapy, Istituto Oncologico Veneto-IRCCS, Padua, Italy; [4]Dept. Medicine (Dimed), University of Padova, Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Italy; [5]University of Padua, Department of Medicine (Dimed), Endocrinology Unit, Padua, Italy; [6]Endocrinology Unit, Padua University, Padua, Italy; [7]Department of Surgery Oncology and Gastroenterology, University of Padova, Padua, Italy; [8]University of Padua, Department of Surgical, Oncological and Gastroenterological Sciences (Discog), Endocrine Surgery Unit, Padua, Italy; [9]University of Padua, Department of Medicine (Dimed), Surgical Pathology and Cytopathology Unit, Pathology Unit, Padua, Italy; [10]Operative Unit of Endocrinology, Department of Medicine (Dimed), Endocrinology Unit, University of Padua, Padua, Dept. of Medicine, Padova, Italy

Background: Differentiated thyroid carcinoma (DTC) display usually an excellent prognosis, only a minority of cases exhibiting a poor clinical outcome. A deep knowledge of clinical, pathological and molecular features of aggressive DTC is essential to improve the diagnostic frame and lead to tailored protocols of therapy and follow-up.

Materials and methods: a BRAF, RAS, TP53, PTEN and PIK3CA genes and TERT promoter analysis has been assessed in 105 high-risk DTC (>40mm and/or metastatic) and in 144 low-risk DTC; clinical outcomes and molecular aspects were compared in the two groups.

Results: in the high risk group, subjects with metastatic tumor or with both metastatic and larger cancers had a poorer outcome than subjects with only larger cancers: during the follow-up they had a persistent disease or were dead in 64% and 85% respect to 12%, they were also more likely to undergo a second treatment (67% and 85% respect to 8%) and had a reduced Disease-Free Survival (DFS). Indeed, high-risk DTC had also a poorer clinical outcome than low-risk ones: they were more likely to have second treatment and had reduced DFS too. Metastatic DTC had a higher prevalence of TERT promoter mutations than subjects with only larger size tumors (27% vs 14%, p = 0.0398). High-risk DTC carried lower frequency of BRAF (27% versus 61%), but higher frequency of TERT promoter (21% versus 3%) and RAS mutations (11% versus 2%) than low-risk DTC. By multivariate analysis only lymph node involvement, distant metastases and, among molecular markers, TERT promoter mutations, resulted independent factors of a worse outcome.

Conclusions: patients with high-risk tumors, particularly the metastatic ones, had the worst outcome. TERT mutations, lymph node involvement and distant metastases were found to be independent factors of a poor prognosis. No link was found between other molecular events and the clinical-pathological features.

P2-04-123

IMPACT OF BRAF MUTATION ON THE VOLUME OF SURGICAL TREATMENT AND RECURRENCE RATE OF PAPILLARY THYROID CANCER

Marina Boriskova[1], *Uliana Farafonova*[2], *Polina Pankova*[1]

[1]Pavlov First Saint-Petersburg Medical University, Saint-Petersburg, Russian Federation; [2]Lva Tolstogo 6/8, Sainkt-Petersburg, Russian Federation

Base on the latest clinical guidelines the volume of surgical treatment of localized papillary thyroid cancer (PTC) depends on tumor size. BRAF mutation is influence on prognosis, but not on the volume of surgical treatment. We decided to evaluate correlation of localized PTC surgical treatment volume and recurrence rate based on BRAF mutation status.

Materials and methods: Our study is single center prospective not randomize. We include 166 patients with PTC, operated from 2008 to 2015. We performed genetic study of the FNAB material in all patients. The allele-specific polymerase chain reaction (PCR) method were used for detection of V600E BRAF gene mutation. Median follow-up were 60 months.

Results: Among 166 patients with histologically proven PTC BRAF-mutation was identified with a frequency of 48.2% (80/166), and recurrence rate was 18.7 % (31/166) when observed in up to 60 months. We found no correlation between BRAF mutation and recurrence rate (p = 0.07). But multivariate analysis revealed that BRAF status correlates with recurrence rate in conjunction with the volume of surgical treatment. The highest rate of recurrences (38.7 %) we found in BRAF positive PTC group after hemi/thyroidectomy (TE). In contrast, in group of BRAF positive PTC after thyroidectomy with central compartment lymph node dissection (TE+CLND) recurrence rate were 4.8 % (3/62) (p = 0.002). In the group of BRAF negative tumors, the volume of surgery (TE vs TE+CLND) does not statistically significant affect the recurrence rate (20 % and 32 %, respectively). Reduction of the number of recurrences in the BRAF positive PTC from 38.7 % to 4.8 % is due to increase in the volume of surgical treatment. Moreover, we found no correlation between recurrences rate and tumor size in BRAF positive PTC (p = 0.95), and in BRAF negative PTC we found higher probability of PTC recurrence at progressive T stage (p = 0.02).

Conclusion: BRAF-positive tumor status is indications for thyroidectomy with central compartment lymph node dissection regardless of T stage.

P2-04-124

IDENTIFICATION OF A NOVEL FOUNDER CHEK2 MUTATION IN PORTUGUESE ROMA PATIENTS WITH FAMILIAL NON-MEDULLARY THYROID CARCINOMA

Carolina Pires[1], *Inês Marques*[2], *Ana Saramago*[1], *Daniela Dias*[3], *Valeriano Leite*[4], *Branca Cavaco*[1]

[1]Unidade de Investigação Em Patobiologia Molecular (Uipm), Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [2]Unidade de Investigação Em Patobiologia Molecular (Uipm), Instituto Português de Oncologia de Lisboa Francisco Gentil, Centro de Estudos de Doenças Crónicas (Cedoc), Nova Medical School|faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal; [3]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [4]Unidade de Investigação Em Patobiologia Molecular (Uipm), Instituto Português de Oncologia de Lisboa Francisco Gentil, Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Nova Medical School|faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal

Introduction: Familial non-medullary thyroid carcinoma (FNMTC) is defined by the diagnosis of two or more first degree relatives with NMTC, and family members frequently present multinodular goiter (MNG). Germline mutations in DNA repair-related genes have been reported in thyroid cancer cases.

We identified a Portuguese Roma family with four members affected with papillary thyroid carcinoma (PTC), and three members with MNG.

Aim: To investigate the involvement of DNA repair-related genes in the aetiology of FNMTC in this family.

Methods: 94 cancer predisposition genes were analysed through next-generation sequencing (TruSight Cancer panel). Sanger sequencing was used to confirm and screen likely pathogenic variants. Ten polymorphic markers were genotyped for haplotype analysis in the *CHEK2 locus* (chromosome 22q12.1).

Results: A novel likely pathogenic germline variant in *CHEK2* [c.596dupA (p.Tyr199Ter)], expected to encode a truncated protein, was detected in homozygosity in the proband (PTC) and in his brother (MNG), being heterozygous in his mother (PTC), two sisters (PTC+MNG), and one nephew (MNG). The mother and one sister also had breast cancer. The variant was absent in another nephew (MNG) and in 100 general population controls.

Since the variant was detected in homozygosity, the possibility of a founder effect was investigated. Subsequently, the variant was also detected in 2/32 Roma patients with thyroid cancer, and in 1/15 Roma individuals without thyroid cancer, all apparently unrelated. One haplotype of seven polymorphic *loci*, covering 3.5 Mb (~4 cM) in the *CHECK2 locus*, was detected in the nine Roma mutation carriers, but not in non-carriers (one family member and 30 Roma and general population controls), suggesting a founder effect.

Conclusion: We identified a novel founder *CHEK2* mutation, which is likely to underlie thyroid cancer and other cancer manifestations in the Roma population. Further studies are needed to clarify the role of *CHEK2* and its clinical implications.

P2-04-125

ROUTINE MOLECULAR GENETIC ANALYSIS REVEALED TERT, NRAS AND EZH1 MUTATIONS IN AN ATYPICAL FOLLICULAR THYROID TUMOR

Barbora Pekova[1], *Sarka Dvorakova*[1], *Vlasta Sykorova*[1], *Jitka Moravcová*[1], *Eliska Vaclavikova*[1], *MIlos Laburda*[1], *Jana Drozenova*[2], *Martin Chovanec*[3], *Josef Vcelak*[1], *Bela Bendlova*[1]

[1]Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic; [2]Department of Pathology, 3rd Faculty of Medicine, Charles University in Prague, Royal Vinohrady Teaching Hospital, Prague, Czech Republic; [3]Department of Otorhinolaryngology and Head and Neck Surgery, 3rd Faculty of Medicine, Charles University in Prague, Royal Vinohrady Teaching Hospital, Prague, Czech Republic

Introduction: Preoperative molecular genetic analysis is becoming routine in diagnostics of thyroid nodules beside a FNA cytology. Several genetic markers of malignancy are well known such as *BRAF*, *RET/PTC* and *TERT* mutation with almost 100% risk of malignancy or mutations in *RAS* genes with variable risk of malignancy (41-95%).

Case report: We report the case of 71-year-old woman with two thyroid nodules in the right lobe classified as Bethesda category II and III. Routine mutational screening of FNAB sample from bigger nodule (Bethesda III) by NGS panel (Thyro-ID) revealed C228T mutation in the *TERT* promoter together with G12V mutation in the *NRAS* gene. The patient underwent the total thyroidectomy and histopathological examination revealed encapsulated oncocytic follicular tumour without any signs of invasive behaviour, but part of tumor indicated an atypical microoncocytic growth pattern. Molecular genetic analysis in surgically removed sample confirmed *TERT* and *NRAS* mutations and moreover detected Q571R mutation in the *EZH1* gene.

Conclusions: In this prospective analysis we revealed mutations in *TERT*, *NRAS* and *EZH1* in atypical follicular tumour without any evidence of malignancy, although *TERT* mutations are associated with malignant thyroid tumours with less favourable prognosis. Additionally coexisting *TERT* and *RAS* or *BRAF* mutations worsen prognosis due their synergistic effect in activation of signalling pathways. In literature, *TERT* mutations in benign thyroid tumours were reported only in a few cases with later relaps of metastatic FTC. We supposed that our case could be early stage of FTC and therefore, the patient should be more intensively followed-up.

Supported by AZV 16-32665A and MH CR RVO 00023761.

Diagnosis 1

P2-05-126

COMPREHENSIVE SCREENING OF CAUSATIVE GENES IN CHINESE HAN PATIENTS WITH CONGENITAL HYPOTHYROIDISM

Shuang-Xia Zhao[1]

[1]Shanghai Ninth People's Hospital, Shanghai, China

Objective: Congenital hypothyroidism (CH), the most common neonatal metabolic disorder, is caused by thyroid hormone deficiency present at birth. Untreated CH can lead to mental retardation and growth failure. The incidence of CH in Chinese newborns is one in 2,080. Although several candidate genes have been reported to be associated with CH, comprehensive screening of causative genes has been limited in Chinese.

Design And Methods: We recruited one hundred ninety-two patients with primary CH in this study. All exons and exon-intron boundaries of 21 candidate genes for CH were analyzed by next-generation resequencing. Also, the inheritance pattern of causative genes was analyzed by the study of family pedigrees.

Results: Our results exhibited that 97 patients (50.52%) carried biallelic mutations (containing compound heterozygous mutations and homozygous mutations) in seven genes (*DUOX2*, *DUOXA2*, *DUOXA1*, *TG*, *TPO*, *TSHR, and SLC5A5*) involved in thyroid hormone synthesis. Autosomal recessive inheritance of CH caused by mutations in *DUOX2*, *DUOXA2*, *TG*, *TPO, and SLC5A5* was confirmed by analysis of 42 family pedigrees. Notably, eight mutations in four genes (*FOXE1*, *NKX2-1*, *PAX8* and *HHEX*) that lead to thyroid dysgenesis were identified in eight probands. These mutations were heterozygous in all cases and hypothyroidism was not observed in parents of these probands, suggesting the genetic pattern of the four genes was not autosomal dominant inheritance.

Conclusions: Approximately half cases of CH in China were caused by known CH causitive genes, including the genes of thyroid dyshormonogenesis and the genes of thyroid dysgenesis. However, the majority of CH with known causitive genes were due to thyroid dyshormonogenesis rather than thyroid dysgenesis. And *DUOX2* was the most frequently mutated gene in in Chinese patientis with CH. Our study expanded the mutation spectrum of CH in Chinese patients, which was significantly different from Western countries.

P2-05-127

VIDEO AND FACE-TO-FACE CONSULTATIONS IN AN OUTPATIENT THYROID CLINIC RESULT IN SIMILAR DEGREES OF PATIENT SATISFACTION AND DISEASE-SPECIFIC QUALITY-OF-LIFE: A RANDOMIZED CONTROLLED CLINICAL TRIAL

Claudia Cangemi[1], *Thomas Brix*[1], *Anette Christensen*[1], *Mette J. Rothmann*[1], *Jan Erik Henriksen*[1], *Anna Sofie Lillevang*[1], *Iben Fasterholdt*[2], *Anne Lee*[2], *Steen Bonnema*[1]

[1]Department of Endocrinology, Odense University Hospital, Denmark; [2]Odense University Hospital, Denmark

Objective: In a randomized, single-blinded, controlled trial, we compared video consultations with conventional face-to-face consultations. Outcome parameters were impact on quality of life (QoL) and communication issues.

Methods: After the enrolment visit in the thyroid out-patient clinic, patients were randomized according to the week number. In the intervention group (odd weeks), patients downloaded an app on their own electronic device, by which the succeeding video consultation was carried out. Patients randomized to the control group (even weeks) kept seeing the physician face-to-face, and were blinded towards the possibility for video consultations. All patients completed two questionnaires at baseline and after each consultation: 1) the ThyPRO QoL instrument, 2) the Communication Assessment Tool. In addition, the physicians filled in an evaluation questionnaire following each video consultation.

Results: In the intervention group, 79 of 138 eligible patients accepted participation (74 women; age: 50±14 years), of whom 70 completed at least one video consultation. The control group included 78 of eligible 86 patients (76 women; age: 47±15 years), of whom 70 completed at least one

consultation. At baseline, the overall QoL was similar in the two groups. No significant between-group differences were observed during the study. All patients were highly satisfied with their consultations. The duration of the video consultations was on average 3.6 minutes shorter than face-to-face consultations. In the intervention group, approximately one hour of transport to the hospital was saved per patient. Drawbacks for the hospital included expensive technology, no organizational or economical savings, and technical difficulties hindering a seamless video communication.

Conclusions: Our study shows that virtual consultations are non-inferior to conventional consultations in regard to patient-related factors, such as QoL and satisfaction. Limitations exist, however, and a range of factors should be taken into account, before a virtual outpatient thyroid clinic is implemented on a large scale.

P2-05-128

USEFULNESS OF URGENT TSH TESTING IN THE SCREENING OF THYROID DYSFUNCTION IN PATIENTS ATTENDING AN EMERGENCY DEPARTMENT

Irene Campi[1], *Antonella Dubini*[2], *Giovanni Battista Perego*[3], *Massimiliano Andreasi*[2], *Guia Vannucchi*[4], *Gianfranco Parati*[5], *Luca Persani*[6], *Laura Fugazzola*[7]

[1]Endocrinology Department, IRCCS Istituto Auxologico Italiano; University of Milan, Milan, Italy; [2]IRCCS Istituto Auxologico Italiano, Clinical Analysis Laboratory, Italy; [3]IRCCS Istituto Auxologico Italiano, Department of Cardiovascular Neural and Metabolic Sciences, Italy; [4]IRCCS Istituto Auxologico Italiano, Department of Endocrinology, Italy; [5]IRCCS Istituto Auxologico Italiano, Department of Cardiovascular Neural and Metabolic Sciences, University of Milan-Bicocca, Department of Medicine and Surgery, Italy; [6]IRCCS Istituto Auxologico Italiano, Department of Endocrinology, University of Milan, Department of Clinical Sciences and Community Health, Italy; [7]IRCCS Istituto Auxologico Italiano, Department of Endocrinology, University of Milan, Department of Pathophysiology and Transplantation, Italy

Objectives: to evaluate the incidence of thyroid dysfunctions in an emergency setting. Methods: retrospective analysis of TSH values of patients admitted to the Emergency Clinic at a single Center during 2018. TSH was included in the routine biochemical assessment of all attending patients, independently from the reason of admission. Abnormal values were rechecked in 24-48 hours in patients requiring medical observation. These latter values were used to calculate the prevalence of thyroid dysfunctions.

Results: 5049 samples from 4085 patients were included from January to December 2018. 260 patients (6.4%) had a TSH<0.5 mU/l, 62 (24%) of them having a TSH <0.07; 86 patients (2.1%) were hypothyroid with a TSH >10 mU/l, 28 (33%) of them having a TSH >20 mU/l. The remaining 3739 (91.5%) were euthyroid. In patients with a TSH>20 or <0.07 at admission, TSH values were always confirmed at reassessment. On the contrary, 3 patients with a TSH 5-10 mU/l and 12 with a TSH 0.07-0.5 mU/l normalized in 24 hrs. Follow up data were available on a limited number of patients referred to the Endocrine Clinic. Eight patients had an amiodarone induced thyrotoxicosis, 5 had an undiagnosed Graves' disease, 7 had a multinodular toxic goiter, 6 had an undiagnosed primary hypothyroidism and 12 had an amiodarone-induced hypothyroidism.

Conclusions: Our data indicate a high prevalence of thyroid dysfunctions, especially of hyperthyroidism in patients attending the Emergency Clinic. The assessment of TSH is a cost effective tool useful for the diagnosis and prompt treatment of thyroid dysfunctions, as well as to prevent possible complications of invasive procedures requiring iodine load administration.

P2-05-129

THYROID DYSFUNCTIONS IN SUBJECTS TREATED FOR PAEDIATRIC/ADOLESCENT NEOPLASIA: ROLE OF MORPHOLOGICAL AND FUNCTIONAL SCREENING IN THE SHORT AND LONG TERM

Martina Tavarelli[1], *Emanuela Cannata*[2], *NIcolò Li Volsi*[2], *Giulia Sapupoo*[3], *Marco Russo*[3], *Francesco Frasca*[3], *Claudia Scollo*[4], *Andrea Di Cataldo*[2], *Gabriella Pellegriti*[5]

[1]Universita' Degli Studi DI Catania, Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Medical Center, Catania, Italy, Catania, Italy; [2]Onco-Ematology Unit, Departiment of Clinical and Experimental Medicine, University of Catania, Italy; [3]Endocrinology, Departiment of Clinical and Experimental Medicine, University of Catania, Italy; [4]Endocrinology Unit, Modica Hospital, Catania, Italy; [5]Endocrinology Unit, Garibaldi Nesima Hospital, Catania, Garibaldi Nesima Hospital, Catania, Italy

Introduction: Patients treated for paediatric cancers have a high incidence of both benign and malignant thyroid diseases. The aim of our study was to evaluate the incidence of thyroid alterations (functional and/or morphological) in a consecutive series of patients treated with Chemo (CHE) and Radiotherapy (RTE) for childhood tumors.

Patients and methods: Between 1976 and 2016, 343 patients were treated for neoplasia: 186 for LLA, 63 for HL, 28 for NHL, 11 for LMA and 55 for other neoplasms. The mean age at time of diagnosis of primary malignancy was 7.8 years. All patients, between 2000 and 2016, underwent thyroidal morphological and functional evaluation.

Results: In our series 51.9 % of patients were treated only with CHE, while 48.1% with CHE + RTE (mean radiation dose 29 Gy). A functional and/or structural thyroid disease was diagnosed in 42.5% (24.2% in the CHE group and 62.4% in the CHE+RTE group p = 0.0001). Noteworthy, 20.7% of patients with no evidence of disease at first evaluation developed thyroid alteration during follow-up. Primitive hypothyroidism was diagnosed in 15.7% of cases, 11.2% in the CHE group vs 20.6% in the CHE+RTE group (p = 0.01). and hyperthyroidism in 4 patients (2 with concomitant thyroid carcinoma). 18.3% of patients developed thyroid nodules, 7.9% in the CHE group and 29.7% in the CHE+RTE group (p<0.0001). In 8.3% of patients was diagnosed a thyroid carcinoma, 12.4% in CHE + RTE group and 4.5% in CHE group (p = 0.007).

Conclusions: Patients treated with CHE + RTE have a prevalence of hypothyroidism and nodular pathology, both malignant and benign, significantly greater than observed the CHE group. However frequency of thyroid alterations in this group is not negligible, even if the pathogenetic mechanisms and/or predisposing factors remain to be clarified.

P2-05-130

SHORTER RECALL PERIOD FOR THE THYPRO SURVEY DID NOT CHANGE THE ACCURACY EVALUATED BY REPEATED MOMENTARY MEASUREMENTS

Victor Brun Boesen[1], *Ulla Feldt-Rasmussen*[1], *Jakob Bjørner*[2], *Per Cramon*[1], *Mogens Grønvold*[2], *Åse Krogh Rasmussen*[1], *Torquil Watt*[3]

[1]Dept. of Medical Endocrinology, Copenhagen University Hospital Rigshospitalet, Denmark; [2]Department of Public Health, University of Copenhagen; [3]Dept. of Medical Endocrinology, Copenhagen University Hospital Rigshospitalet, Dept. of Internal Medicine, Copenhagen University Hospital Herlev Gentofte, Denmark

Background: The ThyPRO survey that has become the gold standard for measuring thyroid-related quality of life uses a 4-week recall period. The impact of the length of recall is unresolved; however, to minimize recall bias the FDA favours short recall periods or measures describing current states. We investigated whether ThyPRO in a 1-week recall version was less prone to recall bias than the original ThyPRO. For this purpose, we conceptualized averaged momentary ThyPRO measurements as the true mean of patients' symptoms.

Methods: Patients newly diagnosed with thyrotoxicosis were included (N = 122). For 28 days participants answered momentary questions three

times daily via a smartphone, weekly retrospective surveys with a 1-week recall period, and the original survey with a 4-week recall period on the last day. Twelve ThyPRO items from four multi-item scales were included in the study. Averaged momentary ratings for each scale were compared with recall ratings of 1-week and 4-week periods, respectively.

Results: Averaged momentary ratings were highly correlated with retrospective ratings and remained rather constant, when decreasing the reporting period from four- to one week. Mean differences between momentary and retrospective ratings were similar for both recall periods. Furthermore, the original 4-week ThyPRO was able to accurately summarize the mean of all 1-week ThyPROs.

Conclusions: Shortening the recall period of ThyPRO from four- to one week was not associated with evidence of less recall bias within this subset of items. Nor did 1-week recall seem to compromise the accuracy of ThyPRO. Thus, either version of ThyPRO can be implemented in future studies.

P2-05-131

MACRO-TSH - A DIAGNOSTIC CHALLENGE

Eva Rabing Brix Petersen[1], *Martin Overgaard*[2], *Sevinch Rustamova*[3], *Steen Joop Bonnema*[4]

[1]Hospital of Southern Jutland, Department of Clinical Biochemistry, Aabenraa, Denmark; [2]Odense University Hospital, Department of Clinical Biochemistry and Pharmacology, Odense, Denmark; [3]Department of Internal Medicine, Hospital of Southern Jutland, Sønderborg, Denmark; [4]Department of Endocrinology and Metabolism, Odense University Hospital, Department of Endocrinology, Odense University Hospital, Denmark, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

Introduction: Analytical problems are likely if there is a discrepancy between the results of biochemical tests and the clinical findings.

Case report: A younger male was referred with persistently elevated TSH (148 mU/L) measured by a sandwich electrochemiluminescence-immunoassay, ECLIA. The patient's c omplaints were unspecific, and he appeared clinically euthyroid. The levels of T4 and T3 were within the normal range, all thyroid autoantibodies were negative, and thyroid ultrasonography was normal. TSH analysed by a different immunoassay (Architect, Abbott) yielded similar result. The level of TSH decreased by thyroid hormone substitution, but hyperthyroid symptoms emerged. A serial dilution was performed without detection of heterophilic antibody interference. MRI of the pituitary gland was normal, and no mutation was detected in either the TSH-receptor-gene or the TSH-beta-gene.

The possibility of complex formation of an unknown component in plasma and TSH was considered. Therefore, chromatography was performed on plasma samples from the patient, a control person with slightly elevated TSH, and a pool of healthy controls, respectively. 100 µL EDTA-plasma was fractioned on a Superdex S-75 column (PBS, pH 7.4; 1 mM EDTA) via Äcta FPLC. Fractions of 500 µL were collected, and TSH analysed by Cobas e801 (Roche). The TSH-peak of the control person eluted at 24 kDa, corresponding to free TSH (theoretically 28 kDa), while the patient´s TSH-peak eluted at 154 kDa, compatible with a TSH-IgG complex (theoretically 178 kDa).

Conclusion: This case illustrates the presence of so-called macro-TSH, which is a rare condition. The complex binding of TSH to other plasma proteins (most often immunoglobulins) results in elevated TSH in plasma. However, the biologically active fraction of TSH is normal, which is reflected by clinical and biochemical euthyroidism. The presence of macro-TSH should be considered, if the mechanisms behind false biochemical results are unclarified.

P2-05-132

NON-THYROID ILLNESS SYNDROME IN CORONARY ARTERY BYPASS SURGERY

Selma Caluk[1], *Jasmin Caluk*[2], *Belkisa Izic*[1]

[1]University Clinical Center Tuzla, Nuclear Medicine Dept., Tuzla, Bosnia and Herzegovina; [2]Kardiocentar Sarajevo, Sarajevo, Bosnia and Herzegovina

Objectives: In large surgical procedures and in serious illness, a particular disorder of thyroid hormones can occur. Being not primarily thyroidal, it is called Non-thyroidal illness syndrome (NTIS), and is characterized by low levels of triiodothyronine (T3), normal or low levels of thyroxin (T4) and paradoxically normal, or low levels of thyroid-stimulating hormone (TSH). NTIS occurres after Coronary artery bypass grafting (CABG). Two main techniques of CABG are: CABG with the use of cardiopulmonary bypass (on-pump coronary artery bypass, ONCAB) and CABG without the use of cardiopulmonary bypass (off-pump coronary artery bypass, OPCAB, 'beating-heart surgery'), the latter thought to be less invasive of the two. We prospectively compared OPCAB and ONCAB in the context of NTIS occurrence.

Methods: Serum levels of free fractions of thyroid hormones (FT3 and FT4) and TSH were analyzed in 70 patients subjected to CABG: in 36 patients operated using ONCAB, and 34 using OPCAB technique. Blood samples for analysis were taken prior to surgery, and 12 hours and 14 days after surgery.

Results: The preoperative, and the early and late postoperative levels of FT3 ($p = 0.46$, $p = 0.63$, $p = 0.87$, respectively), FT4 ($p = 0.66$, $p = 0.30$, $p = 0.41$, respectively), and TSH ($p = 0.25$, $p = 0.06$, $p = 0.32$, respectively) were similar in both groups. Twelve hours after surgery, the levels of FT3 and TSH significantly decreased ($p<0.001$, $p<0.001$, respectively), and the FT4 levels rose ($p<0.0001$). The third measurement showed the reversal of these parameters close to the initial values. NTIS occurred in two-thirds of patients.

Conclusion: NTIS occurs often after CABG. However, there was no significant difference in the occurrence of NTIS between the groups, although the OPCAB is considered to be less invasive. Type of coronary disease has an impact on the occurrence of NTIS. NTIS is spontaneously reversible, and does not require medical therapy.

P2-05-133

AGE AND GENDER IMPACT ON TSH PROFILE - TRANSVERSAL AND LONGITUDINAL STUDY

Vitoria Pires[1], *Catarina Ivo*[2], *David Veríssimo*[2], *João Silva*[2], *Luis Lopes*[2], *Dolores Passos*[2], *João Jácome de Castro*[2], *Mafalda Marcelino*[2]

[1]Hospital Das Forças Armadas, Lisboa, Portugal; [2]Hospital Forças Armadas, Portugal

Objective: The aim of this study was to examine the association of TSH with age and gender in an outpatient population **without evidence of thyroid disease**.

Methodology: Cross-sectional and longitudinal study conducted in an Endocrinology Department. For the transversal study, we identified the latest TSH measurements in **981 patients** from the reference population, aged 19-98. We performed a linear regression analysis using SPSSv.025. Regarding the longitudinal study, we observed serum TSH variations in **272 patients,** aged 40-90, with a minimum of 5 years of follow-up.

Results: Transversal: The correlation between **TSH and age** *was significant at the 0.01 level.*

TSH levels remained fairly stable until the **age of 60**, when they started to gradually increase. Mean serum **TSH was 1,82 mIU/L** (min: 0,16 max: **6,9**). Mean serum TSH for each decade was as follows: 40s – 1,81 mIU/L; 50s – 1,82 mIU/L; 60s – 1,81 mIU/L; 70s – 1,83 mIU/L; 80s – 1,83 mIU/L; 90s – 1,88 mIU/L.

Mean **serum TSH was higher in females** than in males (1,99 vs. 1,78) with a p-value of 0,011.

Longitudinal: At a median of **12 years of follow-up**, serum **TSH increased 0,12 mIU/L** individually. Mean serum TSH increased mostly after the **age of 65.**

Discussion: The findings on the association between age and TSH are consistent with previous reported studies. It remains unclear if this represents a decline in thyroid function or a reset in the TSH set point. Nevertheless, our findings show that most of the results are included in the normal reference range so an age-specific reference interval of serum TSH is debatable.

Regarding gender impact on thyroid function, our finding is similar to the NHANES study that reported that TSH concentration was greater in females.

P2-05-134

IS THERE A CORRELATION BETWEEN BMI AND SERUM TSH?

Catarina Ivo[1], *Vitoria Pires*[1], *David Verissimo*[1], *João Silva*[1], *Luis Lopes*[1], *Dolores Passos*[1], *João Jácome de Castro*[1], *Mafalda Marcelino*[1]
[1]Hospital Forças Armadas, Portugal

Introduction: It is well recognized that overt thyroid dysfunction is associated with changes in Body Mass Index (BMI). However, there is ongoing debate regarding the influence of BMI on thyroid profile in euthyroid subjects.

Objective: The aim of this study is to examine the association of TSH with BMI in an outpatient population without evidence of thyroid disease.

Methodology: Cross-sectional study conducted in an Endocrinology Department. We identified the latest TSH and BMI measurements in **981 patients** from the reference population aged 18-94 years. We performed a linear regression analysis using SPSSv.025.

Results: Mean TSH level was **1,82 mIU/L**. Mean BMI was **29,13 kg/m2**.

No association was found between serum TSH and BMI in euthyroid patients (p-value > 0,05).

In contrast with TSH which increases with age, BMI profile appears to decrease as we age (p-value 0,01).

Discussion: Our results are similar to some of the previous reported studies. However, a recent study in India found a significant relationship between serum TSH and BMI. All studies share the limitation of small sample size. Further large-scale data from the population is required to confirm these findings. Our results support the view that variation in thyroid status, within the normal range, does not have an effect on BMI.

P2-05-135

DIFFUSE THYROID LIPOMATOSIS WITH AMYLOID DEPOSITION - A RARE ASSOCIATION

Daniela Cavaco[1], *Ana Rafael*[2], *Teresa Mendonça*[1], *Rafael Cabrera*[1], *Helena Vilar*[1], *Valeriano Leite*[1]
[1]Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; [2]Cuf Cascais Hospital, Lisboa, Portugal

Introduction: Diffuse thyroid lipomatosis is a rare histopathological condition of unknown etiology, characterized by diffuse fatty infiltration in thyroid stroma, which can result in diffuse goiter with compressive symptoms.

Case report: We report the case of a 46-year-old man with 2-year history of progressive weight loss and fatigue. Thyroid function tests were within normal range, and serum thyroperoxidase antibody, anti-thyroglobulin antibodies and calcitonin were undetectable. Physical examination showed a lobulated diffuse thyroid enlargement. Ultrasound (US) scanning revealed hypoecogenic and solid nodules with 18mm and 15mm in the right and in the left lobes, respectively. Fine-needle aspirates (FNA) from both nodules showed colloid goiter. One year ago, the goiter enlarged and he developed dyspnea, dysphonia and dysphagia. Neck US revealed coalescent nodules, the largest with 20mm. FNA of this nodule was hypocellular, with colloid, macrophages and follicular cells with nuclear size increase, slight chromatin clearing and membrane irregularities, and a diagnosis of a follicular lesion of undetermined significance was done. A total thyroidectomy was performed. The resected specimen weighed 237g and measured 111x40x26mm on the left lobe and 105x65x43mm on the right. The gland was bosselated and the cut section was homogenous, with yellow and hemorrhagic areas, without nodules. Microscopic examination revealed extensive infiltration of the parenchyma by mature adipose tissue, with focal deposition of extracellular eosinophilic material that was confirmed to be amyloid protein by Congo red staining. The follicular epithelium was atrophic and showed no nuclear alterations. A final diagnosis of diffuse lipomatosis of the thyroid gland with amyloid deposition was rendered. FDG-PET scan and echocardiogram showed no abnormalities. Abdominal fat and bone marrow biopsies excluded systemic amyloidosis.

Conclusions: This patient represents a case of diffuse lipomatosis with coexisting deposition of amyloid protein of the thyroid gland and contributes to the better understanding of this extremely rare condition.

P2-05-136

THE ASSOCIATION BETWEEN PEDIATRIC OBESITY AND ELEVATED TSH LEVELS

Michael Yafi[1]
[1]The University of Texas, Pediatrics, Endocrinology and Diabetes, Houston, USA

Backgound: Obese children are often screened and referred to pediatric endocrinology for abnormal thyroid function test. It is well known that TSH levels are mildly increased in obese children but there are no evidence –based data that treating this elevation can change the outcome of obesity.

Objective: To determine the prevalence of elevated thyroid-stimulating hormone (TSH) levels in obese children and adolescents referred to pediatric endocrinology clinics and its association with positive Anti Thyroid Peroxidase Antibodies. (Anti TPO)

Methods: A retrospective review of medical records of 100 obese children referred for abnormal thyroid function test was performed. Children were younger than 18 years of age with BMI above 95th percentile.

Data about age, sex, body mass index, TSH, thyroid functions, thyroid antibodies, were collected.

Results: All patients were referred for abnormal thyroid function tests and got repeated tests along with Anti TPO levels. Interpretation of TSH results showed normal level for age in 65% and slightly elevate TSH but below 10 uiu/ml in 32% Only three obese patients (3%) had Hashimoto disease (positive Anti TPO) and elevated TSH requiring therapy.

Conclusion: Mild elevation of TSH values in the absence of autoimmune thyroid disease is common in obese children and adolescents. This elevation is often a result of obesity rather than a cause. High Leptin level in obese children has been postulated as an etiology.

Many primary care providers and even parents are looking for "an easy fix" of obesity by making the diagnosis of hypothyroidism and treating it. Screening for thyroid dysfunction in obese children should be done based on symptoms and family history rather than dealing with obesity alone.

Hyperthyroidism

P2-06-137

RISK OF ATRIAL FIBRILLATION IN HYPERTHYROIDISM: NATIONWIDE POPULATION-BASED STUDY IN KOREA

Kyeong Hye Park[1], *Tae Mi Yuk*[2], *Cheol Ryong Ku*[3], *Dong Yeob Shin*[4], *Eun Jig Lee*[3], *Daham Kim*[5], *Young Ki Lee*[6]
[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Rep. of South Korea; [2]Clinical Research Management Team, National Health Insurance Service Ilsan Hospital, Goyang, Rep. of South Korea; [3]Yonsei University College of Medicine, Seoul, Rep. of South Korea; [4]Division of Endocrinology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Rep. of South Korea; [5]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Rep. of South Korea; [6]Center for Thyroid Cancer, National Cancer Center, Goyang, Rep. of South Korea

Background: Atrial fibrillation (Afib) is the most common arrhythmia worldwide with increasing frequency noted with age. Hyperthyroidism is a well-known cause of Afib. The prevalence of Afib in hyperthyroidism is known as 16%–60% in foreign countries. However, in Korea, the risk of Afib in hyperthyroidism is not well known.

Methods: We used Korea National Health Insurance Sample Cohort (KNHISC). ICD-10 diagnostic code for hyperthyroidism (E05) was used to select hyperthyroidism patients. Hyperthyroid group was defined as the incident case in 2007-2008. Three age- and sex-matched controls per one hyperthyroid patient was selected by propensity score matching. Those who had any history of arrhythmia or cerebral events were excluded. Total 909 hyperthyroidism group and 2,750 control group were included.

Results: Afib was occurred more frequently in hyperthyroidism group (26/909, 2.86%) than in control group (16/2750, 0.58%). The hazard ratio for Afib was 4.53 (95% CI 2.39-8.62, p<0.01) in hyperthyroid group. In multivariate analysis, the risk of Afib was significantly higher than that of control group (hazard ratio 5.38, 95% CI 2.65-12.21, p<0.001). When the hyperthyroidism group was divided according to the occurrence of Afib, the prevalence of hypertension and the elderly more than 70s were high in group with Afib.

Conclusion: The risk of Afib in hyperthyroidism is about five times higher than general population, even treated. Considering that Afib is an important risk factor for the ischemic cerebrovascular accident and heart failure, patients with hyperthyroidism should be evaluated for the presence of Afib and carefully managed.

P2-06-138

PREDICTING POTENTIAL OF ANTI-TSH-RECEPTOR-ANTIBODIES (TRAB) MEASUREMENTS FOR THE COURSE OF GRAVE'S HYPERTHYROIDISM (GD) AND GRAVE'S ORBITOPATHY (GO) DEPENDING ON THE ASSAY TECHNOLOGY

Anja Eckstein[1], Mareile Stöhr[2], Michael Oeverhaus[3], Simon Lytton[4], Banga Jasvinder Paul[5], Mareike Horstmann[6], Utta Berchner-Pfannschmidt[7]

[1]Univ.-Augenklinik, Molecular Ophthalmology, Department of Ophthalmology, University Eye Hospital Essen, Essen, Germany; [2]University Duisburg Essen, Essen, Germany; [3]University Eye Hospital, Essen, Germany; [4]Dr. Simon D Lytton, SeraDiaLogistics, Munich, Germany; [5]University Duisburg Essen, Kinds Kollege London, Essen, Germany; [6]Univerity Hospital Essen, Molecular Ophthalmology, Essen, Germany; [7]Molekulare Ophthalmologie, Department of Ophthalmology, University Hospital Essen, Essen, Germany

Aim: Because of the recent improvements of assay technology due to monoclonal antibody use, bridge technology and even availability of a commercial cell-based bioassay the aim of the study was to evaluate the predicting potential of TRAb measurements with three different assay systems concerning the course of GO and GD.

Methods: Patient (n = 254) sera from the University Essen GO data- and biobank were evaluated in two automated immunoassays; TRAb Elecys (Cobas Roche) and TRAb bridge assay (Immulite, Siemens). The bioactivity of the anti- TSH-receptor stimulating immunoglobulins (TSAb) was assessed in the cell-based bioassay (Thyretain, Quidel). To identify relapse risk of hyperthyroidism follow up data one year after cessation of at least 10-12 months of antithyroid drug (ATD) therapy must have been available. Severity of GO was classified with the NOSPECS score.

Results: Cut off levels for the prediction of severe course of GO were comparable according to the result that 94% of the patient with severe GO relapsed in comparison to 31% of patients with mild GO. However, especially in late disease stages Thyretain assay consistently showed higher percent positivity than the other TRAb immunoassays.

Conclusion: In comparison to the results of the 2nd generation human TRAb assay about 50-60% of patients with poor prognoses of hyperthyroidism and GO can be identified with high TRAb levels relatively independent of assay technology. The bioassay was more sensitive in late stages.

Cut off for prediction of relapse of hyperthyroidism after cessation of ATD with 90% specificity:

Assay	TRAbElecys	TRAb bridge assay	Thyretain bioassay
	6 months after begin of ATD therapy		
Cut off	11,32 IU/l	5,33 IU/l	687%
Specificity	59%	61,7%	42%
Likelyhood ratio	4,7	6,7	3,3
	12 months after begin of ATD therapy		
Cut off	8,3	2,9	650%
Sensitivity	49%	69%	52%
Likelyhood ratio	5,6	5,6	4,3

P2-06-139

INCIDENCE AND PREVALENCE OF HYPERTHYROIDISM: NATIONWIDE POPULATION-BASED STUDY IN KOREA

Kyeong Hye Park[1], Tae Mi Yuk[2], Daham Kim[3], Dong Yeob Shin[4], Cheol Ryong Ku[5], Eun Jig Lee[5]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Rep. of South Korea; [2]Clinical Research Management Team, National Health Insurance Service Ilsan Hospital, Goyang, Rep. of South Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Rep. of South Korea; [4]Division of Endocrinology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Rep. of South Korea; [5]Yonsei University College of Medicine, Seoul, Rep. of South Korea

Background: The annual incidence and prevalence of hyperthyroidism has been reported to be 0.2-0.9/1000 and 5-10/1000 population in foreign countries, respectively. In Korea, there have been few national epidemiological studies for hyperthyroidism.

Method: We used Korea National Health Insurance Sample Cohort (KNHISC). ICD-10 diagnostic code for hyperthyroidism (E05) was used to select hyperthyroidism patients. From 2006 to 2013, prevalence and incidence rate was calculated by dividing the prevalent and incident case of the year by the population of the year. Prevalent case was defined as those patients who were prescribed antithyroid drugs for more than 60 days, or who had undergone thyroidectomy or radioiodine treatment with the ICD-10 code of E05 in that year. Incident case was defined as those patients who were prescribed antithyroid drugs for more than 60 days, or who had undergone thyroidectomy or radioiodine treatment with E05 ICD-10 code within 120 days from index date. For the incidence estimation, data from 2002 to 2005 was washed out to exclude the patients who had diagnosed previously.

Results: From 2006 to 2013, the incidence of hyperthyroidism was 0.39-0.48/1000 population (male 0.22-0.28/1000, female 0.55-0.70/1000). Females showed 2-3 folds higher incidence than males. The prevalence of hyperthyroidism was 1.97-2.64/1000 population (male 1.19-1.67/1000, female 2.74-3.70/1000).

Conclusion: The estimate value of incidence and prevalence in this study seems to be lower than the actual value. Because we used the claims data, only the patients who received treatment were include and patients who were asymptomatic or untreated were not included in this study.

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

P2-06-140

ACTIVATING MUTATION M453V IN RECEPTOR TSHR AS A CASE OF FAMILIAL HYPERTHYROIDISM

Artur Bossowski[1], *Alexandra Stephenson*[2], *Beata Sawicka*[3], *Markus Eszlinger*[4], *Tanja Diana*[5], *George J. Kahaly*[6], *Ralf Paschke*[7]
[1]Dep.of Pediatric Endocrinology, Diabetology With Cardiology Division. Medical University, Bialystok, Medical University in Białystok, Białystok, Poland; [2]Division of Endocrinology and Metabolism Zone, Departments of Medicine, Oncology, Pathology & Laboratory Medicine, and Biochemistry and Molecular Biology. University of Calgary, Calgary, Canada; [3]Dep.of Pediatric Endocrinology, Diabetology With Cardiology Division. Medical University, Bialystok, Poland; [4]Division of Endocrinology and Metabolism Zone, Departments of Medicine, Oncology, Pathology & Laboratory Medicine, and Biochemistry and Molecular Biology. University of Calgary, Calgary, Canada; [5]Molecular Thyroid Research Laboratory. Johannes Gutenberg University, Mainz, Germany; [6]Johannes Gutenberg University Medical Center, Mainz, Germany; [7]Dept. of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Canada

The most common hyperthyroidism in children is connected with exessive levels of thyroid hormones as an effect of activation thyrotropin receptor (TSHR) by uncontrolled production anti-thyroid-stimulating antibodies in Graves' disease. The other rare cause of hyperthyroidism is activating mutation in receptor TSHR in thyroid gland. We would like to introduce a case of familial hyperthyroidism with a novel mutation M453V in the TSHR in three members. Actually 11-year-old boy is a patient at Outpatient Endocrinology Clinic, Medical University in Białystok for first days after birth. He was born from first pregnancy at term by Caesarean section. During gestation his mother was treated with thyrostatic drugs because of Graves's disease. Thyroid hormones and antithyroid antibodies were checked because of bradycardia in newborn and his thyroid disorders' family history. Then we diagnosed hypothyroidism and started therapy with L-thyroxine (10ug/kg/day orally). Because of rapid normalization of TSH, low levels of his antithyroid antibodies and normal thyroid gland by ultrasonography we decreased the dose of L-thyroxine and finished his therapy with L-thyroxine when he was 6 months. His motor and mental development was normal. When he was 3 years, he lost his body mass, he had tachycardia and advanced bone age (7 years). In laboratory labs TSH was decreased (0uIU/ml); elevated free thyroid hormones (fT3- 8,09 pg/ml (↑); fT4- 2,61 ng/ml (↑), with normal level of anti-thyroid antibodies (TPO- 5 IU/ml; ATG< 10 IU/ml, anti-TSH- 0,77; TSI-52%; TBI-19%). In ultrasonography thyroid tissue was with excessive flow. We diagnosed hyperthyroidism and we started treatment with taking Methamizole in 3 doses (1 mg per kg daily orally), beta- blocker in dose 1 mg per kg once a day and vit.B. We had not observed any side effects connected with the anti-thyroid therapy. We modified the doses of thyrostatic drugs according to levels of thyroid hormones and a plan to radical therapy.

In order to find genetic basic of familial hyperthyroidism we sent blood samples obtained from the two children and both parents to Division of Endocrinology and Metabolism, University of Calgary in Canada. In mother and her children was identified a novel activating mutation M453V in receptor TSHR (heterozygous c.1357A>G), which initiates excessive production thyroid hormones and hyperthyroidism. To summary, in case of familial hyperthyroidism it is worth to find and identify mutation in genes in receptor THSR, which may determinate risk assessment of hyperthyroidism and may use earlier appropriate therapy. The patients with activating mutation in receptor TSHR often need radical therapy, because long term therapy with thyrostatic drugs is ineffective.

P2-06-141

ADVANCED BONE AGE PRESENT IN A NEONATAL CASE OF SPORADIC NON-AUTOIMMUNE HYPERTHYROIDISM BEFORE ONSET OF SYMPTOMS: A CASE REPORT

Alexandra Stephenson[1], *Zoya Punjwani*[2], *Markus Eszlinger*[3], *Pawel Matusik*[4], *Aneta Gawlik*[5], *Ralf Paschke*[6]
[1]Biochemistry and Molecular Biology, University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; [2]Medical Sciences, University of Calgary, Calgary, AB, Canada; [3]1department of Biochemistry and Molecular Biology, Medicine, Oncology and Pathology Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [4]Department of Pediatrics and Pediatric Endocrinology, Medical University of Silesia, Katowice, Poland; [5]Department of Pediatrics and Pediatric Endocrinology, Medical University of Silesia, Katowice, Poland; [6]Department of Biochemistry and Molecular Biology, Medicine, Oncology and Pathology Cumming School of Medicine, University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada

Background: Sporadic congenital non autoimmune hyperthyroidism (SNAH) is rare. Several reported cases show that symptoms were present for at least 2-6 months before diagnosis of hyperthyroidism was established. This late diagnosis of hyperthyroidism often leads to premature bone aging.

Case Presentation: We report a case of SNAH for which the diagnosis of hyperthyroidism was established by chance prior to the onset of symptoms. In spite of early diagnosis at 4 months chronological age, an advanced bone age of 1.5 years was already present. The reason for thyroid hormone assessment of the asymptomatic child at 4 months of age was thyroxine treatment of the mother during pregnancy. There were no dysmorphic features present, her heart rate was in the upper normal range. She showed an enlarged thyroid as assessed by ultrasound. Before the molecular diagnosis was established the patient was treated with thiamazole 5mg/day, this was increased repeatedly. At 13 months of age the patient had a further increase in thyroid gland volume and a further increase in bone age of 2.5 years. Using high resolution melting PCR followed by Sanger sequencing of peripheral blood DNA, a heterozygous thyroid stimulating hormone receptor (TSHR) c.1895C>T mutation, resulting in a T632I amino acid change was detected. This mutation has previously been functionally characterized as constitutively activating. Neither parent carries this mutation, thus it is a sporadic germline mutation.

Conclusions: Early diagnosis of SNAH is essential and challenging in a neonate. This case demonstrates that premature bone aging can be present even before the onset of hyperthyroidism symptoms. Detection of germline TSHR mutation for patients suspicious for SNAH is important to direct therapy as non-autoimmune hyperthyroidism does not generally respond well to antithyroid drug treatment and total thyroidectomy is necessary for these patients.

P2-06-142

SURGICAL TREATMENT OF THE THYROTOXICOSIS SYNDROM PATIENTS: A PROSPECTIVE STUDY OF ANESTHETIC RISK AND ANESTHESIA PARTICULARITIES UNDER THYROIDECTOMIES

Olena Yefimova[1], *Sergii Tarasenko*[1], *Oleksander Tovkay*[1], *Volodymyr Palamarchuk*[1], *Volodymyr Voitenko*[1], *Pavlo Lishchynskyi*[1], *Vasylina Rudenko*[1]
[1]Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of Moh of Ukraine, Kyiv, Ukraine

Objectives: To analyze anesthetic risks and anesthesia particularities in patients with thyrotoxicosis syndrome who were undergone thyroidectomy. A prospective study.

Materials: During the period January 2016 - April 2018, thyroidectomy was performed in 440 patients with thyrotoxicosis syndrome (TTS). Surgical interventions were performed under conditions of general anesthesia with mechanical ventilation by using the low-flow/minimally-flow inhalation anesthesia (LFA/MFA) with sevoflurane in 349 (79.3 %) patients, by the total intra-

venous anesthesia (TIVA) with propofol in 91 (20.7 %) cases. We assessed the physical status on the American Association of Anaesthesiologists (ASA) classification, the frequency of concomitant pathology, the particularities of the anesthesia according to reports of anesthesiologists. All data are presented in form M±m.

Results: Among TTS patients, the 298 (68%) patients were the patients with diffuse toxic goiter (DTG), 104 (23%) patients were with a multinodular goiter (MNG) with TTS, the rest of patient were people with toxic adenoma - 22 (5%), 12 (3%) patients were with relapse of previously operated DTG or MNG. In 4 (1%) cases there was a combined pathology - papillary cancer in the background of MNG with TTS. According to ASA only 105 patients (23.9%) had - ASA I. 76.1 % out of 440 patients with thyrotoxicosis had ASA II–IV class. 21.1 % of patients were at high risk – ASA III and IV. It was analyzed that the physicians-anesthesiologists performed systemic haemodynamic and cardiac rhythm correction by administering antihypertensive, antiarrhythmic, sympathomimetic drugs in 202 (45.9 %) cases, of which 160 (45.8 %) – IA with sevoflurane, 42 (46.2 %) – with TIVA with propofol ($p = 0.551$, no statistically significant difference). Bradycardia appeared in 9.5 % and 2.2 % of cases of IA and TIVA respectively ($p < 0.05$). Perioperative hypertension (PHT), which required medication, arose in 26.1 % of cases and 25.3 % with IA and TIVA respectively ($p > 0.05$). The most commonly observed concomitant diseases in patients with DTG were dismetabolic cardiomyopathy – 55.0 %, and the patients with MNG with thyrotoxicosis had symptomatic arterial hypertension or hypertension – 64.3 %. No fatal case was observed.

Conclusions: TTS impairs the ASA physical status. There was 76.1% of patients with thyrotoxicosis, who had one or more concomitant pathologies - ASA II-IV class. 21.1% of the patients had ASA III and IV. Abnormal anesthesia were noted in 202 (45.9 %) cases, that means than the personified approach to the choice of type of anesthesia is needed.

P2-06-143

MEASUREMENT OF TSH-RECEPTOR ANTIBODY IN HYPERTHYROID PATIENTS ONE YEAR AFTER TREATMENT WITH ANTITHYROID DRUGS

Nevena Manevska[1], *Sinisha Stojanoski*[1], *Tanja Makazlieva*[1], *Anamarija Jovanovska*[1], *Sonja Kuzmanovska*[1], *Daniela Miladinova*[1]
[1]Institute of Pathophysiology and Nuclear Medicine, Medical Faculty, University “Ss Cyril and Methodius”, Skopje, Macedonia

Introduction: Graves’ disease is characterized by circulating TSH receptor antibodies (TRAb). The aim of this study was to determine the concentration of TRAb in patients with Graves’ disease; to register the presentation of both Graves’ disease and Hashimoto disease, to evaluate the association of TRAb with goiter phenomenon and presence of relapses in patients with higher concentration of TRAb, one year after treatment with antithyroid drugs.

Materials and methods: 39 hyperthyroid patients (10 males, and 29 females, mean age 45,3±12,9) were included in the study. All patients underwent standard thyroid function tests (FT4, TSH, aTPO) as well as ultrasonography of the thyroid was performed. TRAb were assessed with sandwich immunoluminometric assay on Maglumi 800 automatic analyzer, Snibe.

Results: All patients had laboratory test that showed hyperthyroid state (high level of FT4, low level of TSH). TRAB were positive in n = 25, 64,10% of the patients; n = 12, 31% were associated with Graves’ orbitopathy. Hashimoto disease was present in 17 hyperthyroid patients (43,6%) that had elevated both TRAb and aTPO, Hashimoto disease was present in 17 hyperthyroid patients (43,6%) that had elevated both TRAb and aTPO, while 8 patients (21%) with high TRAbs, were without Hashimoto disease. Thyroid enlargement was positively associated with higher concentration of TRAB in more than half of the patients (n = 21, 54%). Only 6 patients (15,4 %) were in remission, and 4 of them (10%) had high TRAb, while the others were still treated with antithyroid drugs, because of disease relapse, and (n = 12, 31%) had high-concentration of TRAb, while (n = 10, 25,6%) had negative TRAb values.

Conclusion: TRAb measurements are useful to diagnose Graves’ disease patients and for treatment algorithm regarding TRAb concentration.

P2-06-144

DIAGNOSTIC AND THERAPEUTIC OPTIONS IN THE MANAGEMENT OF HYPERTHYROIDISM

David Veríssimo[1], *Catarina Ivo*[1], *Vitória Duarte*[1], *João Silva*[1], *Dolores Passos*[1], *Luis Lopes*[1], *João Jácome de Castro*[1], *Mafalda Marcelino*[1]
[1]Department of Endocrinology, Armed Forces University Hospital, Lisboa, Portugal

Objective: Characterize the therapeutic options and outcomes in patients with hyperthyroidism.

Method: Retrospective study of 219 patients diagnosed with Graves’ Disease (GD) and Toxic Nodular Goiter (TNG) between 1987 and 2017, with a minimum follow-up of 5 years after last round of therapy.

Results: 219 patients, mostly women (70,3%), mean age of 50 years-old, 61,6% with GD and 38,4% with TNG.

In GD patients, first-line treatment was Anti-thyroid Drugs (ATD) in 85,9% of the patients, Radioactive Iodine (RAI) therapy in 9,63% and surgery in 4,4% of cases.

Treatment with ATD had an average period of 20 months of treatment with complete remission rate of 31%. Relapse rates were 25%, 6,9% e 33,6% in the 1º, 2º e 5º year of follow-up. 34,5% of the patients never achieved remission.

RAI treatment achieved a remission rate of 92,3% (medium dose of 9 mCi). Hypothyroidism occurred in 69,2% of the patients.

In TNG, ATD was first-line treatment in 46,4% of the patients, RAI therapy in 14,3% and surgery in 39,3%.

Treatment with ATD had an average period of 27 months, with complete remission rate of 15,4% after 5 years of follow-up. 69,23% of the patients didn’t achieved remission and 15,4% relapsed.

RAI treatment achieved a remission rate of 91,7% (mean dose of 7,8 mCi), achieving remission afterwards. Hypothyroidism occurred in just 16,7% patients.

All patients who underwent surgery (42,4% subtotal and 57,6% total thyroidectomy) had complete remission.

Conclusion: Our department follows the trend of other European countries. This data will improve our therapeutic approach to insure better remission rates, with lower relapse and less side-effects.

P2-06-145

INVASIVE COMPLETE HYDATIDIFORM MOLE AS AN UNUSUAL CAUSE OF HYPERTHYROIDISM

Pedro Rodrigues[1], *Sara Correia*[2], *Maria João Oliveira*[3]
[1]Endocrinology Department, Chvng/E, Faculty Medicine, Porto University, Vila Nova de Gaia, Portugal; [2]Endocrinology Department of Centro Hospitalar Vila Nova de Gaia Espinho, Portugal; [3]Centro Hospitalar Vila Nova de Gaia/Espinho, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal

Introduction: Hydatidiform mole (HM) is a form of gestational trophoblastic disease and can be categorized as complete or partial. Patients commonly present with vaginal bleeding, pelvic pressure or pain, and hyperemesis. Although less frequently, hyperthyroidism may be present due to the effect of tumor-derived hCG upon the TSH receptor.

Case report: A 53-year-old Caucasian multiparous woman presented with a one-month history of nausea, vomiting and nervousness. She went to the emergency department due to aggravated complaints and abdominal pain during the previous week. A tender hypogastric mass suggestive of enlarged uterus and cervix blood loss upon examination with a speculum were observed. Pelvic ultrasound showed an 81-mm-thick echogenic material filling the uterine cavity. Beta-hCG was >10000mIU/mL (0-2). She underwent uterine aspiration curettage and was admitted to the gynecology department. Baseline thyroid testing showed TSH 0.01µUI/mL (0.27-4.20), free T_4 2.26ng/dL (0.93-1.70) and free T_3 4.85pg/mL (2.57-4.43). She also presented tachycardia with a sinus rhythm, fine distal tremor and palpable non tender thyroid gland. TgAbs, TPOAbs and TRAbs were negative. Ultrasonography revealed a homogeneous thyroid gland, no nodules and normal color Doppler flow. Medical therapy with propranolol and methimazole was initiated providing improvement of hyperthyroidism symptoms and normalization of free T_4 and free T_3 two days later. Then she was submitted to total hysterectomy with bilateral oophorectomy. Three days after surgery beta-hCG levels dropped to 5023mIU/mL. Propranolol and methimazole doses were gradually tapered

and discontinued at discharge. Pathology analysis established the diagnosis of invasive complete HM. Chest X-ray was normal. Six weeks following surgery she presents beta-hCG 201.2mIU/mL and normal thyroid function and is also being followed at the outpatient gynecology clinic.

Conclusions: Laboratory evaluation of HM should include thyroid function tests. Appropriate control of hyperthyroidism is important until surgical removal of the source of beta-hCG secretion can be completed.

P2-06-146

ATTENTION DEFICIT HYPERACTIVITY DISORDER, HYPERTHYROIDISM OR SOMETHING ELSE?

Michael Yafi[1]
[1]The University of Texas, Pediatrics, Endocrinology and Diabetes, Houston, USA

The Case: A seven- year- old female had a history of early onset and severe attention deficit hyperactivity disorder (ADHD). A thyroid function test was obtained and showed elevated TSH and T4. The mother was told that hyperactivity was related to hyperthyroidism and was referred for a formal evaluation. The patient was not taking any medication and had no allergies.

The family history was significant for hyperthyroidism in maternal grandmother and an unexplained case of thyroidectomy in maternal uncle.

On physical examination, vital signs were normal; the weight was at 30th percentile while the height was at 40th percentile. There was no thyromegaly or tachycardia. Tanner Staging was I.

Laboratory work up showed:

TSH 23.5 UIU/ml (normal range 0.5-4.5)

T4 19.2 ugl/dl (normal range 4.5-12)

Free T4 2.4 ng/dl (normal range 0.8-1.6)

All levels of Antithyroid Peroxidase antibodies (Anti TPO), Thyroid Stimulating Immunoglobin (TSI) and Antithyroiglobulin (anti TG) were within normal range.

Based on symptomatology and thyroid function test, the diagnosis of thyroid resistance was suspected. An MRI of the pituitary gland showed no pituitary adenoma. Genetic testing showed a heterozygous thyroid hormone receptor β (*THRB*) gene mutation confirming the diagnosis. The mother was educated about this diagnosis; she revealed that many family members have had brain MRIs for the same suspicion. The patient was referred for behavioral therapy and special education school.

Discussion: Evaluation of thyroid axis is often performed in children with attention deficit-hyperactivity disorder. The result of thyroid tests should be evaluated based on the child's age -specific normal range and clinical symptoms. Attention deficit-hyperactivity disorder has been often associated with RTH. Resistance to the Thyroid Hormone (RTH) is a very rare disorder. This can be at the level of peripheral tissues, pituitary or both (glob al resistance). The symptoms of RTH may include same feature of hypo and hyperthryoidism based on affected tissues. Delayed bone maturation, learning disabilities and even mental retardation can be some features. The diagnosis of RTH is complicated and often misinterpreted as hyperthyroidism or pituitary adnoma, resulting in unnecessary therapy. Specific molecular genetic testing can confirm the diagnosis and understand the specific tissue related level of resistance. There are many reported genetic defects that can cause resistance to TH. Therapy is nonspecific, many therapeutic approach aim to control the symptoms of hyperthyroidism especially to control heart rate but generally speaking, there is no successful treatment for RTH itself.

P2-06-147

GRAVES DISEASE AND ACQUIRED HEMOPHLIA A- RARE DISEASE AND RARE ASSOCIATION

Mirjana Stojkovic[1], *Jasmina Ciric*[1], *Biljana Nedeljković-Beleslin*[1], *Milos Stojanovic*[1], *Marija Miletic*[1], *Nata Joksimović*[2], *Milos Zarkovic*[1]
[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [2]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia

Acquired hemophilia (AH) is a rare bleeding disorder, with an estimated incidence of about 1.5 case per million persons/year, caused by circulating autoantibodies directed against a specific clotting factor. As factor VIII (FVIII) inhibitors are the most commonly reported autoantibodies, AH, in the majority of cases, is an acquired FVIII deficiency (acquired hemophilia A, AHA). The incidence of AHA increases with age, with more than 80% of reported patients being 65 years or older. In contrast to the incidence of congenital hemophilia A, a recessive X-linked genetic disorder, AHA affects men and woman almost equally. As the inhibitors developed in AHA are autoantibodies, the disease may have an autoimmune cause and may be associated with autoimmune disease. About half of the cases is associated with post-partum period, autoimmune diseases, malignancies, infections or use of medications. AHA usually develops suddenly. Severe or life-threatening bleeds, requiring hemostatic and transfusion treatment occur in 70–90% of patients, being fatal in 5–10% of cases.

Graves' disease is an autoimmune thyroid disease (AITD) and a common cause of hyperthyroidism. Graves' disease is an example of an organ specific autoimmune disease, but, besides thyroid-specific antibodies, patients with AITD also often develop other "organ specific" antibodies and can have different autoimmune diseases.

We present a 49 years old woman with Graves' disease diagnosed a month after signs and symptoms of hypermetabolism occurred. At the time od diagnose thyroid hormonal status was as followed: fT4 51.1 pmol/L; fT3 20.85 pmol/L; TSH <0.005 mIU/L; TPOAb 2.25IU/mL; TgAb 358.65 IU/mL; TRAb 12.4IU/mL. She was started thyrosupressive drug therapy and soon became euthyroid with maintaining euthyroid state on small doses of thyrosupressive drug. She had a history of menometrorrhagia in the past year and easily bruising in past few months. A month after diagnosed with Graves' disease, during routine venipuncture, she experienced a severe bleeding in her arm muscles. Her blood analyses showed aPTT 70.2s PT 108% and FVIII 2%. "Cross match" test showed the presence of F VIII inhibitor (3.84 NBU). Kaolin Clotting time (KCT) was >200s, Thrombin time (TT) 17.7s. She was treated with corticosteroid infusions along with activated prothrombin complex concentrates (APCC). After initial rising of FVIII, APCC was discontinued, and corticosteroid therapy continued with addition of cyclophosphamide, with F VIII maintained in range 50-70%.

According to the literature, until now, there are only two published cases of Graves' disease associated with acquired hemophilia A.

Nodules 2

P2-07-148

DIAGNOSTIC SIGNIFICANCE OF SHEAR WAVE ELASTOMETRY FOR THYROID NODULES

Elina Gasparyan[1], *Olga Goroshko*[1]
[1]Medical Centre "Professor", Saint-Petersburg, Russian Federation

Aim: To evaluate diagnostic significance of shear wave elastometry for thyroid nodules.

Material and Methods: We have observed 253 patients (aged 17–72), directed to our medical centre for carrying out fine needle aspiration biopsy (FNAB). Nodule sizes were 23±11 mm. All patients underwent ultrasound assessment with the use of B-regime, Colour Doppler, and sonoelastography (SEG). When doing SEG we checked shear wave velocity (SWV) in nodules, using Acoustic Radiation Forced Impulse (ARFI) technology of Acuson S2000 (Siemens). From 5 to 10 measurements in m/s were carried out with calculations of arithmetical average. Elastometry indexes were retrospectively compared with a nodule cytological picture.

Results: It turned out that SWV indexes in thyroid nodules were dependent on the character of the cytological picture of nodules, as well as on their size, structure and vascularization. Thus, SWV in nodules of papillary cancer was 2.8±1.0 m/s, which is definitely higher ($p<0.001$) than in colloid nodules (1.8±0.5 m/s) and pseudonodules in Hashimoto's thyroiditis (2.1±0.5 m/s), as well as in follicular tumors (2.1±1.3 m/s). In suspicious hypoechogenic nodules of less than 15 mm with uneven and fuzzy contours, avascular, and having a homogeneous structure or with calcinations, SWV indexes reached 2.8–3.8 m/s. In nodules of more than 15 mm having isoechogenic structure and degenerative changes with intra/peri vascularization SWV is significantly lower – 1.3–2.1 m/s.

Conclusions:

* Sonoelastometry indexes depend on the cytological picture, nodule sizes, their structure, and vascularization.
* cancer nodules have definitely higher SWV indexes, probably due to their significant density.
* Shear wave elastometry can serve as an additional criterion of nodule selection for FNAB in patients with numerous nodules.

P2-07-149

MOLECULAR TESTING FOR CITOLOGICALLY INDETERMINATE THYROID NODULE: A SINGLE INSTITUTIONAL EXPERIENCE

Claudia Cipri[1], Giovanna De Maglio[2], Elda Kara[1], Silvia Maria Sciannimanico[1], Silvia Galasso[1], Maria Carpentieri[1], Stefano Pizzolitto[2], Marco Piemonte[3], Fabio Vescini[1], Franco Grimaldi[1]

[1]University Hospital Santa Maria Della Misericordia, Endocrinology and Metabolism Unit, Udine, Italy; [2]University Hospital Santa Maria Della Misericordia, Pathology Unit, Udine, Italy; [3]University Hospital Santa Maria Della Misericordia, Otolaryngology Unit, Udine, Italy

Objectives: Fine-needle aspiration (FNA) cytology represents the gold-standard procedure to identify benign thyroid lesions. However 15-30% of thyroid FNA are cytologically indeterminate. Molecular tests have been recently introduced to improve the diagnostic management of these cases. Aim of the study: was the evaluation of cyto-histological and molecular patterns in a single-institution cohort of patients.

Methods: We reviewed 139 cases with FNA cytology classified according to Bethesda System, followed up in Udine University Hospital in the years 2017-2018. Molecular analysis was performed on DNA extracted by smears samples, with real time PCR method for a 4-gene panel (4GP) BRAF/NRAS/HRAS/KRAS.

Results: On the basis of the citology 118 (73%) cases were classified as Tyr3a while 21 (13%) as Tyr3b. Among them 52 (37%) underwent thyroidectomy. Molecular classification of Tyr3a cases was: BRAFmut 16 cases (14%), KRASmut 3 (2%), NRASmut 9 (8%), HRASmut 6 (5%). Tyr3b were subdivided in: BRAFmut 7 cases (33%), KRASmut 1 (5%), NRASmut 2 (10), HRASmut 0 (0%), Mutations detected were: BRAF V600E, KRAS G12D, G12V and Q61R, NRAS G13R, Q61K and Q61R, HRAS Q61x. All the mutations were mutually exclusive.

Among surgically Tyr3a resected cases 23 out of 39 (60%) had a positive histology for thyroid cancer (TC) as well as 7 out of 13 (54%) Tyr3b cases. Positive predictive value (PPV), negative predictive value (NPV), sensitivity (S) and Specificity (Sp) are summarized in the table.

Conclusions: Our data confirmed the high S and PPV of BRAF V600E mutation for malignant nodules detection, supporting its rule-in role in indeterminate FNA cytology samples. Despite the low S of each single genes, the 4GP allows a higher S in the detection of malignancy and confirms a possible important role of molecular panel analysis in this setting. However, the low PPV both of 4GP and of each single gene (except of BRAF) confirmed the necessity of managing molecular data in a complete clinical context evaluation, as reported in all guidelines about management of thyroid nodules.

Tyr3a/Tyr3b	*PPV*	*NPV*	*S*	*Sp*
BRAFmut	94%		57%	95%
KRASmut	33%		7%	82%
NRASmut	40%		13%	73%
HRASmut	50%		3%	95%
RASmut	39%		20%	50%
BRAF-NRAS-KRAS-HRASmut	67%		80%	45%
RAS-WT		38%	43%	50%
all-WT		63%	20%	55%

P2-07-150

THERAPEUTIC EFFICACY OF PERCUTANEOUD ETHANOL INJECTION (PEI) IN THE MANAGEMENT OF CYSTIC THYROID NODULES IN A LARGE SERIES OF PATIENTS

Guia Vannucchi[1], Irene Campi[2], Danila Covelli[3], Stefano Borgato[2], Chiara Carzaniga[2], Carla Colombo[2], Laura Fugazzola[2]

[1]Endocrinology Department, IRCCS Istituto Auxologico Italiano; University of Milan, Milan, Italy; [2]Endocrine and Metabolic Department, Istituto Auxologico Italiano IRCCS, Italy; [3]Ospedale Maggiore Policlinico, Italy

Therapeutic efficacy of percutaneous ethanol injection (PEI) in the management of cystic thyroid nodules in a large series of patients.

Objectives: To evaluate the outcome of PEI in the treatment of benign cystic thyroid nodules.

Methods: retrospective analysis of a cohort of 212 euthyroid patients treated from 2008 to 2019 by the same team. All patients were studied by ultrasound with calculation of nodule volume and previously submitted to evacuation of the cystic liquid. At the first PEI session blood samples for measurement of TSH, FT4, FT3 or reflex TSH (from 2014), TgAb, TPOAb and calcitonin were collected. PEI was performed every 30 days for a maximum of 5 procedures.

Results: Overall, the procedure was well tolerated with no side effects in 81% of patients; 7% of patients reported moderate local pain during ethanol injection, 11% a transient pain after PEI session and less than 1% required analgesic medical treatment. Mean basal nodule volume was 21ml (range 3.1-313ml). The mean percentage of nodule volume reduction was 75±25ml (range 15-99%). 52% of patients underwent a single PEI session because of disappearance or marked reduction of nodule. In particular, in 53% of nodules we observed a complete evacuation of the cystic cavity with only residual collapsed capsule. Overall, smaller nodules had a better response to treatment (Spearman test: P = 0.02), however five patients with very large nodules (45-313 ml) showed a reduction of 94% or more. Half of the patients were cured after the first PEI and 30 % at the second one. Nearly 10% of patients responded after 4-5 sessions of PEI, while 5% did not respond to treatment and underwent surgery or thermal nodule ablation because of persistent mixed/solid large nodule.

Conclusions: PEI is the first-line therapy for benign cystic thyroid nodules. Nodules smaller than 40 ml are better responsive. However, PEI should be considered also for very large cystic nodules due to possible impressive shrinkage, safety and very low cost.

P2-07-151

THE CALCITONIN IN FINE-NEEDLE ASPIRATE WASHOUT FLUID AND SERUM OF DIFFERENT THYROID NODULES AND ITS INFLUENCE FACTORS

Jing Wu[1], *Jian Long*[2], *Xiao Ya Zheng*[3], *Zhiwei Tang*[3], *Wenwen He*[3], *Qifu Li*[4]

[1]The Department of Endocrinology of the First Affiliated Hospital of Chongqing Medical University, Chong Qing, China; [2]The Department of Endocrinology of the First Affiliated Hospital of Chongqing Medical University, Mont St Aignan, France; [3]The Department of Endocrinology of the First Affiliated Hospital of Chongqing Medical University, China; [4]The First Affiliated Hospital of Chongqing Medical University, the Department of Endocrinology of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Objective: The calcitonin in fine-needle aspirate washout fluid (FNA-CT) can be used to assist in the diagnosis of medullary thyroid cancer. However, the cut-off values and the influence factors of FNA-CT are not clear.

Methods: We investigated 338 thyroid nodules of 304 patients. After smearing, the syringe and needle used for the FNA were rinsed with calcitonin free serum (0.25 mL). The calcitonin in the washout was measured by ECLIA.

Results: In the 338 thyroid nodules of 304 patients, 3 cases (0.88%) were diagnosed as MTC by FNAC, which sCT value was 21.8-1755pg/ml (median 292pg/ml) and FNA-CT value was 2000-8000pg/ml (median 2000pg/ml). In 335 cases of non-MTC nodules, the sCT value was < 0.5-17.53pg/ml (median 1.29pg/ml),and FNA-CT was detected in 37.6% (126/335) of non-MTC nodules which the value was 0.51-2000 pg/ml (median 16.51pg/ml). The levels of FNA-CT of MTC were significantly higher than that of non-MTC (P = 0.004).Among non-MTC nodules, the levels of sCT and FNA-CT in males were higher than those in females (sCT P = 0.000; FNA-CT P = 0.017). The FNA-CT level of the middle pole nodules was significantly different from that of the upper pole and the lower pole (P = 0.001). There was no significant difference in the levels of sCT and FNA-CT among different groups of age, echo propertie, TI-RADS grading and FNAC(Bethesda classification) (P>0.05).

Conclusions: The FNA-CT level of MTC were significantly higher than that of non-MTC, so FNA-CT can be used to assist in the diagnosis of medullary thyroid cancer. However, FNA-CT can also be detected in 37.6% of non-MTC nodules, in which the FNA-CT level may be related to gender and node location. Non-MTC nodules with detectable FNA-CT need to be carefully distinguished from MTC by other methods.

Keyword: Medullary thyroid carcinoma; Thyroid nodules; FNAC; FNA-CT; sCT

P2-07-152

THE PREVALENCE OF POLYCYSTIC THYROID DISEASE IN PEDIATRIC PATIENTS

Tamar Peshkova[1], *Liana Jashi*[2], *Inga Abesadze*[1], *Maia Tugushi*[1]

[1]Batumi Endocrinology Center, Batumi, Georgia; [2]Batumi Seamen"S Medical Centre, Dept of Internal Medicine, Dept of Endocrinology, Batumi, Georgia

Objective: Pediatric polycystic thyroid disease (PCTD) is an uncommon condition, frequently asymptomatic and often discovered incidentally. The occurrence and significance of this condition in children is unclear. The objective of this study was to determine the prevalence of PCTD in patients who visited our hospital.

Methods: We retrospectively reviewed ultrasound (US) characteristics of the 521 pediatric patients aged 17 and less who underwent thyroid US at our institution from April 2017 to February 2019. The diagnosis of PCTD was based on the presence of four or more thyroid cysts, negative tests for antithyroglobulin antibodies (TgAb) and antithyroperoxidase antibodies (TPOAb), no evidence for thyroid diseases other than their thyroid cysts. Patients were stratified into age groups: 3-10 years (group I) and 11-17 years (group II). The prevalence of PCTD was evaluated and compared with respective of patient's gender and thyroid status in each group.

Results: Seventy three patients (24 - group I; 39 - group II) received the diagnosis of PCTD. Cysts were more common in boys than in girls in group I and was reversed in group II. Among these 73 children 15 (4 - group I ; 11 - group II) had subclinical hypothyroidism (TSH level above 5.0 mUI/mL and normal free thyroxine), 2 (0 - group I, 2 - group II) had overt hypothyroidism (TSH level above 10.0 mUI/mL and free thyroxine level below 0.7ng/dL).

Conclusion: Our results highlights that little is known about the evolution of PCTD. It may be prudent to arrange long term follow up of pediatric patients identified with polycystic thyroid as they may gradually demonstrate loss in thyroid function over time.

P2-07-153

PERCUTANEOUS ETHANOL INJECTION AS A TREATMENT STRATEGY FOR BENIGN CYSTIC AND MIXED THYROID NODULES

Catarina Machado[1], *Lúcia Almeida*[2], *Patrícia Tavares*[2], *Ana Lopes*[3], *Joana Ferreira*[4], *Marta Ferreira*[2], *Gustavo Rocha*[2], *Cláudia Freitas*[3], *Ana Paula Marques*[4], *Luís Raposo*[5], *Maria João Oliveira*[2]

[1]Ch de Vila Nova de Gaia/Espinho, Centro Hospitalar Vn Gaia, Vila Nova Gaia, Portugal; [2]Endocrinology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal; [3]Endocrinology Department, Centro Hospitalar Do Porto, Portugal; [4]Endocrinology Department, Unidade Local de Saúde de Matosinhos, Portugal; [5]Endocrinology Department, Centro Hospitalar Lisboa Ocidental, Portugal

Background: Thyroid nodules (TN) are common in clinical practice. Large cystic or partially cystic TN, although benign, may cause symptoms and require specific intervention. Percutaneous ethanol injection (PEI) has been proposed as a treatment strategy. We aim to analyse the efficacy and safety of ultrasound (US) guided PEI in the treatment of benign cystic and mixed TN.

Material and Methods: Prospective study with euthyroid patients with cystic or partially cystic TN. The internal fluid was aspirated and the volume of injected ethanol corresponded to approximately 50% of the aspirated fluid. US revaluation 1 week and 3 weeks after PEI. Therapeutic success was defined as volume reduction of, at least, 50% associated with disappearance of clinical symptoms.

Results: Eighteen patients had PEI, 12 (66.7%) female with mean age 49.7±14.7years. PEI was repeated in 6 patients (33.3%). The median largest diameter of the thyroid cyst was 4.0 cm (interquartile range [IQR] 3.5-5.1 cm; range 2.8-6.6 cm); the median volume pre-PEI was 16.6 mL (IQR 8.7-24.7 mL; range 4.9-87.9 mL). There was a 50% or greater reduction in nodule volume in 6 patients (33.3%) just one week after first PEI and in 8 (44.4%) after 3 weeks. In the most recent imaging available [median follow-up of 4 months (range 7 days-10 months)], only one patient had restitution of nodule volume after 8 months, with the rest being asymptomatic with progressive reduction of TN volume. Sixteen (88.9%) patients had a 50% or greater reduction in nodule volume (median volume decrease 70.0% [IQR 59.3%-88.0%]). Adverse effects occurred in 3 patients (16.7%) and were mild and temporary (slight pain after injection and headache).

Conclusion: PEI seems to be an effective and safe procedure to treat benign cystic and mixed TN, without serious side effects. In symptomatic patients, it may be considered the first treatment option.

P2-07-154

CORRELATION BETWEEN THYROID ULTRASOUND AND HISTOPATHOLOGY REPORT - ARE WE SEEING THE SAME?

Ana Lopes[1], *Tiago Santos*[1], *Sheila Koch Jamal*[2], *André Couto de Carvalho*[1], *Cláudia Freitas*[1], *Maria Helena Cardoso*[1]

[1]Centro Hospitalar e Universitário Do Porto, Porto, Portugal; [2]Centro Hospitalar de Trás-Os-Montes e Alto Douro, Portugal

Objectives: The aim of this study was to evaluate the correlation between morphological and structural thyroid gland features on ultrasound and histopathology.

Methods: Imaging and pathology records of patients submitted to total thyroidectomy (TT) were retrospectively reviewed. The thyroid volume was calculated using the formula *length X width X thickness X 0.479* for each of the two lobes. Only the largest nodule identified in each thyroid lobe was selected for analysis.

Results: Two hundred and seven patients were included (82.6% females) with mean age of 53 ±14 years. The main indications for TT were large goiter

(n = 103, 49.6%) and "suspicious" cytology (n = 77, 37.2%). For thyroid volume evaluation, 89 patients were considered. The median ultrasonographic volume was 23.7 cm^3 (IQR 27.5) and the median histopathologic volume was 56.7 cm^3 (IQR 60.9). The median of these differences was 30.1 cm^3 (IQR 42.8). For nodule dimension, 284 nodules were included. The median size of the largest nodule on ultrasound was 27 mm (IQR 23) and on histopathologic evaluation was 18 mm (IQR 19). The median of these dimension differences was 7 mm (IQR 9). The description of thyroid parenchyma echostructure was available in 60 patients. In 47 patients (78.3%) the thyroid gland parenchyma was classified as "heterogeneous", but only 17 (36.2%) of these presented concurrent lymphocytic lesions on the histopathology report.

Conclusion: Our work revealed potentially relevant differences between the ultrasonographic and histopathologic evaluation of the thyroid gland morphology and structure. The median difference of the volume obtained by the two methods suggests that ultrasound tends to underestimate total thyroid volume. The median difference of the nodules largest dimension found indicates that ultrasound may overestimate nodular size.

P2-07-155

THE INCIDENCE OF THYROID NODULES INCREASES WITH AGE IN WOMEN OF REPRODUCTIVE AGE

Edvard Pirnat[1], *Tina Ušaj*[2], *Katja Tuta*[2], *Katica Bajuk Studen*[1], *Nataša Bedernjak Bajuk*[1], *Miha Jesenko*[1], *Nina Ostaševski Fernandez*[1], *Katja Zaletel*[1], *Simona Gaberscek*[3]
[1]Department of Nuclear Medicine, University Medical Centre Ljubljana, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Slovenia; [3]Department of Nuclear Medicine, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Slovenia

Objectives: By ultrasound examination, thyroid nodules are found in 19 to 65% of unselected individuals. In the older age groups, the incidence of thyroid nodules increases with age. In the younger age groups as well as in pregnant women, data on the incidence of thyroid nodules is scarce. The aim of our study was to establish the incidence of thyroid nodules in pregnant and non-pregnant women of reproductive age.

Methods: In this prospective clinical study we included 142 pregnant and 306 non-pregnant female volunteers of reproductive age. Women with the known thyroid disease were not included in the study. In every volunteer, thyroid ultrasound was performed using a 7.5-MHz linear transducer. The number of volunteers with thyroid nodules was detected.

Results: Pregnant women were significantly older than non-pregnant women (32.9±5.1 and 29.8±7.1 years, respectively, $p<0.001$). Thyroid nodules were detected significantly more frequently in pregnant than in non-pregnant women (21.2% and 12.7%, respectively, $p = 0.032$). Furthermore, in the larger group of non-pregnant women of reproductive age, the frequency of thyroid nodules significantly increased with age ($p<0.001$). In the age group up to 24 years, thyroid nodules were detected in 4.1% of women, in the age group 25-30 years, thyroid nodules were detected in 7.2%, in the age group 31-35 years, thyroid nodules were detected in 12.7%, and in the age group above 35 years, thyroid nodules were detected in 31.2% of women.

Conclusions: Our results show that the incidence of thyroid nodules in women of reproductive age significantly increases with age. With the increasing age of pregnant women, beside Hashimoto's thyroiditis also thyroid nodules may represent a challenge in the screening strategy.

P2-07-156

THYROID NODULES AND OBESITY

Hermine Danielyan[1], *Armine Danielyan*[2], *Nona Martirosyan*[3]
[1]Medical Center Surb Grigor Lusavorich, Yerevan, Armenia; [2]Yerevan State Medical Univercity, Armenia; [3]Nairi Medical Center, Armenia

Thyroid nodule is an abnormal growth of thyroid cells that forms a lump within a thyroid gland. Thyroid disorders have no age limitations, but are more common in older adults .It was found that there is a complex relationship between thyroid disease, body weight and metabolism.

Study background: Data from epidemiological studies demonstrate correlation between BMI (body mass index) and the risk of mortality rate. Insulin resistance may contribute to the development of nodular thyroid disease. Changes in thyroid morphology have been reported in obese patients. For each patient a thyroid ultrasound was initially performed in the hospital. 100 patients with benign thyroid nodules with hypo and euthyroidism were enrolled. Patients were to live in Armenia (a highland country, with mild iodine deficiency) native Armenians. We examined the frequency of nodular thyroid disease in obese patients BMI >30 kg/m2, waist circumference > 90, and investigated the metabolic parameters which may play a role in thyroid nodule formation. All patients made laboratory blood measurements, including TSH, TPO antibodies, FT4 . BMI was calculated using standard protocols. Association BMI with the presence of thyroid nodules were evaluated. Patients were in the different age groups**.**

SEX AND AGE DATA

20-40	1	5
40-60	9	24
60 and older	17	44

BMI	NUMBER OF PATIENTS
25-30	3
30-40	73
40 and over	24 (all patients included)

Aim of the Study: the incidence of thyroid nodules is increasing, as is that of obesity. This study investigated association between thyroid nodules and obesity.

Results of the Study: Analysis showed that age, gender, BMI and eating habits were independently correlated with presence of thyroid nodules.

Conclusion: the higher the BMI is, the higher is the possibility of thyroid nodules. This study seems to indicate the association between obesity and thyroid nodules.

P2-07-157

MANAGEMENT OF PATIENTS WITH AUTONOMOUSLY FUNCTIONING THYROID NODULES AND NORMAL TSH BLOOD LEVEL

Miodrag Lacic[1]
[1]Polyclinic Lacic, Thyroid Department, Zagreb, Croatia

Objectives: The purpose of this study was to evaluate the results of radionuclide therapy with iodine-131 (I-131) in patients (pts) with autonomously functioning thyroid nodules (AFTNs) and a normal thyroid stimulating hormone (TSH) blood level.

Methods: In this study 91 cytological benign AFTNs in 81 pts (69 female and 12 male) with normal TSH level have been treated with a fixed I-131 doses (370 MBq). Clinical exam, ultrasonography with color Doppler (US), fine needle aspiration biopsy (FNAB), TSH, FT4, FT3, anti-TPO, anti-Tg and thyroid scan (scintigraphy) have been performed in all pts before and 6 months after I-131 therapy.

Results: The median age of the pts was 60 (range 35 - 90) years. AFTNs were located more frequently in the right thyroid lobe (52 nodules) than in the left lobe (39 nodules). In 14 pts a solitary AFTN has been found on ultrasonography and the other 67 patients had AFTNs in multinodular goiter. Ten pts had two AFTNs. On post I-131 therapy thyroid scan in 63 AFTNs complete therapy effect has been observed, but in 28 AFTNs a scintigraphycally partial effect has been noted. Statistical analysis showed a significant reduction in the thyroid (p = 1,2674E-19) and AFTNs (p = 0,00047) volume after J-131 therapy. TSH value significantly increased (p = 0,00013) and FT4 value significantly decreased (p = 1,2525E-05) after I-131 therapy. FT3 (p = 0,3598), anti-TPO (p = 0,8179) and anti-Tg (p = 0,2211) values did not change significantly.

Conclusion: This study shows that radionuclide therapy with I-131 in pts with AFTN and normal TSH blood level is a simple, cheap and very effective modality. The effect of the I-131 therapy on AFTNs can be evaluated with a thyroid scan 6 months after I-131 therapy.

P2-07-158

HYALINIZING TRABECULAR TUMOUR MIMICKING HASHIMOTO'S THYROIDITIS

Meri Davitadze[1], *Levan Ramishvili*[1], *Teona Azanishvili*[2], *Punith Kempegowda*[3]

[1]V. Iverieli Endocrinology, Metabology, Dietology Center "Enmedic", Tbilisi, Georgia; [2]Cancer Research Center, Tbilisi, Georgia; [3]Institute of Metabolism and Systems Research, University of Birmingham, Health Education West Midlands, Birmingham, UK

Introduction: Hyalinizing trabecular tumour (HTT) is a rare thyroid neoplasm with unclear aetiology. Although current consensus suggests HTT is a benign condition, the diagnosis may be missed due to its rarity. We present one such case which was initially diagnosed as autoimmune thyroiditis.

Case report: A 54-year-old male presented with worsening neck discomfort for a year. He denied any structural or functional dysthyroid symptoms such as pain, dyspnoea, dysphagia, hoarseness, changes in weight, appetite, bowel movement or palpitation. He had hypertension and hypercholesterolaemia and was on appropriate medications. There was no history of radiation exposure. His younger sister is diagnosed with autoimmune thyroiditis.

On examination, he was clinically unremarkable with no obvious neck signs. Blood tests revealed biochemical euthyroidism. Neck ultrasound showed multinodular goitre with a dominant hypoechoic solid nodule measuring 8x6 mm. Patient refused any further investigation at this point. He returned a year later with ongoing symptoms. Clinical examination and blood tests remained unremarkable. Ultrasound examination showed multinodular goitre and the dominant hypoechoic solid nodule had increased in size, now measuring 11x8mm. There were no changes in regional lymph nodes. Fine needle aspiration cytology (FNAC) of the nodule showed abundant Hürthle cell groups and small groups of follicular cells wraped in lympho-infiltrates suggestive of autoimmune thyroiditis. In view of predominant Hürthle cells on FNAC and enlarging nodule, patient underwent total thyroidectomy.

Histology of the lesion revealed trabecular structures with extensive hyalinization and nuclear atypia in thyrocytes in keeping with HTT. Patient has been on regular follow-up for three years now on physiological replacement of thyroxine and has no further complications.

Conclusion: HTT may mimic autoimmune thyroiditis on FNAC. Although our patient underwent total thyroidectomy for different indication, awareness of HTT and their characteristic features is valuable for their recognition and management as well as for the possible prevention of overtreatment for benign disease.

P2-07-159

THE BENEFIT OF PARATHYROID HORMONE MEASURMENT IN FINE-NEEDLE ASPIRATION WASHOUT IN THE DIAGNOSIS OF CYSTIC PARATHYROID ADENOMA CONFUSED WITH THYROID NODULE: A CASE REPORT

Anar Aliyev[1], *Ayan Mammadova*[2], *Farida Nasirova*[2], *Aygun Guliyeva*[2], *Nigar Aliyeva*[3], *Rashad Ismayilov*[2]

[1]Department of Nuclear Medicine, Department of Thyroid Center, Baku, Azerbaijan; [2]Department of Nuclear Medicine, Azerbaijan National Center of Oncology, Baku; [3]Department of Clinical Biochemistry, Azerbaijan National Center of Oncology, Baku

Introduction: Cystic parathyroid adenoma is very rare and it constitutes 0.01% of all neck masses. Patients often present with complaints of neck swelling and sometimes mistakenly diagnosed as thyroid nodules. In the diagnosis, neck ultrasonography (USG) and Tc-99 m MIBI parathyroid SPECT/CT imaging methods are frequently used.

Case report: A 52-year-old woman admitted to the department of endocrine surgery with complaints of swelling of the anterior neck in the last week. The patient did not have any complaints other than swelling. Neck USG revealed a cystic nodule greater than 3 cm in the right lobe of the thyroid gland and then the patient was referred to our department to perform a fine aspiration biopsy (FNAB). The control USG evaluation during the FNAB procedure suggested that the lesion might be outside the thyroid capsule, and a portion of the aspirated fluid was sent to the biochemistry laboratory for parathyroid hormone (PTH) washout test. Cytology results were evaluated as cell deprived cyst fluid, and because the PTH washout test's result was higher than 5000 ng/dl, serum PTH, calcium, phosphorus, creatinine, vitamin D, and Tc-99 m MIBI parathyroid SPECT/CT analyses were performed. Serum PTH was 126 pg/ml (normal: 15-65 pg/ml), calcium was 2.64 mmol/l (normal: 2.15-2.5 mmol/l), phosphorus, creatinine and vitamin D tests were normal. In the SPECT/CT study, Tc-99 m MIBI involvement was not observed in the back localization of the right lobe. As a result of all this information, the patient was referred to the head and neck surgery department. Cystic parathyroid adenoma was described histopathologically after the surgical operation.

Conclusions: Although cystic parathyroid adenoma is rare, in some studies, up to 20% of patients MIBI involvement cannot be monitored in SPECT/CT as in this case. In such cases, PTH measurement in the cystic fluid is an easy method, and it can play an important role in the diagnosis and direct the clinician in the management of the patient.

Thyroid Hormone and Inflammation

P2-08-160

AUTOIMMUNITY TO SELENOPROTEIN P IN THYROID PATIENTS

Qian Sun[1], *Sebastian Mehl*[2], *Christian L. Görlich*[3], *Julian Hackler*[4], *Kostja Renko*[5], *Waldemar Minich*[2], *Lutz Schomburg*[6]

[1]Charité- Universitätsmedizin Berlin; Institut für Experimentelle Endokrinologie, Charite-Berlin, Berlin, Germany; [2]Charite Berlin, Germany; [3]Charité- Universitätsmedizin Berlin; Institut für Experimentelle Endokrinologie, Berlin, Germany; [4]Charité-Universitätsmedizin Berlin; Institut für Experimentelle Endokrinologie, Berlin, Germany; [5]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institut für Experimentelle Endokrinologie, Berlin, Germany; [6]Charité- Universitätsmedizin Berlin, Institut für Experimentelle Endokrinologie, Berlin, Germany

Autoimmunity is characterized by an impaired self-tolerance, and is the major cause for the two common autoimmune thyroid diseases (AITD), Hashimoto thyroiditis (HT) and Graves' disease (GD). In AITD, the autoantibodies (aAb) to thyroglobulin (Tg), thyroperoxidase (TPO), and TSH receptor (TSH-R), respectively, are characteristic diagnostic markers. The thyroid gland is rich in the trace element selenium (Se), which may modulate the endocrine-immune interface and affect hydrogen peroxide metabolism, inflammation and aAb generation. Se transport is mediated by selenoprotein P (SELENOP), and low Se supply is known to increase HT risk. We hypothesize that autoimmunity to SELENOP may contribute to the development of AITD.

A quantitative assay for aAB to SELENOP was established and used to analyze serum samples from a cohort of thyroid patients and healthy probands. Serum Se concentrations were assessed by total reflection X-ray fluorescence (TXRF), serum SELENOP by ELISA, and serum glutathione peroxidase (GPX3)-activity by a photometric enzyme assay.

Prevalence of SELENOP-aAB in thyroid patients was higher than in controls, and higher in HT as compared to GD. SELENOP-aAB positive patients displayed relatively increased serum Se and SELENOP concentrations in comparison to controls. Immunoglobulins isolated from SELENOP-aAb positive samples precipitated measurable Se concentrations, in contrast to control immunoglobulins, verifying their specificity.

These results indicate that SELENOP-aAB affect Se and SELENOP status, and may be of pathophysiological relevance in AITD.

P2-08-161

4-METHYLUMBELLIFERONE INHIBITS HYALURONAN SYNTHESIS IN ORBITAL FIBROBLASTS

Erika Galgoczi[1], *Florence Jeney*[2], *Monika Katko*[3], *Annamaria Erdei*[3], *Annamaria Gazdag*[3], *Miklós Bodor*[4], *Eszter Berta*[5], *Bernadett Ujhelyi*[6], *Steiber Zita*[7], *Ferenc Gyory*[8], *Endre Nagy*[9]

[1]Division of Endocrinology, University of Debrecen, Faculty of Medicine, Department of Medicine, Debrecen, Hungary; [2]Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [3]University of Debrecen, Debrecen, Hungary; [4]Department of Medicine, Division of Endocrinology, University of Debrecen, Debrecen, Hungary, Division of Clinical Pharmacology, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary; [5]Division of Endocrinology, Department of Medicine, University of Debrecen, Debrecen, Hungary, Division of Clinical Pharmacology, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary; [6]Department of Ophthalmology, Faculty of Medicine, University of Debrecen; [7]Department of Ophthalmology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [8]Department of Surgery, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [9]Division of Endocrinology, Dept. of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

Objectives: Graves' orbitopathy (GO) is an autoimmune disease of the orbits characterized by excessive production of hyaluronan (HA), mainly by fibroblasts. HA can bind large amount of water leading to the edematic swelling of orbital soft tissues and resulting in the progression of the symptoms of the disease. 4-methylumbelliferone (4-MU) is a specific inhibitor of the synthesis of HA with beneficial effects on inflammation and certain autoimmune diseases in animals. 4-MU is registered as an OTC spasmolytic in Europe.

Methods: HA production and mRNA expression of hyaluronan synthases (*HAS1*, *HAS2*, and *HAS3*) and hyaluronidases (*HYAL1* and *HYAL2*) were measured by ELISA and RT-PCR, respectively, in the presence and absence of 4-MU in unstimulated and TGF-β stimulated fibroblasts of GO orbital (n = 4), non-GO orbital (n = 4) and dermal origin (n = 4). The effect of 4-MU on proliferation was measured using BrdU incorporation.

Results: 4-MU treatment (1 mmol/L) resulted in an average 87% reduction of HA synthesis ($p<0.001$) and 75% reduction of proliferation rate ($p<0.001$) in fibroblasts irrespective of the site of origin without a decrease in cell viability. After 4-MU treatment, the expression of *HAS2*, which is the dominant isoform of HA synthases in the orbit, decreased by 80% ($p<0.0001$), while an average 2.5-fold increase in *HYAL2* expression ($p<0.001$) was detected which was not dependent on the origin of fibroblasts. In addition to the observed effects of 4-MU in unstimulated cases, TGF-β stimulated HA production was decreased by 4-MU via inhibition of the TGF β induced elevation in *HAS1* expression.

Conclusions: Any intervention which can decrease local HA production may diminish intraorbital soft tissue volume and could interfere with the pathogenesis of GO. We found that 4-MU is an effective inhibitor of HA synthesis in orbital fibroblasts *in vitro*, adding it to the list of putative therapeutic agents in GO.

P2-08-162

MODULATION OF T-CELL MIGRATION AS A THERAPEUTIC OPTION FOR GRAVES' DISEASE AND ORBITOPATHY

Utta Berchner-Pfannschmidt[1], *Svenja Plöhn*[2], *Matthias Hose*[3], *Curdt Claudia*[4], *Mareike Horstmann*[5], *Anke Schlüter*[6], *Lars Michel*[3], *Banga Paul*[7], *Hansen Wiebke*[8], *Anja Eckstein*[9]

[1]Molekulare Ophthalmologie, Department of Ophthalmology, University Hospital Essen, Essen, Germany; [2]Molecular Ophthalmology, Essen, Germany; [3]Universitätsklinikum Essen; [4]Universität Duisbug-Essen; [5]Univerity Hospital Essen, Molecular Ophthalmology, Essen, Germany; [6]Department of Otorhinolaryngology, University Hospital Essen, Essen, Germany; [7]University Hospital Essen, Essen, Germany; [8]Universität Duisburg-Essen; [9]Univ.-Augenklinik, Molecular Ophthalmology, Department of Ophthalmology, University Eye Hospital Essen, Essen, Germany

Aim: Graves' disease (GD) is caused by autoimmunity mainly against the stimulating thyrotropin receptor (TSHR). In this study we explored modulation of T-cell migration as a therapeutic option for GD in a preclinical mouse model.

Methods: In this model autoimmune hyperthyroidism and orbitopathy was genetically induced by four subsequent immunizations with a plasmid encoding the *human* TSHR A-subunit. In order to modulate T-cell migration the antagonist of sphingosine-1-phosphate receptor, FTY720, was administrated orally via drinking water (0.5 mg/kg body weight daily) to the mice. TSHR immunized mice received the drug either in a preventive manner during disease onset or thereafter in a therapeutic manner. Weight, body temperature and heart rate of living mice was monitored. Lymphocyte composition was evaluated in blood and spleen by flow cytometry. TSHR antibody titer and activity were evaluated in sera by binding assay and cell-based bioassay. Thyroid and orbita were immunohistologically analysed for abnormalities.

Results: TSHR immunized mice developed elevated levels of CD4+, CD8+ and CD25+ effector T cells in blood and spleen. Treatment with FTY720 in either manner decreased these levels while B cells remained stable. Moreover, preventive treatment strongly decreased the titer of anti-TSHR antibodies and TSHR stimulating activities in immunized mice. In contrast, TSHR blocking activities were induced upon therapeutic treatment. Hyperthyroidism in TSHR immunized mice was characterized by weight gain, elevation of body temperature, tachycardia, elevated serum T4 concentration and hyperplastic thyroid morphology. Hyperthyroidism was, however, completely prevented upon treatment with FTY720. Moreover, examination of orbital tissue showed amelioration of orbitopathy by reduction in orbital CD3 T cell infiltration, adipogenesis and hyaluronan deposition.

Conclusions: Classification of total disease outcome revealed that preventive treatment with FTY720 blocked development of GD while therapeutic treatment prevented progression into severe disease. Our study discovered that modulation of T-cell migration has a potential for early treatment of GD and orbitopathy.

P2-08-163

CONTRIBUTION OF INFLAMMATORY AND HYPOXIC FACTORS TO ORBITAL IMMUNOPATHOLOGY IN GRAVES' DISEASE

Gina-Eva Görtz[1], *Anke Schlüter*[2], *Christoph Jesenek*[3], *Mareike Horstmann*[4], *J Paul Banga*[5], *Sven Brandau*[6], *Anja Eckstein*[7], *Utta Berchner-Pfannschmidt*[8]

[1]University Hospital Essen, Molecular Ophthalmology, Essen, Germany; [2]Department of Otorhinolaryngology, University Hospital Essen, Essen, Germany; [3]University Hospital Essen, University of Duisburg-Essen, Molecular Ophthalmology, Department of Ophthalmology, Essen, Germany; [4]Univerity Hospital Essen, Molecular Ophthalmology, Essen, Germany; [5]King's College London, Molecular Ophthalmology, Department of Ophthalmology, Diabetes and Endocrinology, London, UK; [6]Klinik für Hals-, Nasen-, Ohrenheilkunde, University Hospital Essen, Department of Otorhinolaryngology, Essen, Germany; [7]Univ.-Augenklinik, Molecular Ophthalmology, Department of Ophthalmology, University Eye Hospital Essen, Essen, Germany; [8]Molekulare Ophthalmologie, Department of Ophthalmology, University Hospital Essen, Essen, Germany

Graves' disease is an autoimmune thyroid disorder caused by autoantibodies against the thyrotropin stimulating hormone receptor leading to hyperthyroidism. Graves' orbitopathy (GO) is the main extra-thyroidal manifestation which is characterized by inflammation, remodeling of the orbital connective fat and muscle tissue. GO patients individually develop disease subtypes with either more inflammation, proptosis or muscle dysfunction. Inflammation and expansion of the retroocular tissue can cause induction of hypoxia-inducible factor (HIF) and NF-kB dependent pathways. In this study we investigated whether cytokines such as TNF-α and INF-γ and hypoxic conditions influence the action of HIF, NF-kB and induction of immunomodulatory markers. We isolated orbital fibroblasts (OF) from retrobulbar fat biopsies of GO patients and from murine orbital tissue of experimental GO model. OF were stimulated with TNF-α and INF-γ under normoxic and hypoxic conditions. HIF-1α and NF-kB levels were determined by western-blot analysis. Expression of immunomodulatory markers like PD-L1, ICAM-1 and HLA-DR as well as receptors like TSHR and CD90 were analyzed by flow cytometry and real time PCR. We found increased HIF-1α levels in OF upon TNF-α/INF-γ-stimulation under normoxia and also under hypoxia. Also, NF-kB expression was enhanced under hypoxia and further induced upon TNF-α/INF-γ stimulation in OF. Consequently, immunomodulatory markers like PD-L1, ICAM-1, HLA-DR

and the TSHR were strongly induced after treatment with TNF-α/INF-γ. Our results indicate that inflammatory processes combined with hypoxia contribute to expression of immunomodulatory factors in GO.

P2-08-164

CYTOKINES, PPAR-GAMMA, OR PPAR-ALPHA AGONISTS DIFFERENTIALLY MODULATE CXCL8 VERSUS CXCL10, IN PRIMARY CELLS FROM GRAVES' DISEASE AND OPHTHALMOPATHY

Silvia Martina Ferrari[1], *Francesca Ragusa*[1], *Giusy Elia*[1], *Sabrina Rosaria Paparo*[1], *Ilaria Ruffilli*[1], *Maria Pia Bartolomei*[2], *Francesco Nasini*[3], *Marco Nardi*[4], *Poupak Fallahi*[5], *Alessandro Antonelli*[1]

[1]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy; [2]Aoup, U.O. Oculistica Universitaria, Pisa, Italy; [3]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, Pisa, Italy; [4]University of Pisa and University Hospital of Pisa, Department of Surgical, Medical and Molecular Pathology, Ophthalmopathy Unit I, Pisa, Italy; [5]University of Pisa, Department of Translational Research of New Technologies in Medicine and Surgery, Pisa, Italy

Thyrocytes secrete C-X-C chemokines, in particular (C-X-C motif) ligand (CXCL)8 and CXCL10, though its physiopathological significance is still unknown.

The aim of this study is to evaluate the modulation of CXCL8 secretion *versus* CXCL10, in human thyroid follicular cells (TFC) in Graves' disease (GD), and in primary fibroblasts (OF) or preadipocytes (OP) from Graves' ophthalmopathy (GO).

CXCL8 and CXCL10 were measured in the supernatants of TFC, OF or OP cells basally and after 24h of treatment with IFNγ (1000 IU/mL) and/or TNFα (10 ng/mL), in presence/absence of different concentrations of the PPARγ agonist pioglitazone (0, 0.1, 1.0, 5, 10, 20 μM), or the PPARα agonist fenofibrate (5, 10, 50, 100 μM).

CXCL8, not CXCL10, was detected basally in TFC, OF and OP. The treatment with TNFα stimulated the CXCL8 secretion in a dose-dependent manner. CXCL10 secretion was significantly induced by IFNγ (P<0.01) and not by TNFα, whereas CXCL8 was induced by TNFα (P<0.01), and inhibited by IFNγ (P<0.01), in TFC, OF and OP. The co-treatment with TNFα+IFNg synergistically induced the IFNγ-stimulated CXCL10 secretion (P<0.01) and reversed the TNFα-stimulated CXCL8 secretion (P<0.01), in TFC, OF and OP. Pioglitazone had no significant effect on the TNFα-stimulated CXCL8 secretion, while inhibited CXCL10. Fenofibrate significantly inhibited both CXCL8, and CXCL10.

In conclusion, these data first show that TFC, OF, and OP secrete CXCL8 and CXCL10 differentially, stimulated by specific proinflammatory cytokines or their combination, finally determining the nature of infiltrating lymphocytes in human GD and GO. This could reflect a different role of the two chemokines in the course of the disease, as CXCL10 could be associated with the initial phase of the disease when IFNγ prevails, while CXCL8 with a later chronic phase, when TNFα is preponderant. PPARα agonists are promising molecules to be evaluated in GD.

P2-08-165

ANALYSIS OF CHOSEN POLYMORPHISMS RS 7138803 A/G FAIM2, RS 7093069 C/T IL-2RA, RS 5742909 C/T CTLA-4 IN PATHOGENESIS OF AUTOIMMUNE THYROID DISEASES IN CHLDREN

Artur Bossowski[1], *Joanna Goscik*[2], *Natalia Wawrusiewicz-Kurylonek*[3], *Anna Bossowska*[4], *Tomaso Aversa*[5], *Domenico Corica*[5], *Adam Kretowski*[6], *Malgorzata Wasniewska*[7]

[1]Dep.of Pediatric Endocrinology, Diabetology with Cardiology Division. Medical University. Bialystok, Medical University in Białystok, Białystok, Poland; [2]Centre for Experimental Medicine, Diabetology with Cardiology Division, Medical University of Białystok, Białystok, Department of Endocrinology and Diabetes with Internal Medicine, Medical University in Białystok, Białystok, Poland; [3]Department of Endocrinology and Diabetes with Internal Medicine, Medical University in Bialystok, Białystok, Poland; [4]Division of Cardiology, Internal Affairs Ministry Hospital in Białystok, Bialystok, Poland; [5]Department of Human Pathology of Adulthood Abd Childhood, University of Messina, Italy; [6]Department of Endocrinology and Diabetes with Internal Medicine, Medical University in Białystok, Bialystok, Poland; [7]University of Messina, Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy, Department of Human Pathology of Adulthood Abd Childhood, University of Messina, Italy

Introduction: Autoimmune thyroid diseases are multifactorial diseases with a genetic susceptibility and environmental factors. A potential role of the Fas apoptotic inhibitory molecule 2 (FAIM2) gene, the high-affinity alpha subunit (CD25) of the interleukin-2 receptor (IL-2RA) gene, the cytotoxic T cell antigen 4 (CTLA-4) gene polymorphisms on autoimmune thyroid diseases (AITDs) in children has not been established equivocally yet.

Objective: To estimate the association of polymorphisms of FAIM2, IL-2RA and CTLA-4 genes with the predisposition to Graves' disease (GD) and Hashimoto's thyroiditis (HT) in children.

Methods: The study was performed in 170 patients with GD, 81 with HT and 110 healthy volunteers from two endocrine centers (Białystok, Messina). The three single nucleotide polymorphisms (SNPs): Rs7138803-FAIM2, Rs7093069-IL-2RA and Rs5742909-CTLA-4 were genotyped by TaqMan SNP genotyping assay with platform QuanStudio 12K Flex - OpenArray plates using the real-time PCR.

Results: Rs7138803 A/A genotypes were more frequent in HT and GD patients in comparison to healthy subjects ($p = 0.009$ with OR = 3.5; $p<0.0075$ with OR = 2.9, respectively). Rs7138803 A alleles were more frequent in GD patients in comparison to healthy subjects ($p = 0.019$ with OR = 1.5).

Rs7093069 C alleles were more frequent in HT patients in comparison to healthy subjects ($p = 0.032$ with OR = 1.61). That means that risk for development of HT is exactly 1.6 higher for C allele in comparison to T allele.

Rs5742909 C alleles were more frequent in HT patients in comparison to healthy subjects ($p = 0.045$ with OR = 1.8).

Conclusions: Rs7138803 A/G, Rs7093069 C/T and Rs5742909 C/T polymorphisms could contribute to development of HT in children. The main risk factor for rs7093069 and rs5742909 is allele C. In case of rs7138803 the main risk factor is allele A for development of both GD and HT.

P2-08-166

ASSOCIATION BETWEEN INTERLEUKIN-8 AND INTERLEUKIN-10 LEVELS AND CLINICAL ACTIVITY OF GRAVES' ORBITOPATHY

Mariya Stoynova[1], *Alexander Shinkov*[1], *Ralica Ivanova*[1], *Mashka Angelova*[1], *Gergana Todorova*[1], *Georgi Kirilov*[1], *Roussanka Kovatcheva*[1]

[1]Medical University-Sofia, University Hospital of Endocrinology, Bulgaria

Objectives: To compare interleukin-8 (IL-8) and interleukin-10 (IL-10) levels in patients with Graves' orbitopathy (GO), patients with Graves' disease without GO and healthy subjects; to follow the changes in interleukin levels during treatment of GO; to assess the correlation between the two interleukins and clinical activity score (CAS).

Material and methods: Thirty-one patients with GO, 30 patients with Graves' disease without GO and 30 healthy subjects were enrolled. In all of them thyroid function was assessed, plasma IL-8 and IL-10 were measured. GO patients were treated with systemic glucocorticoids (GCs) for 3 months with a total dose of 5500 mg. CAS, IL-8 and IL-10 were assessed at baseline, after the first 1500 mg GCs and at the end of the therapy.

Results: IL-8 baseline levels were highest in patients with Graves' disease without GO and lowest in healthy controls ($p = 0.044$). At baseline IL-10 was highest in healthy controls and lowest in GO patients ($p = 0.024$). The relative change of IL-8 and IL-10 after the first 1500 mg GCs was 10.3% ($p<0.001$) and 13.5%, respectively ($p = 0.001$). Neither IL-8, nor IL-10 correlated with CAS at baseline and at the end of the therapy. Although both CAS and the interleukin levels decreased significantly after the first 1500 mg GCs, the correlation between them was not statistically significant ($p>0.05$).

Conclusions: The interleukin baseline levels differed between the three studied groups: IL-8 was lowest in healthy controls, while IL-10 was lowest in GO patients. In GO patients their levels changed early in the GC course, as did CAS. Further investigation is needed to assess their practical applicability in clinical practice.

The study was funded by Medical University-Sofia, "Grant-2017", № 8523/12.12.2016.

P2-08-167

ASSOCIATION BETWEEN IL-17 AND TH17-RELATED CYTOKINE, AND TIGHT JUNCTION PROTEIN IMMUNOEXPRESSION IN PATIENTS WITH AUTOIMMUNE THYROID DISEASE

Tatjana Zake[1], *Sandra Skuja*[2], *Ieva Kalere*[3], *Ilze Konrade*[4], *Valerija Groma*[2]

[1]Institute of Anatomy and Anthropology, Riga Stradins University, Riga East University Hospital, Riga, Latvia; [2]Institute of Anatomy and Anthropology, Riga Stradins University, Riga, Latvia; [3]Riga Stradins University, Riga Stradins University, Department of Human Physiology and Biochemistry, Riga, Latvia; [4]Riga Stradins University, Department of Internal Medicine, Riga East University Hospital, Riga, Latvia

Objectives: Th17 lymphocytes have changed the classical paradigm of Th1/Th2 dichotomy in the pathogenesis of autoimmune thyroid diseases (AITD). We aimed to investigate the relationship between immunohistochemical expression of Th17 cell hallmark cytokine IL-17 and tight junction (Tj) proteins – claudin-1 and zonula occludens-1 (ZO-1) as well as cytokines driving differentiation of pathogenic Th17 lymphocytes – IL-23 and IL-1β in AITD patients.

Methods: Twenty-one patients with Hashimoto's thyroiditis (HT) and 8 patients with Graves' disease (GD) who underwent thyroid surgery were enrolled in this study. Eighteen age and gender-matched patients with colloid goiter displaying an absence of thyroid antibodies served as controls. Forty-seven paraffin-embedded thyroid tissue blocks were obtained from the Pathology Centre of Latvia. Immunohistochemical staining including IL-17, claudin-1, ZO-1, CD68, IL-23, and IL-1β was performed in each case. Five thyroid tissue samples obtained during surgery were processed for immunofluorescent and immunogold labeling.

Results: IL-17 immunopositivity in the thyroid follicular cells was significantly higher in HT and GD patients compared to colloid goiter patients, whereas expression of IL-1β and IL-23 was higher in HT patients than in GD and colloid goiter patients. In HT patients, a positive association between IL-17 and IL-23, and IL-17 and IL-1β expression was found. Expression of ZO-1 was reduced in HT patients, however, no difference was observed in claudin-1 immunopositivity in HT and GD patients compared to colloid goiter patients. In HT patients, IL-17 overexpression in the thyrocytes was strongly associated with the presence of intrafollicular CD68-positive cells. HT patients did not show any significant correlation between IL-17 and claudin-1 or ZO-1.

Conclusions: Overexpression of IL-23 and IL-1β was found in HT but not in GD patients. Both ILs were correlated with IL-17 expression, suggesting that they may play a role in HT pathogenesis. No association between IL-17 and Tj protein expression was found in AITD.

P2-08-168

LOWER PROPORTIONS OF CD19+IL-10+ AND CD19+CD24HI+CD27+IL-10+ BREG CELLS IN CHILDREN AND ADOLESCENT WITH AUTOIMMUNE THYROID DISEASES

Artur Bossowski[1], *Karolina Stozek*[2], *Kamil Grubczak*[3], *Vivianna Marolda*[4], *Andrzej Eliasiewicz*[3], *Marcin Moniuszko*[4]

[1]Dep.of Pediatric Endocrinology, Diabetology With Cardiology Division. Medical University. Bialystok, Medical University in Białystok, Białystok, Poland; [2]Dep.of Pediatric Endocrinology, Diabetology With Cardiology Division. Medical University. Bialystok, Medical University in Bialystok, Białystok, Poland; [3]Department of Regenerative Medicine and Immune Regulation, Medical University of Bialystok, Białystok, Poland; [4]Department of Regenerative Medicine and Immune Regulation, Medical University of Bialystok, Medical University in Bialystok, Białystok, Poland

Introduction: Regulatory B cells (Bregs) control inflammation and autoimmunity. The aim of this study was to estimate the expression of Bregs (phenotype $CD19^+CD24^{hi}CD27^+$ IL-10^+,$CD19^+$IL-10^+, $CD1d^+CD5^+CD19^+$IL-10^+ and $CD1d^+CD5^+CD19^+CD24^+CD27^+$) in pediatric cohort with autoimmune thyroid diseases (AITD) and health controls.

Methods: A total of 100 serum samples were obtained from 53 pediatric patients with Graves' disease (GD) (N = 12 newly diagnosed, mean age 12.5±3.5 and N = 17 during methimazole therapy, mean age 12.7±4.4), Hashimoto's thyroiditis (HT) (N = 10 newly diagnosed, mean age 13.3±2.9 and N = 10 during L-thyroxine therapy, mean age 13.7±3.4) and compared with healthy controls (C) (N = 15, mean age 13.1±3.1). The expression of the immune cells populations were analyzed by the four-color flow cytometry using a FASC Canto II cytometer (BD Biosciences).

Results: There is decreasing tendency in number of B10 cells among all B lymphocytes and also among all lymphocytes, in every studied group, comparing to C. We report reduction of IL-10 production in Bregs cells with expression $CD19^+CD24^{hi}CD27^+$IL-10 and $CD1d^+CD5^+CD19^+$IL-10^+ in both untreated and treated AITD.

Conclusion: The reduction in number of Bregs with $CD19^+CD24^{hi}CD27^+$ IL-10^+ and $CD19^+$IL-10^+ expression could be responsible for breaking the immune tolerance and AITD development in children.

Keywords: autoimmune thyroid diseases, Bregs, cytokine 10, TSH receptor antibodies, children

Monday, September 9th, 2019
Poster Session 3

Autoimmunity 2

P3-01-167

LEVELS OF ANTITHYROID ANTIPEROXIDASE AND ANTITHYROGLOBULIN ANTIBODIES IN PATIENTS WITH GRAVES HYPERTHYROIDISM - PREDICTORS OF INITIAL AND SUSTAINED REMISSION AND CONSECUTIVE HYPOTHYROIDISM

Sinisha Stojanoski[1], *Nevena Manevska*[1], *Tanja Makazlieva*[1], *Magdalena Mileva*[1], *Toni Tripunoski*[1]

[1]Institute of Pathophysiology and Nuclear Medicine, Medical Faculty, University "Ss Cyril and Methodius", Skopje, Macedonia

Objectives: To investigate the predictive value of antithyroid antiperoxidase (aTPO) and antithyroglobulin (aTg) levels on remission rate or hypothyroidism in subjects with Graves hyperthyroidism (GH) treated with antithyroid drugs (ATD).

Material and methods: Randomized, prospective, longitudinal study in the period 2013 – 2019 was performed. 80 GH patients (TSH < 0,01 mIU/L, FT4 > 30 pmol/L, FT3 > 8 pmol/L), 59 females (73,75%) and 21 males (26,25%), aged 51±12 years were included. Subjects were divided into 4 subgroups (20 patients each) according to aTPO and aTg levels: group I - no antibodies; group II (< 500 IU/ml), group III (500 - 1000 IU/ml) and group IV (> 1000 IU/ml). All subjects underwent 24 months of propylthiouracil (PTU) treatment with follow up of 24 months after remission (TSH > 0,4 mIU/L, FT4 11-25 pmol/L, FT3 2,8-6,5 pmol/L). Blood samples were analyzed every 4 months.

Results: In group I, 11 (55%) of the patients attained remission. In the follow up period 5 (45%) of them had disease relapse. In group II, 12 (60%) attained remission and 5 (42%) had disease relapse. In group III, 15 (75%) attained remission, 2 (13%) had disease relapse and 4 (26%) developed hypothyroidism. In group IV, 18 (90%) attained remission, 1 (5%) had disease relapse and 9 (50%) developed hypothyroidism. Group II patients attained remission in 60%, similar as group I in 55% ($p < 0,3$). Patients in group III and IV had significantly higher remission rate compared to group I and II ($p < 0,001$). Baseline values of aTPO and aTg > 1000 IU/ml were significant predictors of consecutive hypothyroidism ($p < 0,05$).

Conclusion: Baseline aTPO and aTg values above 500 IU/ml were significantly prognostic for attaining and sustaining remission in GH and values above 1000 IU/ml were significant predictors of consecutive hypothyroidism.

P3-01-168

THYROID DISORDERS IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITION THERAPY

Silvia Paredes[1], Claudia Costa[2], Joana Oliveira[2], Ana Paula Santos[2], Isabel Torres[2]

[1]Hospital de Braga, Braga, Portugal; [2]Ipo Do Porto, Portugal

Background: Immune checkpoint inhibitors (ICI) (anti-CTLA-4, anti-PD-1) are effective therapeutic options for certain cancers. Nevertheless, ICI are associated with several immune-related adverse events and immune-related thyroiditis is among the most prevalent. The aim of this study was to evaluate thyroid abnormalities in patients treated with ICI.

Methods: We performed a retrospective study involving patients evaluated at IPO do Porto, one of the 3 oncologic centers of Portugal, between January/2017 and January/2019. All patients treated with ICI and referred for endocrinology evaluation were included.

Results: Twelve patients were included, 8 men (66.7%) with a mean age of 61.2±13.1 years at diagnosis. Seven patients (58.3%) were treated with pembrolizumab, 4 patients (33.3%) with nivolumab and 1 patient (8.3%) with ipilimumab. Half of the patients had lung cancer, followed by melanoma 25% (n = 3), bladder 8.3% (n = 1) and gastric cancer 8.3% (n = 1) and Hodgkin lymphoma (n = 1). Three patients (25%) had preexisting autoimmune thyroid disease and aggravated their hypothyroidism, which was previously compensated. Six patients presented with hypothyroidism, with a median of 109 days (range 14-332) since the start of ICI. Two patients presented with thyrotoxicosis, 41 and 50 days after starting ICI. Both evolved to hypothyroidism, after 39 and 43 days, respectively. During follow-up, 1 patient died, and the remaining are under levothyroxine substitution. The median time on treatment with levothyroxine is 277 days (range 82-453). One patient presented with subclinical hyperthyroidism and is under surveillance. No patient needed interruption of ICI because of thyroid dysfunction, nevertheless 2 patients stopped the drug due to progressive disease; one died and the other is still under levothyroxine treatment.

Conclusions: Thyroid disorders manifested mostly as hypothyroidism and even thyrotoxicosis seems to be followed by hypothyroidism. Patients require long-term levothyroxine substitution. Our results emphasize the importance of close monitoring of thyroid function in patients treated with ICI.

P3-01-169

THYROID BLOOD FLOW DOPPLER AND TSH RECEPTOR ANTIBODIES ARE ACTIVITY PARAMETERS WITH DIFFERENT KINETICS IN GRAVES` THYROTOXICOSIS TREATED WITH ANTI-THYROID DRUGS

Emmanouela Koutouridou[1], Panagiotis Tsoupidis[1], Kleoniki Tsoumani[1], Erik Uddman[1], Tereza Plank[2], Tomas Jansson[3], Mikael Lantz[4]

[1]Department of Endocrinology, Skåne University Hospital, Malmö, Sweden; [2]Department of Endocrinology, Skåne University Hospital, Malmö, Sweden, Department of Clinical Sciences, Lund University, Lund, Sweden, Malmö, Sweden; [3]Department of Biomedical Engineering, Lund University, Lund, Sweden; [4]Department of Endocrinology, Lund University, Skåne University Hospital, Malmö, Sweden

Objective: TSH receptor antibodies (TRAb) are currently used as the major activity parameter for Graves' disease (GD), both in early and later treatment phase as well as when patients are suggested to stop anti-thyroid drugs (ATD) treatment. The aims of this study were to define a unit for the quantification of thyroid blood flow by measuring color Doppler pixels in the region of interest and to use this unit as an estimation of disease activity in ATD-treated patients with GD.

Methods: Patients with GD treated with ATD (n = 15) were followed with regular visits and analysis of TSH, thyroid hormones, TRAb and thyroid-peroxidase antibodies (anti-TPO). Thyroid color Doppler was performed in the largest transversal cross-sectional area and three separate pictures were saved from both the right and the left lobe. The margins of the largest transversal cross-sectional thyroid areas were outlined and the number of red and blue pixels, which represent the active blood flow, was calculated as a percentage of total pixels in the region of interest by a specifically designed program.

Results: Thyroid blood flow color Doppler fulfilled the criteria as an activity parameter and decreased in parallel with TRAb. However, the kinetics differed and in most cases blood flow Doppler signal showed a continuous decrease although TRAb had already reached a stable low titer. The decrease in blood flow Doppler signal was similar in both lobes but the magnitude could differ between the two lobes, especially in the later treatment phase.

Conclusion: We have demonstrated that thyroid blood flow color Doppler can be quantified with a new method and that both blood flow Doppler and TRAb are GD activity parameters with different kinetics.

P3-01-170

THE EMERGENCE OF GRAVES' DISEASE FOLLOWING RADIOIODINE TREATMENT OF BENIGN THYROID DISEASES

Katja Zaletel[1], Danijela Krković[2], Tjaša Zaletel[3], Edi Pirnat[4], Simona Gaberščček[5]

[1]Department of Nuclear Medicine, University Medical Centre Ljubljana, Department of Nuclear Medicine, University Medical Centre Ljubljana, Department of Nuclear Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Department of Nuclear Medicine, University Medical Centre Maribor, Slovenia; [3]School of Biological Sciences, University of Cambridge, UK; [4]Department of Nuclear Medicine, University Medical Centre Ljubljana, Slovenia; [5]Department of Nuclear Medicine, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Slovenia

Aim: The occurrence of Graves' disease (GD) following radioiodine (I-131) treatment of toxic nodular goitre has been described in approximately 5% of treated patients. Given that less data is available explaining the etiology of this phenomenon, our aim was to evaluate the incidence and risk factors of I-131 induced GD in patients with benign thyroid disorders of different etiologies living in an iodine sufficient area.

Materials And Methods: In this retrospective study we included consecutive patients with benign thyroid disease that we treated with I-131 during the period between January and June 2014. Before the treatment, we measured the uptake of iodine 123 (I-123) at 20-hours or the uptake of technetium-99m-pertechnetate (Tc-99m). In all patients without history of GD, we evaluated "*de novo*" occurrence of GD for a period of 12 months following

I-131 application. We estimated thyroid function, thyrotropin receptor antibodies (TRAb) concentration and we performed thyroid scintigraphy. Mann-Whitney analysis was applied, p value <0.05 was considered statistically significant.

Results: During observed period, 304 patients (254 females and 50 males; mean age, 62.3±17.4 years) were treated with I-131. Among them, 101 (33.2%) were treated for GD, 98 (32.2%) for solitary toxic adenoma, 95 (31.3%) for toxic nodular goitre, 6 (2.0%) had Hashimoto's thyroiditis and 4 (1.3%) patients had euthyroid nodular goitre. Compared with other causes of hyperthyroidism, GD patients showed significantly higher uptake of I-123 (median, 76% and 31%, respectively, $p < 0.01$) or Tc-99m (median, 3.02% and 1.09%, respectively, $p < 0.01$). The treatment activity in GD patients was significantly lower than in other patients (median, 726 MBq and 745 MBq, respectively, $p < 0.01$). Amongst 203 patients with no history of GD, "*de novo*" GD occurred following I-131 therapy in only 5 (2.5%) patients (3 females, 2 males), whereby 2 were treated for toxic adenoma, 2 for toxic nodular goitre and 1 had Hashimoto's thyroiditis. These patients were significantly younger than those without GD after I-131 therapy (mean, 48.2±18.2 and 67.9±14.4 years, respectively, $p < 0.01$) and received lower activity of I-131 (median, 579 MBq and 746 MBq, respectively, $p = 0.06$). However, Tc-99m uptake before the therapy did not differ significantly (median, 1.12% and 1.01%, respectively, $p = 0.90$).

Conclusion: I-131 induced GD occurs rarely in I-131 treated patients with benign thyroid disorders and no history of GD. According to our preliminary data, possible risk factors include younger age and lower I-131 activity.

P3-01-171

POTASSIUM IODIDE (KI) SENSITIVE GRAVES' HYPERTHYROIDISM. (1) TOO SENSITIVE PATIENTS WHO BECAME HYPOTHYROID

Ken Okamura[1], *Kaori Sato*[1], *Megumi Fujikawa*[1], *Sachiko Bandai*[1], *Hiroshi Ikenoue*[1], *Takanari Kitazono*[1]
[1]Dept of Medicine and Clinical Science, Graduate School of Medicine, Kyushu University, Fukuoka, Japan

Iodide induced hypothyroidism was well known in patients with Hashimoto thyroiditis but iodide sensitivity in Graves' hyperthyroidism (GD), another autoimmune thyroid disease, has not been well elucidated. Since KI therapy was shown to be effective for the treatment of GD who showed side-effects to thionamide antithyroid drugs (JCEM99:3995,2014), we tried KI treatment in patients with untreated GD. In this study, we will report on the iodide-induced hypothyroidism. [Materials & Methods] Between 1996 and 2011, 504 patients with untreated high^{123}I uptake GD were treated with 100mg KI and initial response was evaluated after 180 days. [Result] Serum free T_4 (fT_4) level became low with high TSH level in 65 (12.9%) (Group A1, too sensitive), fT_4 became low with suppressed TSH in 45 (8.9%)(A2), both fT_4 and TSH level became normal in 78(15.5%) (Group B, sensitive), fT_4 and fT_3 level became normal with suppressed TSH in 149 (29.6%) (Group C1) or remained T_3 toxicosis in 83 (16.4%) (C2) (partially sensitive) and fT_4 level remained high in 84 (16.6%)(Group D)(resistant). Escape was suggested in about 35% in Group C, 83% in Group D but in 0 – 10% in Group A and B. In Group A1, serum fT_4 level became low after 68 (14 – 175) days and TSH level elevated after 104 (35 – 269) days. Remission was observed in about 50% and another 30% was well controlled with KI in Group A and B. [Discussion] Our study suggested that about 37% of the GD patients were iodide sensitive becoming eu- or hypothyroid without thionamide antithyroid drugs. Apparent TSH elevation was observed in 13% of GD patients who were too sensitive to KI and successfully treated with KI and L-thyroxine. [Conclusion] Not only Hashimoto thyroiditis but also about a third of the patients with GD were considered to be iodide sensitive or too sensitive.

P3-01-172

PREDICTION OF RELAPSE IN GRAVE´S DISEASE

Lucia Almeida[1], *Catarina Machado*[2], *Patrícia Tavares*[3], *Marta Ferreira*[4], *Ana Sousa*[4], *Helena Alves*[4], *Maria João Oliveira*[5]
[1]Centro Hospitalar Vila Nova de Gaia, Vila Nova de Gaia, Portugal; [2]Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova De Gaia, Portugal; [3]Centro Hospitalar Vila Nova de Gaia, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal; [4]Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal; [5]Centro Hospitalar Vila Nova de Gaia/Espinho, Centro Hospitalar de Vila Nova de Gaia e Espinho, Vila Nova de Gaia, Portugal

Introduction: Grave's disease (GD) is the most prevalent cause of hyperthyroidism. Usually, first treatment option is anti-thyroid drugs (ATD). However, the risk of relapse is high and there are several pretreatment predicting risk factors. The aim of our study was to investigate which factors could be involved.

Methods: Retrospective review of patients with GD followed in an Endocrine outpatient clinic from 2012 to 2018, with follow-up of at least 12 months after ATD withdrawal. Demographic and clinical data was collected. SPSSv.2.3 was used for statistical analysis; p value <0,05 was considered with statistical significance.

Results: We included 152 patients (73.7% female) with 49.5±14.1 years old; 24.3% were smokers.

Orbitopathy was described in 27.6% and Goiter in 86.2%. The most common ATD used was tiamazol (96.1%).

Thirty-two patients (21.1%) never reached remission: 84.4% were treated with radioiodine, 6.3% with surgery; 9.3% continued ATD treatment, for at least 12 more months.

After a median time of 13 months, 78.9% of patients reached remission but 38.3% of those relapsed after 5 months at least.

Men relapsed more than women: 42.5%*vs*25.9% (p = 0,08).

Relapse was established in 45.2% with orbitopathy *vs* 24.5% in those with no orbitopathy (p<0,05). 35.1% of smokers have relapsed *vs* 21.7% in non-smokers (p<0,05).

Mean initial TRAbs was higher in patients relapsing: 9.1*vs*3.65 (p<0,01). TRAbs at ATD withdrawal were also higher in patients who relapsed: 4,0*vs*1.6 (p = 0,014).

Baseline FT4 and FT3 were higher in patients who relapsed (p>0,05).

Discussion/Conclusions: This analysis allowed us to find several risk factors that may predict DG relapse. Like Struja T et al., we believe they should be part of a risk score developed to better guide treatment decisions. Based on such score we could avoid prescription or soon interrupt ATD therapy in patients with the highest risk of relapse from the very beginning.

P3-01-173

CARDIOVASCULAR RISK FACTORS, AUTOIMMUNITY, THYROID VOLUME AND LIPID PROFILE IN GRAVES' DISEASE

Celestino Neves[1], *João Sérgio Neves*[2], *Sofia Castro Oliveira*[2], *Oksana Sokhatska*[3], *Miguel Pereira*[2], *Ana Oliveira*[2], *José Luís Medina*[4], *Luís Delgado*[3], *Davide Carvalho*[1]
[1]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário de São João, Faculdade de Medicina Da Universidade Do Porto, Institute for Research and Innovation in Health Sciences, Faculdade de Medicina Da Universidade Do Porto, Porto, Portugal; [2]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário de São João, Faculdade de Medicina Da Universidade Do Porto, Porto, Portugal; [3]Service and Laboratory of Immunology, Centro Hospitalar Universitário de São João, Porto, Portugal; [4]Faculdade de Medicina Da Universidade Do Porto, Porto, Portugal

Introduction: Graves' disease is an autoimmune disease accounting for the majority of hyperthyroidism cases, with a multisystemic influence. Our aim was to assess the interrelationships between cardiovascular risk factors, autoimmunity and insulin resistance in Graves' disease.

Material and Methods: We measured free T3 (FT3), free T4 (FT4), TSH, thyrotropin receptor antibodies (TRAb), anti-thyroglobulin and anti-TPO antibodies, thyroid volume (TV), BMI, glucose, HbA1c, HOMA-IR (Homeostatic

Model Assessment for Insulin Resistance), levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides, apolipoprotein B (apoB), apoA1, lipoprotein(a), CRP (C-reactive protein), folic acid, B12 vitamin in 85 patients with Graves' disease, defined by TSH <0.35 μUI/mL, T3L >3.71 pg/mL and/ or T4L >1.48 ng/dL and TRAb >1.8 U/L. Patients were divided in subgroups according to autoimmunity profile [positive TRAb (9.4%) or negative TRAb (81.2%)] and according to performed treatment [surgery (27.1%), I131 (10.5%) or anti-thyroid drugs (62.4%)]. Then we divided anti-thyroid drugs subgroup in remission (42.4%) or in treatment with anti-thyroid drugs (20%). Pearson correlation, t-test and Mann-Whitney test were performed for statistical analysis.

Results: The mean age of the population was 52.9±13.0 years with 89.4% female patients. Regarding TRAb subgroups there was a positive correlation between TSH and PCR (r = 0.8,p = 0.010) in positive TRAb subgroup. Comparing with the remission subgroup, significantly higher TV (20.7±9.9 vs 15.4±7.7 mL, p = 0.048) and thyroglobulin [45.9 (18.4-59.4) vs 7.5 (1.3-16.2) ng/mL, p = 0.001] and significantly lower TSH [0.7 (0.4-1.4) vs 2.7 (1.1-2.9) μUI/mL, p = 0.002] were found in patients currently treated with antithyroid drugs. There was a positive correlation between TV and apoB (r = 0.97, p = 0.034) and between TSH and CRP (r = 0.60, p = 0.034) in currently treated subgroup. TV and HbA1c (r = 0.43, p = 0.026) were positively correlated in remission subgroup. Regarding evaluation by performed treatment, a positive correlation between FT3 and HOMA-IR (r = 0.57, p = 0.010) was found in patients who performed thyroidectomy.

Conclusion: The interrelationships found between autoimmunity, insulin resistance, inflammation and lipid profile may contribute to the cardiovascular risk in Graves' disease.

P3-01-174

ANTI - PD-1: PEMBROLIZUMAB INDUCED THYROID DYSFUNCTION

Rumaisa Banatwalla[1], *Sabah Chaudry*[1], *David Russell Jones* [1], *Roselle Herring* [1]
[1]Royal Surrey County Hospital, Surrey, UK

Introduction: Immunotherapy agents are increasingly being used for treatment of various different malignancies. Inhibition of cell death 1 pathways by targeted therapy using such agents has been shown to improve survival rates. In treatment of metastatic non-small-cell lung cancer (NSCLC), guidelines advise the use of PD-1 such as pembrolizumab in cases where tumours are PD-1-positive. Immunotherapy induced thyroiditis is increasingly being reported. Immunotherapy related thyroid dysfunction can be either related to thyroid gland or secondary hypophysitis. Up to 50% of thyrotoxicosis cases can be transient, with patients reverting back to euthyroid state.

Case Report: A 77-year old women presented with 4 day history of feeling generally unwell, increased shortness of breath, cough and feverish. She reported palpitations, anxiety, tremulousness and feeling more lethargic over the last three weeks. Medical history includes NSCLC of the right lung, for which she had received pembrolizumab three weeks prior. On examination, she was flushed, pyrexial and in atrial fibrillation (AF). The initial working diagnosis was community acquired pneumonia with probably thyroiditis secondary to her immunotherapy.

Routine bloods, T3, T4, TSH and thyroid antibodies were requested. She was commenced on carbimazole, propranolol and antibiotics. Investigations a week after completion of immunotherapy showed a TSH <0.03 and free T4 of 36.5. On admission her TSH receptor antibodies were 2.1, and her TPO of 99. She felt clinically well on the carbimazole, but remained in AF. The TFTs on 10 days of carbimazole reported TSH at 3.4, T3 at 2.5 and T4 at 13.5. She was discharged on carbimazole, DOAC and propranolol. Post discharge her TSH was 52, T3 3.1 and T4 7. Carbimazole was stopped and levothyroxine 50 mcg was commenced. She was advised to repeat TFTs and to be seen in the endocrine clinic.

Conclusion: Transient biochemical and clinical features of thyroiditis may resolve in 2-4 weeks in patients, hence symptomatic management is advised. If there is evidence of persistant symptoms of thyrotoxicosis or thyroid eye disease, autoimmune thyrotoxicosis will need ot be considered in addition to referral to endocrinology for. Immunotherapy can be continued, once patient is clinically stable and on appropriate endocrine therapy.

Screening and management of thyroid dysfunction has been suggested for patients whilst on PD-1 inhibition. Prior and during baseline TFTS should be considered, followed by routinely checking TFTs every 6 months. In cases of thyrotoxicosis, whilst on PD-1 inhibition one needs to evaluate for thyroiditis more commonly than Graves' disease; TFTs needs to be monitored every 2-3 weeks for development of primary hypothyroidism or normalisation of TFT or persistent thyrotoxicosis.

P3-01-175

COMPARISON OF CALCIUM-PHOSPHATE METABOLISM IN FEMALE PATIENTS WITH PRIMARY HYPERPARATHYROIDISM, WITH AND WITHOUT CONCOMITANT HASHIMOTO'S THYROIDITIS

Inna Yankova[1], *Gergana Ivanova*[1], *Alexander Shinkov*[1], *Roussanka Kovatcheva*[1]
[1]Department of Endocrinology, Medical University of Sofia, Bulgaria

Hashimoto's thyroiditis (HT) is the most common autoimmune disease reported in 1-20 % of adults depending on studied population. The main immunological markers of HT are antibodies against thyroid antigens – thyroid peroxidase (antiTPO) and thyroglobulin (TAT). HT often coexists with primary hyperparathyroidism (PHPT) – a chronic disease characterized by increased secretion of PTH and high serum calcium levels.

The aim of this study: was to compare biochemical and functional markers of calcium-phosphate metabolism in PHPT female patients with and without HT.

Design and methods: The study included 123 females diagnosed with PHPT, mean age 58.3 (± 12.8). Serum calcium, inorganic phosphate, PTH, 25OHD, creatinine, cystatin C and urinary calcium excretion were measured. Glomerular filtration rate (GFR) was calculated through CKD-EPI and MDRD equations. TSH, FT4, TAT and antiTPO were measured and thyroid ultrasound was performed. One of the following criteria identified HT: positive TAT, antiTPO or presence of typical ultrasound changes in the thyroid parenchyma with increased vascularization. In all patients, the parathyroid adenoma was localized by ultrasound. The biochemical and functional markers of calcium-phosphate metabolism were compared between the subjects with and without HT.

Results: The PHPT-patients with HT were 43 (35%) and those without HT – 80 (65%). There was no significant difference in serum calcium, phosphate, PTH, 25OHD, creatinine, cystatin C, GFR and urinary calcium excretion between the two groups. BMI was significantly higher in patients with HT (p = 0.04). HT was associated with lower risk of nephrolithiasis when controlling for age, BMI, PTH and PT adenoma volume. Odds ratio for nephrolithiasis from the logistic regression analysis was 0.18 (0.36-0.91), p = 0.038.

Conclusion: We found no association of HT with the markers of calcium-phosphate metabolism in female patients with PHPT. Further studies are necessary to estimate the clinical significance of the observed decreased risk of nephrolithiasis in cases with concomitant HT.

P3-01-176

A CASE OF STEROID-RESPONSIVE ENCEPHALOPATHY AND ASSOCIATED AUTOIMMUNE THYROIDITIS (SREAT/ HASHIMOTO ENCEPHALOPATHY) OR PARANEOPLASTIC AUTOIMMUNE ENCEPHALOPATHY (PAE)?

Gábor László Kovács[1], *Zsuzsanna Beleznay*[2], *Zita Bíró*[3]
[1]Department of Internal Medicine, Flor Ferenc Hospital, Kistarcsa, Hungary; [2]Institute of Laboratory Medicine Semmelweis University, Department of Immunology, Budapest, Hungary; [3]Department of Neurology Flor Ferenc Hospital, Kistarcsa, Hungary

Steroid-responsive encephalopathy and associated autoimmune thyroiditis (SREAT/Hashimoto encephalopathy) is characterized by convulsions, tremor, ataxia, cognitive deficiency, personality disorder, psychosis and the presence of anti thyroid peroxidase (antiTPO) and antithyroglobulin. The paraneoplastic encephalopathy (PAE) has the same symptoms with autoimmune mechanism without thyroid background.

53 year old female patient treated by thyroxine for a year presented at Neurology Department there months after transient stroke-like episodes with dizziness, headache, and confusion, somnolence, limbic and cerebellar

involvement. The cranial MRI, and cerebrospinal fluidum (CSF) showed normal conditions. The paraneoplastic and autoimmune encephalitis antibody scan were negative but immunohistochemistry using on monkey cerebellum slides showed the Purkinje cell plasm slightly granulated stained by the patient's serum but not with her CSF. This staining was different from the typical onconeural antibodies(AB) (PCA-1,PCA-2, PCA-Tr) and the systematic neoplasm screening was negative. As the anti TPO was increased (>1300 IU/L) therefore SREAT was diagnosed. 1g/day intravenous methylprednisolon (MP) therapy for 5 days followed by 1mg/bw orally administered. The symptoms improved, but the MP was unable to be omitted. After total thyroidectomy the MP could be successfully finished, but the anti TPO remained at high level as the atypical AB binding against Purkinje cells.

Because of the unknown antibody binding we repeated the neoplasm screening and breast cancer (cc ductale, 14mm pT1cpN0 ER/R and HER2 +) was detected.

After breast cancer complex treatment the atypical AB binding against Purkinje cells was disappeared, but the anti TPO is still on high level in serum.

This case describes that the SREAT and PAE symptoms are overlapping, therefore the high antiTPO level is inadequate to set up SREAT diagnosis, and probably not the trigger factor for this syndrome. PAE is an important diagnostic consideration in patients with autoimmune thyroiditis, the positive test can draws attention to a tumour in early stage.

P3-01-177

INCREASED TSH AND INCREASED THYROID ANTIBODIES - IS IT ALWAYS SUBCLINICAL PRIMARY HYPOTHYROIDISM OR MAYBE SOMETHING ELSE?

Raluca Trifanescu[1], *Dana Terzea*[2], *Anda Dumitrascu*[2], *Mariana Purice*[2], *Florin Alexiu*[2], *Catalina Poiana*[1]

[1]Carol Davila University of Medicine and Pharmacy, C.I. Parhon National Institute of Endocrinology, Bucharest, Romania; [2]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania

Background: Chronic autoimmune thyroiditis is a common disease; however, interpretation of increased TSH in a patient with autoimmune thyroiditis could be difficult in rare cases.

Case report: A 41-year-old woman was diagnosed with chronic autoimmune thyroiditis and increased TSH (6 mIU/L) and received low-dose levothyroxine treatment. After one year, the patient developed bradimenorrhoea. Levothyroxine treatment was stopped. Thyroid function tests revealed increased FT4 and increased TSH and imaging revealed a pituitary macroadenoma with supra and parasellar extension (left cavernous sinus invasion). The patient was submitted to transsphenoidal adenomectomy, with partial removal of the pituitary adenoma, but restoration of normal thyroid function. Immunohistochemistry was performed, revealing a TSH co-secreting pluri-hormonal pituitary adenoma (TSH, FSH, ACTH positive in tumor cells, GH positive in rare tumor cells). Immunohistochemistry for somatostatin receptor revealed that the tumor was positive for SSTR2, but not for SSTR5. In case of developing thyrotoxicosis due to pituitary tumor, somatostatin analogue treatment would be an option.

Conclusion: even in the presence of positive antithyroid antibodies, inappropriate secretion of TSH should lead to the diagnosis of thyrotropinoma, a rare pituitary tumor, after exclusion of resistance to thyroid hormone's syndrome.

Cancer Case Reports

P3-02-178

WITHDRAWN

P3-02-179

MULTIFOCAL TUMORS IN A PATIENT WITH CRIBRIFORM-MORULAR VARIANT OF PAPILLARY THYROID CARCINOMA ARE AN IMPORTANT CLUE FOR DIAGNOSIS OF FAMILIAL ADENOMATOUS POLYPOSIS: REPORT OF 5 NOVEL GERMLINE MUTATION OF THE APC GENE

Jun Park[1], *Hyunju Park*[2], *So Young Park*[3], *Tae Hyuk Kim*[2], *Sun Wook Kim*[1], *Jae Hoon Chung*[4]

[1]Samsung Medical Center, Seoul, Rep. of South Korea; [2]Samsung Medical Center; [3]Samsung Medical Center, Internal Medicine, Seoul, Rep. of South Korea; [4]Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Rep. of South Korea

Cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC) is a rare subtype of PTC, which occurred predominantly in young women. This disease much more frequently presented in patients with familial adenomatous polyposis (FAP). FAP is an autosomal dominant inherited disease, which arises from germline mutations of APC gene. To clarify the distinctive clinical features of CMV-PTC, a comparison study was performed between familial types and sporadic types. Between 2007 and 2018, 15 CMV-PTC patients underwent thyroidectomy in Samsung Medical Center. The clinical features of these patients were retrospectively reviewed. All patients were women with a median age of 28 years (range 17-46 years). The mean maximum diameter was 1.4 cm (range 0.4-3.5 cm). All patients underwent immunostaining (12/12) presented nuclear and/or cytoplasmic staining for β-catenin. On ultrasonography (US), most nodules had well-defined, hypoechoic, oval to round shapes without calcification. However, a few of nodules had capsular invasion and taller than wide shape. In preoperative fine-needle aspiration, five patients (33%) were diagnosed as CMV-PTC, nine (60%) as PTC, but one (7%) as follicular neoplasm or PTC-follicular variant. Six patients (40%) had FAP, and four of them had total colectomy due to FAP. Five of them had family history of FAP or colon cancer or thyroid cancer. The germline mutations of APC gene were found in all six patients with CMV-PTC associated with FAP, and five of them had de novo mutations. All of FAP associated CMV-PTC had multiple tumors. All CMV-PTC patients had excellent response to initial therapy. Most nodules in CMV-PTC patients were diagnosed as benign on US findings, but most patients except one had malignant cytology. β-catenin immunostaining is essential for definitive diagnosis. Because of its co-occurrence with FAP or colon cancer, we emphasize that an analysis of APC gene mutation and colonoscopy should be done when patients with CMV-PTC present multiple thyroid tumors.

P3-02-180

RE-DIFFERENTIATION OF METASTATIC RADIOIODINE RESISTANT THYROID CANCER: PRELIMINARY RESULTS FROM TWO CASES

Kirstie Lithgow[1], *Helen Huang*[2], *Denise Chan*[3], *Moosa Khalil*[4], *Mike Bristow*[3], *Vincent Dinculescu*[3], *Peter Grundy*[1], *Markus Eszlinger*[2], *Ralf Paschke*[5]

[1]Dept. of Medicine; Cumming School of Medicine; University of Calgary, Calgary, Canada; [2]Departments of Oncology, Pathology and Laboratory Medicine, Biochemistry and Molecular Biology, and Arnie Charbonneau Cancer Institute; Cumming School of Medicine, University of Calgary, Calgary, Canada; [3]Dept. of Radiology; Cumming School of Medicine; University of Calgary, Calgary, Canada; [4]Dept. of Pathology & Laboratory Medicine; Cumming School of Medicine; University of Calgary, Calgary, Canada; [5]Departments of Medicine, Oncology, Pathology and Laboratory Medicine, Biochemistry and Molecular Biology, and Arnie Charbonneau Cancer Institute; Cumming School of Medicine, University of Calgary, Calgary, Canada

Re-differentiation of metastatic radioiodine resistant thyroid cancer: preliminary results from two cases

Introduction: Inhibition of MAPK pathway signaling can restore uptake of radioactive iodine (RI) in RI resistant thyroid cancer.

Case 1: 29 yo female underwent thyroidectomy with partial neck/upper mediastinal dissection 6 years ago for 4.5 cm papillary thyroid carcinoma sclerosing variant T3N1b, KRAS, NRAS, BRAF, RET/PTC 1 and 3 negative, followed by 100 mCi of RI. 12 months later complete neck dissection was performed for lymph node metastases. PET CT 9 months later showed multiple new lung nodules, so 100 mCi RI was given. Subsequent progression of lung metastases and rising thyroglobulin suggested RI resistance. She received selumetinib followed by 325 mCi RI (based on dosimetry with I-124 and I-131). Post treatment scan demonstrated very high uptake in the pulmonary metastases. Two years later, thyroglobulin levels have declined to nadir of 76 ug/L (250 ug/L before 325 mCi), thyroglobulin doubling time has decreased from 0.96 to -2.52 years, and lung metastases have not progressed.

Case 2: 53 yo male underwent thyroidectomy four years ago for 5 cm poorly differentiated thyroid cancer T3N0M1, NRAS positive. He received 100 mCi RI; post treatment scan showed uptake in both lungs, and thyroglobulin subsequently was increasing, so further 200 mCi RI was given. One year later he received 150 mCi of RI due to rising thyroglobulin. During follow-up, RI resistance was demonstrated by progression of lung nodules, and increase in thyroglobulin doubling time (1.25 to 0.85 years) within six months after RI. He received trametinib followed by 150 mCi RI, pulmonary uptake was seen on post treatment scan. Within one month of RI, thyroglobulin declined from 1805 to 1323 ug/L, and imaging showed decrease in size of the largest pulmonary nodules.

Conclusion: These cases have shown promising initial responses to RI resensitization with PFS and limited side effects, thus allowing deferral of TKI treatment.

P3-02-181

LONG-TERM PARTIAL RESPONSE IN TWO CASES OF PANCREATIC METASTASIS FROM THYROID CANCER TREATED WITH LENVATINIB

Jeehee Yoon[1], *A Ram Hong*[1], *Hee Kyung Kim*[1], *Ho-Cheol Kang*[1]

[1]Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Rep. of South Korea

Objective: Pancreatic metastasis from thyroid cancer is extremely rare. The resectable isolated pancreatic metastasis could be treated by surgical resection, however unresectable cases have few treatment choices including systemic chemotherapy and tyrosine kinase inhibitors (TKIs). Most of previous reports showed unsatisfactory outcomes in patients with unresectable pancreas metastasis from the thyroid. Here we share our experience in two patients with pancreatic metastasis from thyroid cancer, who showed long-term partial response to lenvatinib with manageable side effects.

Cases: A 67-year-old male diagnosed with papillary thyroid cancer (PTC) and follicular variant PTC had repeated surgeries and radioactive iodine (RAI) therapies due to recurrent cervical lymph node metastases. Distant metastases to pancreas, liver, lung and bones were detected 16 years after the initial operation. Pancreatic metastasis was documented by endoscopic ultrasound-guided core needle biopsy. Lenvatinib therapy for 1 year reduced the target tumor size from 6.9 cm to 2.5 cm. The second patient was a 56-year-old male with BRAFV600E positive PTC who underwent repeated surgeries and RAI therapy. One year after the initial operation, distant metastases to pancreas, bones and lung were detected. Percutaneous CT-guided biopsy revealed pancreas metastasis. The pancreatic metastasis was gradually decreased from 7.0 cm to 2.8 cm after lenvatinib therapy for 1 year. Initial lenvatinib doses were 20 mg in both patients and the doses were reduced to 14 mg due to hypertension and proteinuria. No severe adverse effects beyond grade 3 occurred during lenvatinib therapy.

Conclusion: Lenvatinib therapy could be an efficient and relatively safe treatment modality for unresectable pancreas metastasis from differentiated thyroid cancer.

P3-02-182

A RARE CASE OF THYROID METASTASIS FROM A SQUAMOUS CELL CARCINOMA OF THE TONGUE

Mira Valentinova Siderova[1], *Gergana Tosheva*[2], *Elitsa Encheva*[3], *Kiril Hristozov*[4], *Doroteya Malinova*[5], *Pavel Bochev*[6]

[1]Univesity Hospital “St. Marina”, Medical University Varna, Department of Endocrinology, Varna, Bulgaria; [2]Medical University Varna, Bulgaria; [3]University Hospital “St. Marina”, Medical University Varna, Department of Diagnostics Imaging and Radiotherapy, Bulgaria; [4]University Hospital “St.Marina”, Medical University Varna, Department of Endocrinology, Bulgaria; [5]Univesity Hospital “St. Marina”, Medical University Varna, Department of Pathology, Bulgaria; [6]Univesity Hospital “St. Marina”, Medical University Varna, Department of Diagnostics Imaging and Radiotherapy, Bulgaria

Introduction: We present a rare case of a male patient with tongue cancer with metastases to the thyroid gland and lymph nodes. Tongue cancer belongs to the head and neck squamous cell carcinoma (HNSCC), estimated to be the sixth most common cancer worldwide. Its poor 5-year survival has not been improved in the past three decades despite medical therapy advances. HNSCC most often metastasizes by the lymphatic route. The most common sites for hematogenous metastases are lungs, bones, liver and skin. The thyroid gland is a rare location for metastatic cancer. Fewer than 450 cases of metastases to the thyroid gland of all kind of origin are reported in literature with ten from HNSCC and only two cases from tongue cancer.

Case report: A 79-year old man presented to the University Hospital in Varna, Bulgaria. Two months before admission he noticed swelling of the tongue, difficulty swallowing and progressive weight loss. The inspection of the oral cavity revealed vaguely boundless lesion on the left margin of the tongue with ulceroproliferative areas. The histology of the tongue lesion was highly to moderately differentiated squamous cell carcinoma of the tongue. Ultrasound examination of the neck revealed suspicious neck lymph nodes and a hypoechoic nodule in the right thyroid lobe. The latter underwent FNAB with cytology confirming a metastasis from squamous cell carcinoma of the tongue to the right thyroid lobe. A computed tomography (CT) scan of head, neck and chest, as well as fluorine 18-fluoro-2-deoxy-glucose-positron emission tomography (18F-FDG-PET) scans were performed to stage the disease. The primary tumour of the tongue and the lymph node metastases were metabolically active on 18F-FDG-PET imaging, whereas the thyroid nodule did not have increased tracer uptake. The patient underwent concurrent chemoradiation therapy (CCRT). He completed 70 Gy (devided in 35 fractions) using intensity modulated radiation therapy along with Cisplatin. Despite the treatment the patient died.

Conclusion: Distant metastases from tongue cancer to the thyroid gland are extremely rare and mostly occur in the advanced stages of a malignancy.

P3-02-183

HYALINIZING TRABECULAR TUMOR OF THE THYROID - A RARE ENTITY

Diana Martins[1], *Alexandra Vieira*[1], *Daniela Guelho*[1], *Nuno Vicente*[1], *Maria Inês Coelho*[2], *Ana Inácio*[2], *Maria Fernanda Cunha*[3]
[1]Serviço de Endocrinologia, Diabetes e Metabolismo Do Centro Hospitalar de Leiria, Portugal; [2]Serviço de Cirurgia Geral Do Centro Hospitalar de Leiria, Portugal; [3]Serviço de Anatomia Patológica Do Centro Hospitalar de Leiria, Portugal

Introduction: Hyalinizing Trabecular Tumor (HTT) is a rare type of thyroid follicular neoplasm. Cytological features of HTT frequently overlap with those of papillary thyroid carcinoma and medullary thyroid carcinoma to a varying extent, which can lead to frequent misdiagnosis.

Clinical case: A 49-year-old woman with medical history of autoimmune thyroiditis presented to the Endocrinology Department due to cervical discomfort that has been progressing since several years ago. Physical examination was remarkable for an enlarged thyroid gland with palpable, bilateral, non-tender nodules. Patient was biochemically euthyroid on L-thyroxine therapy, 75 mcg/day.

Thyroid ultrasound showed multiple thyroid nodules, with mention of an isoechoic right thyroid nodule measuring 3.0 cm and a hypoechoic left thyroid nodule with 2.2cm. Ultrasound-guided FNA of both areas was compatible with follicular hyperplasia (Bethesda II).

Due to cervical symptomatology, patient underwent total thyroidectomy. Histopathological examination of surgical sample revealed aspects of focal nodular hyperplasia and in the right lobe, a 3.2 cm HTT, consisting of pink and whitish "star tissue". The tumor was limited to thyroid parenchyma, with no lymphovascular invasion and with negative margins of resection. Immunohistochemistry analysis resulted positive for thyroid transcription factor-1 and thyroglobulin, and negative for calcitonin, supporting the diagnosis of HTT. Given the result of the surgical pathology report, further postoperative radioiodine remnant ablation therapy and suppression therapy with levothyroxine were not provided.

Conclusions: Hyalinizing trabecular tumor arising from the thyroid gland is an uncommon and controversial finding, with sporadic cases reported in the literature. Misdiagnosis is frequent due to prominent hyaline distribution that mimics amyloid deposits, characteristics of medullary thyroid cancer. Furthermore, concomitant Hashimoto's thyroiditis, as seen in our patient, may hinder the correct cytology result, contributing to misdiagnosis.

A correct identification is crucial to provide proper management and avoid overtreatment. Given the benign clinical course of this tumor, further postoperative suppression with levothyroxine and radioiodine remnant ablation therapy are not required however, it is relevant for the medical community to better define a definitive management approach of this entity.

P3-02-184

AN INCIDENTAL CASE OF MEDULLARY THYROID CARCINOMA WITH METASTASES IN MALE BREAST

Lali Tigishvili[1], *Nino Kekelidze*[2], *Khatuna Khatchapuridze*[3], *Maya Mchedlishvili*[4]
[1]"Enmedic" Clinic, Endocrinology Department, City Hospital N1, Tbilisi, Georgia; [2]Aexandre Natishvili Institute of Morphology, Tsu, Tbilisi, Georgia; [3]Alexandre Natishvili Institute of Morphology, Tsu, Tbilisi, Georgia; [4]Enmedic Clinic, Alexandre Natishvili Institute of Morphology, Tsu, Tbilisi, Georgia

Introduction: Medullary Thyroid Carcinoma is a malignant tumor of C-cells, which can be manifested in different organs as a metastatic disease. The most common metastatic sites are - bones (45%), lungs (33%), brain (1-5%) skin and rarely in breast. According to the literature only 25 cases of medullary thyroid cancer metastasis in breast are described. None of them was primarily manifested in male breast involving axillary lymph nodes as well.

Materials and methods: This article describe clinical cases of two patients with medullary thyroid carcinoma. The first case describes 71 years old man with clinical diagnosis of breast cancer, lesions localization - in the upper-lateral quadrant of the breast, tumor size macroscopically - 3.2x2.0x1.8cm.

Results: Immuno-histochemistry showed negative expression of ER,PR,HER2; expression of proliferation marker Ki67 was very low (1%) as well; S100 (+) – positively expressed in tumor cells; Calcitonin was strongly positive; With Congo-red, special histochemical staining sample showed positive expression in stroma. Based on this information, breast surgical tissue examination revealed Medullary Thyroid Carcinoma with metastasis in breast. After breast surgery thyroid ultrasound was performed. Ultrasound revealed 1.7 cm tumor in the left lobe. Calcitonin level in blood was 1037. 4pg/ml. The multiple metastasis caused death of patient three years later. Following our recommendation patient's grand-child (13 years old boy) examined and 0.4 cm tumor in the left thyroid lobe was revealed. With fine-needle cytology, Medullary Thyroid Carcinoma was diagnosed without tendency of disease's progression.

Conclusion: There are extremely rare cases of Medullary Thyroid Carcinoma with clinical manifestation in male breast as a "classical" breast cancer. "Triple negative" malignant lesions of breast need carefully examination due to exclude tumor metastasis in breast. In order to verify malignancy at an earlier stage, screening of patient's family members is very important.

P3-02-185

ONE HOT NODULE AND HURTLE CELL THYROID CANCER

Iulia Chiriac[1], *Andrei Goldstein*[2], *Dumitru Ioachim*[2], *Corin Badiu*[3]
[1]Endocrinology and Isotopic Therapy Department, National Institute of Endocrinology "C.I. Parhon", Bucharest, Romania; [2]National Institute of Endocrinology, Bucharest, Romania; [3]"C.I. Parhon" National Institute of Endocrinology, "C. Davila" University of Medicine, "C. Davila" University of Medicine and Pharmacy, Romania

Patients with hyperthyroidism and multinodular goiter for the initial work-up need a sonographic assessment of thyroid nodules and the blood samples for functional evaluation. Another useful tool in this context is thyroid scintigraphy that can be done with 99mTcO4- or with radioactive iodine. However, in rare cases hot nodules could harbour a thyroid cancer.

The case report that we are presenting is a 65 years old male, from an iodine deficiency area, with hyperthyroidism known for 2 years that was referred to our department for radioiodine therapy. The sonographic aspect of a 2 cm nodule on the right lobe was classified as EU-TIRADS 5, and the 131I scintigraphy revealed a "hot" nodule. The next step was to do a fine needle aspiration biopsy, showing a Bethesda score 4, therefore total thyroidectomy was performed. The pathology result revealed a sclerosing papillary thyroid carcinoma with tall and oxyphilic cells. Afterwards the patient received an ablative dose of 100mCi 131I (3.7 GBq 131I).

"Hot" nodules, hyperthyroidism and thyroid cancer are estimated in the general population to be less than 5%. Careful evaluation of hyperfunctioning multinodular goitre is needed prior to the radioiodine therapy.

P3-02-186

CONTRALATERAL LYMPH NODE METASTASIS TEN YEARS AFTER TOTAL THYROIDECTOMY FOR PAPILLARY THYROID CANCER IN A PATIENT WITH BREAST CANCER

Georgios Boutzios[1], *Eleni Koukoulioti*[1], *Grigorios Kouraklis*[2], *Konstantinos Kontzoglou*[2]
[1]Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Athen, Greece; [2]Second Department of Propaedeutic Surgery, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Contralateral lymph node metastasis ten years after total thyroidectomy for papillary thyroid cancer in a patient with breast cancer.

Introduction: Most thyroid neoplasms arise from follicular cells, and are well differentiated with good prognosis. More aggressive thyroid cancers may incorporate a combination of other treatments beyond surgery and radioactive iodine (RAI). We present an unusual case of a late relapse of Papillary Thyroid Cancer (PTC) as a lateral cervical mass, ten years after thyroidectomy.

Case report: A 74 year-old-female, with a history of PTC (1.4 cm at the right thyroid lobe with capsular invasion) who underwent total thyroidectomy ten years ago, was referred to our department because of a slow growing left lateral cervical mass in the last 6 months. Ten years ago, after thyroidectomy, the patient received RAI ablation. Post RAI and one-year after surgery the

whole-body scans (WBS) with I^{131} were normal. The patient received thyroxine suppression therapy. Furthermore, the patient was operated for breast cancer (left mastectomy with axillary lymph node dissection) 2 years ago and was treated with local radiotherapy and tamoxifen.

Sonography revealed two suspicious hypogenic lymph nodes at the fourth left lateral compartment, with a diameter of 22 and 14.5 mm, respectively. A WBS with I^{131} was performed without pathological findings. In the post-rh-TSH stimulation test, TSH was 152 mIU/L, and Thyroglobulin (Tg) was 12.4 ng/ml with positive Tg antibodies. Due to her history of breast cancer, a chest CT was performed, without pathological findings. The patient was submitted to excision of the largest lymph node for diagnostic reasons. Histology revealed a papillary thyroid cancer, TTF-1 positive and GATA-3 negative.

Conclusion: The presentation of this case has the intention to stress out the suspicion for thyroid malignancy, even in contralateral neck compartments, ten years after total thyroidectomy. We would also like to annotate that histology, is the gold standard examination on differentiating cervical lymph nodes.

P3-02-187

A RARE CASE OF A NEUROECTODERMAL TUMOUR IN THE THYROID GLAND AND A SYSTEMATIC REVIEW OF LITERATURE

Nebu A. George[1], *Shirish Patil*[1]
[1]Regional Cancer Institute, Head and Neck Oncosurgery, Trivandrum, India

Medulloepithelioma (ME) is a rare embryonal tumor predominantly located in the eye or in the central nervous system without an established treatment. We report of a case of a peripheral ME in the thyroid gland treated with surgery and local radiotherapy. Also a literature review analyzing all the data available on peripheral medulloepithelioma in the neck either as primary or as a metastatic lesion in the neck and their management.

Our current understanding and literature review shows that metastatic and peripheral medulloepitheliomas have a poor prognosis and there is no optimal treatment protocol. Hence there is a lot of scope for research and molecular analysis of this disease.

Cancer Clinical 3

P3-03-188

INITIAL RISK STRATIFICATION BASED ON CERVICAL LYMPH NODE METASTASES AFTER LOBECTOMY FOR 1-4CM SIZED PAPILLARY THYROID CARCINOMA

Eyun Song[1], *Jonghwa Ahn*[2], *Dong Eun Song*[3], *Won Woong Kim*[2], *Min Ji Jeon*[4], *Tae-Yon Sung*[2], *Tae Yong Kim*[5], *KI-WOOK CHUNG*[6], *Won Bae Kim*[7], *Youngkee Shong*[8], *Suck Joon Hong*[9], *Suck Joon Hong*[10], *Won Gu Kim*[1]
[1]Asan Medical Center, Seoul, Rep. of South Korea; [2]Asan Medical Center; [3]Asan Medical Center, Rep. of South Korea; [4]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Rep. of South Korea; [5]University of Ulsan College of Medicine, Asan Medical Center, Asan Medical Center, Seoul, Rep. of South Korea; [6]Ulsan University College of Medicine, Seoul, Rep. of South Korea; [7]Asan Medical Center, University of Ulsan College of Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Rep. of South Korea; [8]Asan Medical Center, University of Ulsan, Endocrinology, Seoul, Rep. of South Korea; [9]Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Rep. of South Korea; [10]Department of Surgery, Asan Medical Center, Seoul, Rep. of South Korea

Background: In the era where the value of thyroid lobectomy is revisited for papillary thyroid carcinoma (PTC) measuring 1-4cm, clinical guidelines for management of neck lymph node (LN) metastases after lobectomy are limited. This study aimed to determine an appropriate postoperative surveillance for these patients.

Methods: Patients who underwent thyroid lobectomy for 1-4 cm sized PTC were included (n = 571). Disease-free survival (DFS) was compared according to the American Thyroid Association (ATA) risk stratification and specific LN characteristics were evaluated to sub-classify patients with higher risk of recurrence.

Results: Based on the LN criteria of ATA risk stratification, 379 patients had N0 disease, 65 fell under low risk N1a (low-N1a) disease, and 127 under intermediate risk N1a (intermieiate-N1a) disease. When DFS was evaluated according to the overall ATA risk stratification, there were no significant differences in DFS among the low-, intermediate-, and high-risk groups ($p = 0.9$). However, patients with intermediate-N1a disease exhibited significantly poorer DFS compared to those with N0 ($p = 0.035$), while patients with low-N1a disease did not ($p = 0.287$). Extranodal extension (ENE) was the most powerful characteristic for structural persistent/recurrent disease (HR [hazard ratio] 8.2. 95% CI [confidence interval] 3.32-20.51, $p = 0.001$) with the number and maximal diameter of metastatic LNs also being significant factors. However, clinical N1a disease was not associated with increased risk for structural persistent/recurrent disease ($p = 0.680$). Intermediate-N1a group was modified by leaving cN1a disease out and considering the ENE status. Accordingly, intermediate-N1a/ENE+ group was associated with poorer DFS (HR 8.45, 95% CI 3.08-23.17, $p<0.001$) compared to N0 group while intermediate-N1a/ENE- group was not ($p = 0.399$).

Conclusions: This study suggests that risk stratification based solely on LN metastases is more reasonable in predicting structural persistence/recurrence for patients undergoing lobectomy. Our results confirmed the importance of the number and maximal diameter of metastatic LNs in predicting recurrence after lobectomy, and extended the stratification with taking ENE into account for selecting patients with higher risk of recurrence to minimize further unnecessary treatments.

P3-03-189

[^{18}F] DOPA-PET/CT FOR THE EVALUATION OF PERSISTENT AND RECURRENT MEDULLARY THYROID CARCINOMA

Eva Rainer[1], *Sazan Rasul*[1], *Christian Scheuba*[2], *Marius Mayerhofer*[3], *Gorgos Karanikas*[1], *Peter Mazal*[4], *Marcus Hacker*[1], *Shuren Li*[1]
[1]Medical University of Vienna, Division of Nuclear Medicine, Department of Biomedical Imaging and Image-Guided Therapy, Vienna, Austria; [2]Medical University of Vienna, Medical University of Vienna, Department of Surgery, Austria; [3]Medical University of Vienna, Department of Biomedical Imaging and Image-Guided Therapy; [4]Medical University of Vienna, Department of Pathology

Aims: The aim of this study is to evaluate the role of [^{18}F] DOPA PET/CT for the imaging of primary or recurrent medullary thyroid carcinoma especially the possible correlation between calcitonin (CT) levels (basal CT (bCT) and stimulated CT (sCT)) and tracer uptake of [^{18}F] DOPA as well as a gender difference in the [^{18}F] DOPA PET results.

Methods: Eighty-nine [^{18}F] DOPA PET/CT examinations were performed in 50 patients (26 female, 24 male patients, mean age 65 ± 18 years) with histologically verified primary or recurrent MTC. 5 patients had a hereditary MTC. Serum bCT and CEA were measured in all patients. Calcium stimulation test (CST) was performed in 42 of the 50 patients. SUVmax was calculated for each lesion. Correlation and cutoff values were determined with IBM SPSS Statistics 24 using Pearson's correlation, Chi square test and ROC.

Results: Positive [^{18}F] DOPA PET/CT results were shown in 71 examinations with a sensitivity of 80%. 43 patients had positive [^{18}F] DOPA PET/CT scans with a sensitivity of 86%. 22 male patients (92%) had positive findings in [^{18}F] DOPA PET/CT, whereas only 21 female patients (80%) were positive in the [^{18}F] DOPA PET/CT. However, we found no significant difference in sensitivity between female and male patients. All 5 patients (100%) with hereditary MTC had positive PET/CT scans. Correlation between bCT and SUVmax was significant ($p<0,01$). Correlation between sCT and SUVmax was also significant ($p<0,01$). 58 examinations with positive [^{18}F] DOPA PET had bCT levels> 48pg/mL with a sensitivity of 82% and a specificity of 72%. [^{18}F] DOPA PET was positive in 35 examniations with sCT levels > 1808 pg/mL with a sensitivity of 73% and a specificity of 64%. Cutoff value for CEA values > 4ng/L had a sensitivity of 82% and a specificity of 67%.

Conclusion: Tracer-uptake of [^{18}F] DOPA (SUVmax) correlates significantly with bCT as well as sCT. We observed higher sensitivity of [^{18}F] DOPA PET/CT in male patients than in female patients, however no significant difference was shown. Higher sensitivity of [^{18}F] DOPA PET/CT tends to be

found in patients with hereditary MTC as compared to patients with sporadic MTC. [^{18}F] DOPA PET/CT may be especially useful in patients with bCT levels > 48 pg/mL or sCT levels > 1808 pg/mL or CEA > 4ng/L.

P3-03-190

THRESHOLDS OF CALCIUM STIMULATED CALCITONIN FOR PRECOCIOUS DIAGNOSIS OF MEDULLARY THYROID CANCER IN WOMEN

Mara Baetu[1], *Ruxandra Dobrescu*[2], *Cristina Alexandra Olariu*[1], *Cristina Stancu*[1], *Gabriel Moldoveanu*[3], *Cristina Corneci*[2], *Andra Caragheorgheopol*[2], *Dumitru Ioachim*[3], *Corin Badiu*[4]
[1]National Institute of Endocrinology, Dpt. Thyroid Disorders, Bucharest, Romania; [2]National Institute of Endocrinology, Bucharest, Romania; [3]"C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania; [4]"C.I. Parhon" National Institute of Endocrinology, "C. Davila" University of Medicine, "C. Davila" University of Medicine and Pharmacy, Romania

Objective: We aim to establish specific cut-offs for stimulated serum calcitonin (sCT) for medullary thyroid carcinoma (MTC) diagnosis for female (F) gender.

Methods: Women admitted for thyroidectomy were informed about the study protocol and gave their written consent. CT samples were measured during calcium-stimulation test (25mg/kgBW adapted to ideal body mass index) before and at 2, 5 and 10 minutes after administration of calcium gluconate in 41F with thyroid nodules before thyroidectomy. The study included 23F with abnormal bCT (>9.82 pg/ml) and a control group of 18F with normal bCT (<9.82 pg/ml). Median age: 48 years (23-78). CT was measured by immunochemiluminescence. Histopathological reports were correlated to sCT.

Results: The test was well-tolerated, with minimum side-effects. In the control group, the mean bCT was 2.06±2.44 pg/ml (range:<1-9.23) and the mean peak-sCT was 31.11±47.7 pg/ml (range:1.02-167). The best thresholds for sCT to discriminate MTC or CCH (C-Cell hyperplasia) from other pathologies and normal subjects were: 208.2 pg/ml (sensitivity-70%; specificity-79%), AUC 0.8 (CI:0.67-0.94), p = 0.002. Interestingly enough, the cut-off for sCT lowers to 83.95 pg/ml if we want to discriminate patients with either MTC, CCH or macro-PTC (papillary thyroid carcinoma>1cm) from other cases (sensitivity-82%; specificity-60%), AUC 0.74 (CI:0.59-0.89), p = 0.01. Furthermore, the threshold for sCT lowers to 29.88 pg/ml if we want to distinguish patients with any type and any foci dimensions of malignancy from benign lesions (sensitivity-85%; specificity-71%), AUC 0.77 (CI:0.61-0.92), p = 0.005. Sex specific differences and genetic data are the focus of further analysis.

Conclusions: Our study identified sCT cut-offs for discriminating MTC or CCH in female group. The calcium stimulation test is well-tolerated. Larger groups studies are needed to enhance precocious diagnosis of MTC, and interestingly enough, maybe also of PTC.

P3-03-191

A COMPLEX MEN2 SYNDROME, A MIXTURE OF 2B AND 2A, ASSOCIATED WITH A NEW RET GERMLINE DELETION

Carlotta Giani[1], *Cristina Romei*[1], *Raffaele Ciampi*[1], *Laura Valerio*[1], *Alessia Tacito*[1], *Teresa Ramone*[1], *Gabriele Materazzi*[2], *Liborio Torregrossa*[3], *Clara Ugolini*[3], *Alessandro Franchi*[3], *Fulvio Basolo*[3], *Laura Agate*[1], *Rossella Elisei*[1]
[1]Department of Clinical and Experimental Medicine, Unit of Endocrinology, University of Pisa, Pisa, Italy; [2]Department of Surgical and Medical Pathology, Unit of Surgery, University of Pisa, Pisa, Italy; [3]Department of Surgical and Medical Pathology, Unit of Pathology, University of Pisa, Pisa, Italy

Introduction: MEN2 syndromes have well-recognized phenotypes.

Case report: We present the case of a 7-year-old girl with a peculiar MEN2 syndrome. The patient was born after a caesarean section at 38 weeks, with a weight of 2400 g. She had newborn jaundice, biliary vomit and failure to pass meconium. At 2-years she was submitted to an exploratory laparotomy for a big pelvic lesion and then multiple biopsy were performed. The histology described a ganglioneuroma. At 7-years she arrived at our observation with an evident marfanoid habitus, mucosal neuromas, high levels of calcitonin and primary hyperparathyroidism (pPTH). The neck ultrasound showed bilateral thyroid nodules, central compartment and left latero-cervical lymph node lesions and a suspicious left hyperplastic parathyroid. The CT-scan showed a megacolon and described the presence of the big pelvic ganglioneuroma. A RET germline deletion in exon 11(c.1892_1899delCGAGCT; p.Glu632_Leu633del) was found. The primary tumoral tissue, the lymph node metastases and the intestinal ganglia were screened and no additional mutations were found. She underwent to total thyroidectomy, central compartment and left latero-cervical dissection and bilateral neck exploration for primary hyperthyroidism. The histology confirmed bilateral medullary thyroid cancer with peri-thyroid soft-tissue invasion and vascular embolization, multiple central compartment and left latero-cervical lymph node metastases, a hyperplastic parathyroid (6 mm) and a parathyroid adenoma (8 mm).

Conclusions: This is the first presentation of a complex MEN2 syndrome that seems to be a mixture of MEN2B and MEN2A. The underlying RET deletion involving the cysteine region had never been described at germinal level. Since we did not find any other RET alteration at germline and somatic level we could hypothesize that this mutation is causative of this complex MEN2. Nevertheless the hypothesis that the co-occurrence of MEN2A and other syndromes (i.e. MEN1) is under consideration and genes causative of these pathologies are under investigation.

P3-03-192

CLINICAL OUTCOMES OF ACTIVE SURVEILLANCE IN PERSISTENT OR RECURRENT CERVICAL LYMPH NODE METASTASIS IN PATIENTS WITH THYROID CANCER

Joana Maciel[1], *Helder Simões*[1], *Valeriano Leite*[2]
[1]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil. Rua Professor Lima Basto, Lisbon, Portugal; [2]Servico de Endocrinologia, Instituto Português de Oncologia de Lisboa, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal

Introduction: Cervical lymph node metastases (CLNM) of thyroid carcinoma (TC) are frequent and the most common presentation of disease persistence/recurrence. The treatment is challenging and active surveillance (AS) is an option.

Objective: To investigate the outcomes of patients with TC with recurrent/persistent confirmed CLNM under AS.

Methods: Single center retrospective study. Patients with CLNM were selected from databases of washout fluid thyroglobulin (WFT) and fine needle aspiration biopsy between 2000-2018. We selected only patients with WFT or cytology proven CLNM, in whom AS was initially proposed, after multidisciplinary decision. Main clinical outcomes were analyzed.

Results: Eighty nine patients with confirmed CLNM in AS were identified, 65%(n = 58) were females. Classic papillary was the most frequent variant (44%;n = 39). Aggressive histological criteria were present in 46%(n = 41) and distant metastasis in 8%(n = 7). Median age at diagnosis of CLNM was 50(15,7–88,8)years and median metastatic lymph node tumor volume was 113(4.2-3052.1)mm^3.

During a median follow-up after CLNM confirmation of 3(0.5-17.2)years, different therapeutic modalities were necessary:

-radioactive iodine (RAI) in 23(26%) patients with a response rate of 30%. Progression disease (PD) was observed in 8 of these patients, half requiring other treatment modalities: surgery in 2 cases, radiotherapy in 1 and repeated RAI treatment in 1;

-surgery was initially required in 9(10%) patients, 1.48(0.5-6.7) years after CLNM confirmation, with one disease related death (DRD) in this group;

-radiotherapy in 3(3%) patients, one developed metastasis and 2 had DRD;

-the remaining 54(61%) patients maintained AS. In this group, PD was observed in 26(48%) due to increase in the number and/or volume of CLNM but did not require further treatments.

Conclusion: In our series of patients with CLNM under AS, PD was observed overall in 52% of the patients but only 17% had clinical relevance and were further treated by surgery or RT. DRD occurred in only 3% of the patients.

P3-03-193

A PHASE 3 (COSMIC-311), RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CABOZANTINIB IN PATIENTS WITH RADIOIODINE (RAI)-REFRACTORY DIFFERENTIATED THYROID CANCER (DTC) WHO HAVE PROGRESSED AFTER PRIOR VEGFR-TARGETED THERAPY: TRIAL IN PROGRESS

Barbara Jarzab[1], *Jolanta Krajewska*[2], *Marcia Brose*[3], *Jaume Capdevila*[4], *Candy Bermingham*[5], *Soham Puvvada*[5], *Anne Borgman*[5], *Bruce Robinson*[6], *Corin Badiu*[7]

[1]Msc Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Department of Nuclear Medicine and Endocrine Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland; [2]Department of Nuclear Medicine and Endocrine Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology - Gliwice Branch, Gliwice, Poland; [3]Head and Neck Surgery, Radiology, University of Pennsylvania, Philadelphia, USA; [4]Vall D'Hebron University Hospital, Vall D'Hebron Institute of Oncology (Vhio), Barcelona, Spain; [5]Exelixis, Inc., Alameda, USA; [6]Kolling Institute, Royal North Shore Hospital and University of Sydney, Australia; [7]"C.I. Parhon" National Institute of Endocrinology, "C. Davila" University of Medicine, "C. Davila" University of Medicine and Pharmacy, Romania

Background: Treatment options are limited for patients with RAI-refractory DTC that is resistant to VEGFR-targeted therapy. Cabozantinib inhibits receptor tyrosine kinases including VEGFR2, MET, AXL, and RET, which are implicated in the development of DTC, and has shown clinical activity in early-phase studies of patients with RAI-refractory DTC. This study evaluates the efficacy and safety of cabozantinib in patients with RAI-refractory DTC who have progressed during or after prior VEGFR-targeted therapy.

Methods: This is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT03690388). The co-primary endpoints are progression-free survival and objective response rate evaluated by blinded independent radiology committee (BIRC) per RECIST v 1.1. Additional endpoints include safety, overall survival, quality of life, and changes in relevant biomarker levels (eg, thyroglobulin). Approximately 300 patients will be randomized in a 2:1 ratio to receive either cabozantinib (60 mg QD orally) or placebo. Randomization is stratified by prior treatment with lenvatinib and age (≤ 65 yrs vs > 65 yrs). Eligible patients must have a pathologic diagnosis of DTC and must have been previously treated with or deemed ineligible for treatment with iodine-131 for DTC. Patients must have received lenvatinib or sorafenib for DTC and progressed during or following treatment with a VEGFR inhibitor. Up to 2 prior VEGFR-targeting TKI agents are allowed. Patients randomized to placebo may be eligible for real time on-study crossover to cabozantinib based on BIRC confirmation of disease progression. Unblinded patients randomized to cabozantinib may continue on study treatment if there is clinical benefit per investigator.

P3-03-194

VALUE OF SERUM MMP-9 AS A CIRCULATING MARKER IN THYROID CANCER IS HIGHLY DEPENDENT ON SAMPLING AND COLLECTION CONDITIONS

Ruxandra Dobrescu[1], *Catalina Picu*[2], *Andra Caragheorgheopol*[3], *Dana Manda*[3], *Corin Badiu*[4]

[1]National Institute of Endocrinology, Dpt. Thyroid Disorders, Bucharest, Romania; [2]National Institute of Endocrinology, Soc Rom Psihoneuroendocrinologie, Bucharest, Romania; [3]National Institute of Endocrinology, Bucharest, Romania; [4]"C.I. Parhon" National Institute of Endocrinology, "C. Davila" University of Medicine, "C. Davila" University of Medicine and Pharmacy, Romania

Background: Matrix metalloproteinase-9 (MMP-9) is involved in multiple stages of cancer progression. In thryoid cancer, tissue expression of MMP-9 can be used as a diagnostic and prognostic marker, but the evidence concerning serum MMP-9 levels is less definitive. We aimed to evaluate the role of serum MMP-9 as a circulating marker of thyroid neoplasia.

Materials and methods: Blood samples were drawn before surgery in 306 unselected patients with nodular thyroid disease in two surgical centers, "CI Parhon" Institute (Center A) and Elias Hospital (Center B). Patients were diagnosed on pathology as benign disease (BD) ($N_A = 88$, $N_B = 85$) and papillary thyroid cancer ($N_A = 97$, $N_B = 36$). Serum MMP-9 was measured by an immunometric assay supplied by R&D Systems. Samples were collected in serum tubes with clot activator; in Center A, samples were centrifuged immediately after clot formation; in Center B centrifugation was delayed for several hours as samples were transported to Center A, where all measurements were performed.

Results: MMP-9 levels were significantly higher in Center B vs Center A patients, with a high variability of results in both BD (1130.2±717.3 vs 541.6±199.2, p<0.0001) and PTC (1096.1±696.5 vs 584.6±239.8, p = 0.0004). As all samples were analysed together the variability is assumed to stem from differences in sample collection. There was no difference in MMP-9 level between patients with benign vs malignant pathology in either hospital group ($p_A = 0.3$, $p_B = 0.691$). In PTC there was no association between MMP-9 levels and histology, multifocality, invasion or tumor size in either center. In Center A, high risk PTC patients had significantly higher MMP-9 levels compared to low-intermediate risk patients (767.5±269.2 ng/ml vs 563.7±228.4 ng/ml, p = 0.019); a cut-off value of 806 ng/ml could identify high risk patients with a sensitivity of 60% and a specificity of 87.36%,p = 0.018.

Conclusion: MMP-9 is significantly influenced by pre-analytical factors. If samples are carefully handled serum could be of use as a complementary prognostic factor in PTC, although it is not useful for diagnosis. Strict standardization of sampling, collection and storage conditions are essential.

P3-03-195

ONLY ONE THIRD OF PATIENTS AFFECTED BY DIFFERENTIATED THYROID CANCER LYMPH NODE RECURRENCE ACHIEVE COMPLETE REMISSION DESPITE OPTIMAL TREATMENT

David Viola[1], *Lorenzo Bedini*[1], *Gabriele Materazzi*[2], *Eleonora Molinaro*[1], *Laura Agate*[1], *Valeria Bottici*[1], *Clara Ugolini*[2], *Fulvio Basolo*[2], *Paolo Vitti*[1], *Rossella Elisei*[1]

[1]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University of Pisa, Italy; [2]Unit of Surgery, Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Italy

Background and aims: Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy with a low mortality but a high rate of lymph node recurrence (LNR). The aims of the study were to evaluate: a) prevalence of "complete remission" in patients with LNR treated with different modalities, b) predictors of disease-free status, c) efficacy of the different treatments (surgery vs 131-I).

Patients: 187 patients diagnosed and treated between 1984 and 2011 for DTC-related LNR were retrospectively studied.

Results: The risk factors for LNR were male gender, larger size of the primary tumor, extra-thyroid extension, multifocality and lymph node metastases at diagnosis. At the end of follow-up (9.9 ± 4.7 years) patients were divided into two groups: disease free or persistent. Predictors of persistent disease included: younger age at diagnosis (p = 0.03), larger primary tumor size (p = 0.0005), presence of extra-thyroid extension (p<0.0001), advanced stage according to AJCC-TNM (III+IV) (p = 0.006) and higher risk class according to the ATA classification (p = 0.0004). We than distinguished: Group-A, those treated with surgery (+/- 131-I) and Group-B, those treated only with 131-I therapy. Group-A had a significantly higher disease-free rate (26.8%) than Group-B (15.8%). However, a non-negligible number of patients in Group-A underwent a third surgical procedure for a second LNR (27.4%). At the end of follow-up, 32.4% of Group-A patients were disease free compared to 15.8% of Group-B. None of them died for the disease.

Conclusions: Patients with LNR are generally younger and with a more advanced disease at diagnosis in terms of lymph node spread and they achieve "complete remission" only in 25-30%. The most effective treatment modality to obtain a disease-free status is surgery that, at least in our series, had an unexpected low complication rate. Nevertheless, the LNR, either cured or not, did not have any impact on the survival of these patients.

P3-03-196

LOW LYMPHOCYTE-TO-MONOCYTE RATIOS ARE ASSOCIATED WITH POOR OVERALL SURVIVAL IN ANAPLASTIC THYROID CARCINOMA PATIENTS

Jong Hwa Ahn[1], *Eyun Song*[1], *Hye-Seon Oh*[1], *Dong Eun Song*[2], *Won Gu Kim*[1], *Tae Yong Kim*[3], *Won Bae Kim*[4], *Youngkee Shong*[5], *Min Ji Jeon*[6];

[1]Asan Medical Center, Seoul, Rep. of South Korea; [2]Asan Medical Center, Rep. of South Korea; [3]University of Ulsan College of Medicine, Asan Medical Center, Asan Medical Center, Seoul, Rep. of South Korea; [4]Asan Medical Center, University of Ulsan College of Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Rep. of South Korea; [5]Asan Medical Center, University of Ulsan, Endocrinology, Seoul, Rep. of South Korea; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Rep. of South Korea

Objectives: The lymphocyte-to-monocyte ratio (LMR), which reflects the tumor infiltrating immune cell status and host immunity, has been reported as a prognostic marker in various cancers. The aim of the present study was to evaluate the role of LMR as a prognostic marker in predicting the survival of patients with anaplastic thyroid carcinoma (ATC).

Methods: We retrospectively included 35 ATC patients with available complete blood cell count (CBC) data. The primary outcome was the overall survival (OS) of patients with ATC.

Results: There were no significant differences between the LMR of the baseline and that of the follow-up CBC (P = 0.53). The patients were divided into two groups based on their baseline LMR: a low LMR group (<4) (n = 23, 66%) and a high LMR group (≥ 4) (n = 12, 34%). The proportion of cervical lymph node (LN) metastasis in the low LMR group was significantly higher than that in the high LMR group (P = 0.021). The OS curves were significantly different based on the LMR values, and the median OS of the low and high LMR groups was 3.0 and 9.5 months, respectively (P = 0.004). In multivariate analysis, low LMR was also an independent risk factor for all-cause mortality in patients with ATC (HR, 2.55; 95% confidence interval (CI): 1.08-6.00, P = 0.032) after adjusting for sex, tumor size and distant metastasis status.

Conclusions: Low LMR is associated with poor survival in patients with ATC. LMR could be a simple and stable prognostic biomarker reflecting host immunity in patients with ATC. Further studies are needed to confirm the prognostic role of LMR in ATC.

P3-03-197

STRATEGIES FOR THE LONG-TERM ORAL ADMINISTRATION OF LENVATINIB ON DIFFERENTIATED THYROID CANCER

Atsumi Tamura[1], *Hidemitsu Tsutsui*[1], *Yukiko Yano*[1], *Junko Ito*[1], *Ryoji Ohara*[1], *Masae Hoshi*[1], *Norihiko Ikeda*[1]

[1]Tokyo Medical University, Tokyo, Japan

Background: Lenvatinib became available for unresectable and radioactive iodine refractory differentiated thyroid cancer in Japan in 2015. There are cases that have been administered with lenvatinib orally over years in our hospital.

Purpose: We study aimed to clarify the factors that enable the long-term oral administration of lenvatinib. We also reviewed planned drug holiday that were implemented by the hospital with the aim of enabling long-term administration.

Methods: We investigated 25 cases of differentiated thyroid cancer to which lenvatinib administration was started in our department between May 2015 and June 2018.

Results: We obtained the following results; mean age of patients, 70 years; median time to treatment failure (TTF), 648 days; first-year overall survival (OS) rate, 72%; second-year OS rate, 64%; overall response rate (ORR), 68%. It was observed that "Eastern Cooperative Oncology Group Performance Status (ECOG PS) Score was 0 when starting" and "no symptoms were found when starting" extended TTF and OS. An administration method in which a planned drug holiday period was established to reduce adverse events was used in 8 cases. After the planned drug holiday was introduced, the adverse events were improved in all 8 cases. There was no disease progression from introducing the planned drug holiday to stopping the administration of the drug.

Discussion: The TTF, OS, and ORR were optimal across all target cases. It is necessary to consider introducing lenvatinib at a stage when the patient's condition is still favorable. Additionally, to continue with oral administration, it is essential to manage adverse events. At our hospital, we introduced a planned drug holiday to manage adverse events. 'Planned drug holiday' is an effective method for continuing of treatment.

P3-03-198

PREDIABETES AND TYPE 2 DIABETES MELLITUS ARE NOT THE FACTORS ATTRIBUTABLE TO INCREASED INCIDENCE OF THYROID CANCER

Tereza Grimmichova[1], *Martin Hill*[2], *Petr Matucha*[2], *Karel Vondra*[2]

[1]Institute of Endocrinology, 2nd Department of Internal Medicine, University Hospital Královské Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic; [2]Institute of Endocrinology, Prague, Czech Republic

Background: Increasing incidence of thyroid cancer may be attributable to sensitive diagnostic tools as well as other secondary and modifiable risk factors. Patients with type 2 diabetes (T2DM) experience generally higher cancer incidence. Mechanisms linking diabetes with cancer include hyperglycemia, insulin resistance and compensatory hyperinsulinemia. The association between DM2 and thyroid cancer is inconclusive

Methods: case-control prospective study in 722 randomly selected patients without history/treatment of thyroid disease in iodine sufficient area. The patients were screened for T2DM and prediabetes (PDM), underwent thyroid ultrasound and biochemical tests. The patients were assigned to group of prediabetes (PDM) (n = 50; 6.9 %), T2DM (n = 77; 10.7 %) and non-DM (NDM) (n = 595). Fine needle aspiration (FNA) was carried out in 221 patients. Multivariate regression and bidirectional orthogonal projection to latent structure were applied.

Results: 33 % of patients with T2DM and specially PDM were newly diagnosed by our screening. Histological examination was done in 67 patients, 25 findings were malignant (3.46 %); especially papillary thyroid carcinoma (52 %). Relevant positive predictors for T2DM (t-statistic = 25.87; $p<0.01$) and PDM (21.69; $p<0.01$) contrary to NDM (-26.9; $p<0.01$) include thyroid volume (ml) (4.79; $p<0.01$), multinodular goiter (4.83; $p<0.01$), thyroid nodule volume (ml) (3.25; $p<0.01$), BMI (22.47; $p<0.01$), age (16.98; $p<0.01$), smoking 2.61; $p<0.05$) and non-thyroid cancers (2.86; $p<0.05$), while negative relevant predictors comprise occurrence of autoimmune thyroid disease (AITD) (-2.01; $p<0.05$), anti-TPO (-5.89;$p<0.01$), anti-Tg (-5.75;$p<0.01$) and fT3 (-2.86;$p<0.05$). Glycemia (2.67; $p<0.05$), Hb1Ac (5.12; $p<0.01$), C-peptide (-12.94; $p<0.01$), HOMA-IR (-7.85; $p<0.01$), smoking (-3.29; $p<0.01$) and AITD (-2.3; $p<0.05$) were relevant predictors for duration of T2DM and PDM (4.52; $p<0.01$).

Conclusion: In the most insulin resistant subjects, diabetic and prediabetic group, we did not observe increased risk for thyroid cancer, in spite of the increased risk for other malignancies. Structural and benign changes as larger and multinodular thyroid gland, in comparison to autoimmune thyroid disease, are present more often in 2 type diabetes and prediabetes. Ageing is important part of this increase.

P3-03-199

ECTOPIC CERVICAL PAPILLARY THYROID CARCINOMA: THREE CASE REPORTS

Joana Saraiva[1], *Cristina Ribeiro*[2], *Miguel Melo*[3], *Lúcia Fadiga*[4], *Gracinda Costa*[5], *Isabel Paiva*[4]

[1]Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar e Universitario de Coimbra, Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal; [2]Serviço de Endocrinologia, Huc, University Hospital of Coimbra, Coimbra, Portugal; [3]Instituto de Investigação e Inovação Em Saúde (I3s), Institute of Pathology and Immunology of the University of Porto (Ipatimup), Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [4]Endocrinology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [5]Serviço Medicina Nuclear, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Introduction: Ectopic thyroid tissue is present in 7-10% of adults. Very rarely it may harbor thyroid carcinoma. Diagnostic dilemma includes the presence of occult primary thyroid carcinoma or the presence of metastatic disease.

Case 1: 47-year-old men submitted to thyroglossal duct cyst excision (4cm) in 1992. Histopathology: capsulated papillary thyroid carcinoma (PTC) with lymph node metastases. Thyroid US was normal. In 2005 US showed 0.28mm left lobe nodule and CT multiple lung metastases. Submitted to total thyroidectomy: follicular variant PTC (290micra). Between 2005 and 2009 was submitted to 6 radioiodine therapies and excision of multiple PTC lung metastases in 2010. Last thyroglobulin (Tg) level (under levothyroxine) was 20ng/mL and 18F-FDG-PET/CT showed stable multiple lung metastases with no metabolic activity.

Case 2: 39-year-old men presented, in 2014, with a 3 month history of left side neck cystic mass that was resected. Histopathology: 5cm thyroglossal duct cyst with 0.4cm PTC. US: left neck lymphadenopathies (FNAC suspicious for PTC) with no thyroid nodules. Total thyroidectomy with neck dissection was performed. Histopathology: left lobe bifocal PTC (12 and 0.5mm) with lymph node metastases. Two radioiodine therapies were administered. In 2017 left neck dissection showed metastases in 4 of 29 lymph nodes. At last consultation in 2017, Tg was 0.2ng/mL, under levothyroxine.

Case 3: 38-year-old men presented in 2017 with right neck adenopatic conglomerate with inconclusive FNAC. In 2018, histopathology of cervical mass showed 2.7cm branchial cyst with PTC/PTC metastasis (?). FNAC of 1.1cm thyroid lobe nodule revealed FLUS. He was submitted to total thyroidectomy and modified cervical dissection in 2019. Histopathology: 12mm right lobe PTC – T3N1b. Radioiodine therapy was planned.

Conclusion: In cystic neck mass, although rare, occurrence of ectopic thyroid tissue and presence of thyroid carcinoma should always be considered. Although thyroid gland can be apparently normal, malignancy must always be considered during follow-up.

Cancer Treatment

P3-04-200

VANDETANIB AND THE PREDICTIVE FACTORS OF DURABLE RESPONSE IN LOCALLY ADVANCED OR METASTATIC MEDULLARY THYROID CANCER: A SINGLE CENTER EXPERIENCE

Laura Valerio[1], *Valeria Bottici*[2], *Antonio Matrone*[2], *Alessia Tacito*[2], *Cristina Romei*[2], *Paolo Piaggi*[3], *Eleonora Molinaro*[2], *Rossella Elisei*[2]

[1]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, 1department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy, Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Italy; [2]Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [3]Phoenix Epidemiology and Clinical Research Branch National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Phoenix, Arizona

Objectives: Vandetanib is an important target therapy in the advanced metastatic medullary thyroid cancer (MTC) treatment. The aim of this study was to evaluate the predictors of durable response to vandetanib in locally advanced or metastatic MTC patients (pts).

Methods: Seventy-nine locally advanced or metastatic, progressive or symptomatic, MTC pts were treated with vandetanib in our center between 2007 and 2018. During follow-up, it was performed clinical, biochemical and morphological evaluation. Twenty-five pts were treated with the drug for < 12 months (Short Responders, SR) while 54 patients were treated for at least 12 months (Long Responders, LR).

Results: The genetic screening showed that RET somatic mutation was present in 82.3% and in 95.3% of SR and LR patients, respectively but it wasn't a predictor of response to vandetanib. Also the metastases site wasn't correlated with the response to the drug. Regarding the other possible predictive factors of durable response, we observed that 87% of LR patients showed at least one adverse events (AE) with a correlation between the AE and the response to vandetanib ($p = 0.02$). Moreover, we observed that a younger age ($\leq$45 yrs) and the absence of progression disease at screening were correlated with a greater response to the drug ($p = 0.01$) and ($p<0.0001$), respectively. Finally, we observed that SR patients had a more aggressive disease and more advanced age at screening than LR patietns.

Conclusions: The younger age, the absence of progression disease at screening and the appearance of AE during vandetanib treatment were the important predictive factors of durable response to the drug. Otherwise, RET somatic mutations were very frequent in our MTC patients but they did not correlate with the response to the drug.

P3-04-201

RE-DISCOVERING CHEMOTHERAPY IN THE FIGHT AGAINST POORLY DIFFERENTIATED AND UNDIFFERENTIATED THYROID CANCERS

Kamilla Mahkamova[1], *Sebastian Aspinall*[2], *Annette Meeson*[3]

[1]Institute of Genetic Medicine, Newcastke University, Newcastle Upon Tyne, UK; [2]Abrdeen Royal Infirmary, NHS Grampian, Aberdeen, UK; [3]Institute of Genetic Medicine, Newcastle University, UK

Objectives: Currently there is a limited scope for using chemotherapy to treat anaplastic thyroid cancers (ATC) due to the quickly emerging chemotherapy resistance. Cancer disease progression is linked to the presence of cancer stem cells (CSC) which express ABC transporters and are associated with multidrug resistance. Hypoxia inducible factors (HIFs) are involved in regulation of stem cell phenotype, which can survive chemotherapy and regenerate ATC. We aim to prevent this by targeting HIFs.

Methods: ATC cell line SW1736 was treated with chemotherapeutic drug Doxorubicin alone or in combination with hypoxia-mimetic cobalt chloride (II) (CoCl2). Untreated cells were used as control.

ABC transporter expression in ATC cell line SW1736 was measured using PCR for mRNA and immunocytochemistry for the protein expression. Thyroid CSC was isolated using Side Population assay (Flow cytometry). MTS assay was used to assess the number of drug- resistant thyroid CSC.

Results: Exposure to Doxorubicin resulted in upregulation of a panel of ABC transporters in the ATC cell line. The effect was further potentiated by activating hypoxia pathway using CoCl2. Introducing HIF 2alpha inhibitor resulted in downregulation of the ABC transporters.

ABC-transporter expressing thyroid CSC population expanded following treatment with Doxorubicin. Further exposure to hypoxia resulted in doubling of thyroid CSC numbers compared to the cells treated with DOX alone. CSC fraction reduced when HIF2 inhibitor was used.

MTS cell viability assay demonstrated increased numbers of the doxorubicin-resistant ATC cells following HIF pathway activation. Partial reversal in the doxorubicin resistance was observed with HIF 2alpha inhibitor.

Conclusions: HIF pathway contributed to the drug resistance by increasing CSC enriched fraction including upregulation of certain ABC transporters. The effects were partially reversed by inhibiting HIF 2alpha. To overcome chemotherapeutic resistance and eradicate thyroid CSC, a combined treatment targeting HIF pathway and specific ABC transporters may be required.

P3-04-202

THE DUTCH RECOMMENDATION FOR TREATMENT OF PEDIATRIC DIFFERENTIATED THYROID CARCINOMA

Chantal Lebbink[1], *Bernadette Dekker*[2], *Schelto Kruijff*[2], *Bart de Keizer*[3], *Rutger-Jan Nievelstein*[1], *Annemiek Kwast*[4], *Paul van Trotsenburg*[5], *Thera Links*[2], *Hanneke van Santen*[1]
[1]Wilhelmina Children's Hospital, Utrecht, Netherlands; [2]University Medical Center Groningen, Groningen, Netherlands; [3]University Medical Center Utrecht, Utrecht, Netherlands; [4]Integraal Kankercentrum Nederland, Netherlands; [5]Emma Children's Hospital, Amsterdam, Netherlands

On behalf of the Dutch Pediatric Thyroid Carcinoma working group

Background: Several international pediatric guidelines for treatment of Differentiated Thyroid Cancer (DTC) exist. However discordances among these guidelines exist. Furthermore, no European or Dutch treatment recommendations for pediatric DTC are available. We aimed to develop Dutch recommendations for pediatric DTC.

Methods: A multidisciplinary working group was formed including pediatric endocrinologist, pediatric radiologist, pathologist, endocrinologist, endocrine surgeon, pediatric surgeon, pediatric oncologist, specialist nuclear medicine, clinical geneticist and a patient representative. A systematic literature search was conducted for all existing guidelines and review articles for pediatric DTC from 2000 until February 2019. The Appraisal of Guidelines, Research and Evaluation (AGREE) instrument was used for assessing quality of the articles. All were compared to determine the dis- and concordances. The American Thyroid Association (ATA) pediatric guideline 2015 was used as framework to develop specific Dutch recommendations. Discussion points based upon expert opinion and current treatment management of DTC in children in the Netherlands were identified and elaborated.

Results: Based on the most recent evidence and expert opinion, a Dutch 2019 recommendation for pediatric thyroid carcinoma has been written.

Conclusion: Pediatric DTC requires a multidisciplinary approach. The Dutch Pediatric DTC Recommendation 2019 can be used for the development of a collaborative European Recommendation for treatment of pediatric DTC.

P3-04-203

LONGTERM EFFICACY OF ULTRASOUND GUIDED PERCUTANEOUS LASER ABLATION FOR PAPILLARY THYROID MICROCARCINOMA. RESULTS OF A 10 YEAR FOLLOW UP

Hyundae Yoon[1], *Jongyup Bae*[1], *Woojin Chang*[1], *Seungil Bae*[1], *JongRyool Oh*[1], *Hojin Kim*[1], *Hanbyul Kim*[1], *Gitak Son*[1], *Hyeyeon Jeong*[1]
[1]Raphael Hospital, Daegu, Rep. of South Korea

Background: Immediate surgery to all PTMC may be considered overtreatment. Therefore, active surveillance can be an option to distinguish invasive PTMC. However, active surveillance not only makes the patient anxious, but it may also require aggressive treatment as cancer progresses. The objective of this study was to evaluate long term clinical efficacy and safety of ultrasound guided percutaneous laser ablation(PLA) for treating PTMC.

Methods: The study was conducted in 109 patients with single PTMC diagnosed by fine needle aspiration biopsy. PTMC adjacent to trachea or recurrent laryngeal nerve and showing extrathyroidal extension at ultrasound examination were excluded. PLA was performed in a single session with one optical fiber (400um plane-cut quartz fiber), a 980nm continuous wave infrared diode laser source, and an output power of 3W. The ablation area exceeded the tumor boundary sufficiently to secure safety margin.

The level of thyroid hormones and thyroid autoantibody were measured before and after PLA and complications were recorded. Ultrasonographic examination was performed regularly for 10years to measure the volume of the ablation area and to check for recurrence. Neck CT, PET CT and FNA was performed according to the circumstances if recurrence was suspected.

Results: PLA procedure was well tolerated without serious side effects. At 3-6months after PLA, all ablation area remained as scar-like lesions. No changes in thyroid function or autoimmunity were observed. Of the 109 patients, 108 patients were treated successfully in a single session. Only one incomplete ablation was detected by immediate US examination after PLA, and a second ablation was recommended, but she refused and chose surgery. The recurrence occurred in five patients (1 patient in central lymph node, 4 patients : new foci in other thyroid parenchyme). The recurrence of lymph node and one recurrence of thyroid gland was detected within several months of treatment, so it should be regarded as an undetected cancer rather than a relapse.

Conclusions: Theses long-term follow up results show that ultrasound-guided PLA appears to be effective and safe alternative treatment strategy of PTMC. Howeverd, thorough examination of multifocality and lymph node metastasis is required before laser treatment.

P3-04-204

YTTRIUM-90 TRANSARTERIAL RADIOEMBOLIZATION (TARE): A NEW TREATMENT FOR THE LIVER METASTASIS (LM) OF MEDULLARY THYROID CANCER (MTC)

Luciana Puleo[1], *Irene Bargellini*[2], *Tommaso Depalo*[3], *Giuseppe Boni*[3], *Francesca Bianchi*[3], *Valeria Bottici*[1], *Eleonora Molinaro*[1], *Rossella Elisei*[1], *Laura Agate*[1]
[1]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa, Italy; [2]Department of Vascular and Interventional Radiology, University Hospital of Pisa, Pisa, Italy; [3]Regional Center of Nuclear Medicine, University Hospital of Pisa, Pisa, Italy

Background: LM occur in 45% of patient with advanced MTC. In some cases LM cannot be treated with local therapy especially if a multifocal extension is present.

Aim of the study: To investigate the biochemical (calcitonin and CEA) and structural response of the LM of MTC to TARE.

Rational and Methods: TARE is a transarterial brachytherapy in which microspheres loaded with β-emitting yttrium-90 are selectively delivered into the hepatic arteries that supply blood to LM with radiation-induced tumor necrosis.

Patients: We treated 8 patients (6 males and 2 females) with an average age of 55 years (range 31-75 aa) and progressive multiple LM of MTC with preserved liver function. Patients were treated from April 2017 to December 2018.

They performed periodic evaluations at 1, 4 and 12 months after TARE and every 6 months thereafter. Two patients were also treated with vandetanib. The pre-TARE mean total hepatic tumor volume was 102.6 ml ± 183 DS (median 31.5 ml; range: 12-551 ml). The radiological response was evaluated with the RECIST 1.1.

Results: One month after TARE, a clinically relevant although not statistically significant (p:022), reduction of the Ct and CEA values was observed in all patients. We also measured the total hepatic tumor at the best response post-TARE of six patients: the mean volume+ was 3.1 ml ± 2.0 DS (median 3.6 ml; range: 0-5.8 ml). Five out of 8 (62.5%) patients completed a 12 months follow-up: 2/5 (40%) showed an apparent CR, 1/5 (20%) a PR and 2/5 (40%) a SD, The only patient with a 18 months follow-up has still a SD.

Conclusions: Our study showed a good response of LM from MTC to TARE. Furthermore, the absence of complications and the good tolerability of this treatment makes TARE a valid therapeutic strategy when LM are multiple and progressive.

P3-04-205

A RARE ADVERSE EVENT (AE) IN A GROUP OF RADIOIODINE-REFRACTORY DIFFERENTIATED THYROID CANCER (RAI-R DTC) PATIENTS IN THERAPY WITH LENVATINIB

Luciana Puleo[1], *Carlotta Giani*[1], *Laura Valerio*[1], *David Viola*[1], *Eleonora Molinaro*[1], *Rossella Elisei*[1], *Laura Agate*[1]
[1]Unit of Endocrinology, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa, Italy

Background: Lenvatinib, a tyrosine multikinase inhibitor (TKI), has been approved for RAI-R DTC with progressive disease. The most frequent AE related to Lenvatinib, as reported in the SELECT study, are: hypertension (67.8%), diarrhea (59.4%), fatigue (59%), anorexia (50.2%), weight loss (46.4%), nausea (41%), hand -and-foot syndrome (31.8%) and proteinuria (31%).

Aim of the study: To evaluate the incidence of an apparent uncommon AE, the cholecystitis, during the treatment with Lenvatinib.

Patients: We retrospectively analyzed the data of 84 RAI-R DTC patients who underwent therapy with Lenvatinib from February 2012 to September 2018.

Results: Acute cholecystitis occurred in 11/84 patients (13.1%). This group of patients was composed of 6 male and 5 female with an average age of 66.63 years ± 9.8 DS (median 69 years; range: 48-81 years). The initial dose of the drug was 24 mg/daily. Only in 2 cases the initial dose was 14 mg/daily. The appearance of acute cholecystitis occurred in an average period of 16.6 months ± DS 24.5 months from the beginning of the therapy (median 3 months; range: 2-74 months). Ten/11 (90.9%) patients presented the distention of the gallbladder, associated to bilious mud in 5/10 (50%) and gallstones 4/10 (40 %). Only in one case cholecystitis was present without the radiological signs indicated above and only 6/11 (54.5%) patients were symptomatic. Six out of 11 (54.5%) patients were submitted to cholecystectomy. In the other cases signs of cholecystitis regressed after the reduction of the daily dose of TKI.

Conclusions: In our series 13.1% of patients presented acute cholecystitis, in the majority of cases after few months of therapy but in some others even after 6 years. This evidence suggests that an assessment of the gallbladder is appropriate before starting TKI in order to evaluate any predisposing factor for the onset of acute cholecystitis.

P3-04-206

EXTERNAL BEAM RADIATION THERAPY FOR MEDULLARY THYROID CANCER

Ana Ferreira[1], *Sara Pinheiro*[2], *Tiago Nunes da Silva*[2], *Valeriano Leite*[3]
[1]Hospital Garcia de Orta, Almada, Portugal; [2]Instituto Português de Oncologia de Lisboa, Lisbon, Portugal; [3]Servico de Endocrinologia, Instituto Português de Oncologia de Lisboa, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal

Introduction: External beam radiation therapy (EBRT) can be used as adjuvant, salvage or palliative treatment for patients with advanced medullary thyroid cancer (MTC), but evidence on outcomes is scarce.

Objective: to evaluate EBRT outcomes in locoregional and metastatic MTC.

Method: retrospective review of data from patients with MTC diagnosed between 1997 and 2018, treated with EBRT. EBRT outcomes were defined as locoregional tumour control, symptomatic relief and 5-year survival.

Results: 22 patients, 64% male, mean age 56 years (29-80), mean follow-up 6.5 years (0.5-19.9). Twenty-seven EBRT treatments were performed: 17 in locoregional setting and 10 in metastatic disease. In the locoregional setting, 5 patients had adjuvant EBRT (dose at surgical site 50-66Gy and cervical lymph nodes 46-60Gy), with 4 having locally controlled disease for a mean of 2.4 years (0.3-5.9) before progression, and 1 having no evidence of progressing local disease until the end of follow-up (4months); ten salvage treatments were performed (mean dose at surgical site 45Gy, cervical lymph nodes 40Gy and mediastinum 37Gy) of which 5 resulted in stable disease until the end of follow-up (mean 1.5 years; 0.8-2.5), 4 had locally stable disease that progressed after a mean of 1.25 years (0.3-3.75) and 1 had progressive local disease immediately after EBRT; 2 patients had palliative EBRT, 1 cervical (20Gy) and 1 mediastinal (50Gy) with no symptomatic improvement. Mean survival was 10.5 years for adjuvant EBRT and 8.7 years for salvage EBRT (p = 0.37); five-year survival was 100% and 74.1%, respectively.

Eight distant metastases treatments were performed in the bone (mean dose 27Gy), 1 in choroid (30Gy) and 1 intracranial (25Gy). Seven out of 10 patients were re-evaluated for symptom control: 3 had no control, 2 had significant clinical improvement, 2 had temporary improvement with relapse after 4 and 7 months, respectively.

Conclusion: EBRT might have a role for local control of disease in MTC as well as for symptomatic relief in palliative setting.

P3-04-207

EVALUATION OF WEIGHT LOSS AND BODY COMPOSITION MODIFICATIONS IN PATIENTS WITH ADVANCED THYROID CANCER DURING LENVATINIB TREATMENT

Simone De Leo[1], *Carla Colombo*[2], *Marta Di Stefano*[3], *Silvia Cozzi*[1], *Luca Persani*[4], *Laura Fugazzola*[5]
[1]Division of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Milan, Italy; [2]Division of Endocrine and Metabolic Diseases, Istituto Auxologico Italiano IRCCS, Milan, Italy, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [3]Department of Clinical Sciences and Community Health; Università Degli Studi DI Milano, Milan, Italy; [4]University of Milan, IRCCS Istituto Auxologico Italiano, Ospedale San Luca, Milan, Italy; [5]Dept. of Pathophysiology and Transpl, Istituto Auxologico Italiano IRCCS, University of Milan, Milano, Italy

Objectives: Lenvatinib treatment is affected by the occurrence of several adverse events. Weight loss is one of the most frequent and is reported in 50-90% of patients. No data are available to date on the extent and the characteristics of the weight loss during tyrosine kinase inhibitors treatment in patients with advanced thyroid cancer. Aim of our study was to evaluate the weight loss and the body composition modifications observed in patients treated with Lenvatinib.

Methods: We followed-up 11 patients with advanced thyroid cancer during treatment with Lenvatinib and performed in all patients the body composition assessment by bioelectrical impedance analysis (BIA). Patients were evaluated, at a single Institution, at 3 months intervals. The longest follow up was of 33 months.

Results: Patients treated with Lenvatinib lost between 4 and 40% of their baseline weight, this was particularly severe during the first year of treatment. Both fat mass (FM) and fat-free mass (FFM) reduced in all patients whose evaluation was available since baseline, and after one year FM and FFM reduction ranged between 18-60% and 3-16%, respectively. In all patients, FM reduction was higher than that of FFM. Body cell mass (BCM) reduction was more severe in patients with a more elevated baseline muscular mass (20-25%), while the other patients had a slight or null BCM reduction (+4 to -7%). Total body water decreased in parallel to weight loss.

Conclusions: Both FM and FFM are affected by Lenvatinib treatment, however the higher reduction is related to the loss of FM, which is likely the first compartment involved, in particular in overweight and obese patients. According to our study, patients treated with Lenvatinib should receive oral nutritional supplements as early as possible, in particular when exercising is recommended for improving fatigue. In some circumstances, parenteral nutrition may be indicated.

P3-04-208

EFFICACY AND SAFETY OF SUNITINIB AND SORAFENIB FOR METASTATIC MEDULLARY THYROID CANCER

Daniela Dias[1], *Inês Damásio*[2], *Joana Simões-Pereira*[3], *Valeriano Leite*[4], *Rita Santos*[5]
[1]Instituto Português de Oncologia de Lisboa, Francisco Gentil, Endocrinology Department, Portuguese Cancer Institute, Lisbon, Portugal, Lisboa, Portugal; [2]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Portugal; [3]Serviço de Endocrinologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Unidade de Investigação Patobiologia Molecular, Instituto Português de Oncologia de Lisboa Francisco Gentil, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal; [4]Servico de Endocrinologia, Instituto Português de Oncologia de Lisboa, Nova Medical School | Faculdade de Ciências Médicas, Lisboa, Portugal; [5]Instituto Português de Oncologia de Lisboa Francisco Gentil, Endocrinology Department, Instituto Portugues de Oncologia de Lisboa, Francisco Gentil, Lisbon, Portugal, Nova Medical School/Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal, Lisboa, Portugal

Introduction: Two tyrosine kinase inhibitors (TKIs), cabozantinib and vandetanib are approved in advanced medullary thyroid cancer (MTC), however, these TKIs are not available in all countries. Sorafenib and sunitinib can be considered for use in selected patients as an *off-label* treatment, since both had encouraging results in phase 2 trials.

Aim: To determine the efficacy and safety of sunitinib and sorafenib in the treatment of advanced MTC.

Methods: Retrospective analysis of patients with metastatic and/or locally advanced and unresectable MTC treated with sunitinib and/or sorafenib at our instituition, from February 2009 to February 2019.

Results: We identified 12 patients (pts), 10 sporadic and 2 with hereditary disease. Three pts were excluded due to short course of therapy. Except for 1 pt who was first treated with vandetanib, all pts had first line treatment with sunitinib and 4 had sorafenib as second line treatment. The mean age at first line TKI initiation was 58.5 ± 9.7 years. Treatment duration was 30.9 ± 31.4 months with sunitinib and 7.7±7.3 months with sorafenib. The best overall response with sunitinib was partial response (PR) in 7 pts (77.8%) who had durable response for 6-80 months until progression. One (11.1%) pt achieved stable disease (SD), while 1 (11.1%) had progressive disease (PD).

Median overall survival with sunitinib was 40±24.2 months (95% CI: 0-87); 1-and 5-year survival rate was 75% and 35.2 %, respectively. Median progression-free survival (PFS) was 57 months± 20.5 (95% CI: 16.8-97.2).

Four pts initiated sorafenib as a second line and best response was SD in 1 pt. The other 2 pts experienced PD, between 2 and 3 months after starting sorafenib.

Sunitinib was discontinued in 5 pts due of toxicities (thrombocytopenia, hypercalcemic encephalopathy, hemolytic anemia; tracheo-esophageal fistula) and intolerance.

Conclusions: sunitinib presented a good clinical response but sorafenib appears to be a little benefit as second line treatment, although this conclusion is limited by the small sample size.

P3-04-209

SERIOUS AND RARE ADVERSE EVENTS OF LENVATINIB IN PATIENTS WITH REFRACTORY THYROID CANCER

Kalliopi Pazaitou-Panayiotou[1], *Pantelitsa Rakitzi*[2], *Achilleas Papanikolaou*[2], *Christina Pamporaki*[2], *Anastasia Deflioti*[2], *Eirini Poimenidou*[2], *Maria Boudina*[2], *Alexandra Chrisoulidou*[2]
[1]Theagenio Anticancer Hospital of Thessaloniki, Thessaloniki, Greece; [2]Theagenio Cancer Hospital, Thessaloniki, Greece

Lenvatinib is a tyrosine kinase inhibitor used to treat metastatic thyroid cancer refractory to radioactive iodine therapy. The experience of its use is small.

The purpose of our study was to report rare but serious adverse effects of lenvatinib treatment.

Methods: This is a study of 10 patients (4 females), mean age at diagnosis of thyroid cancer 57 years. All patients underwent thyroidectomy. Histology was compatible with papillary carcinoma (60%), follicular carcinoma (30%) and poorly differentiated carcinoma (10%). All patients had pulmonary metastases, while 7 of them had multiple metastases involving bone and liver. All had normal baseline renal function. Patients received therapeutic iodine without adverse effects. When lenvatinib treatment was decided and initiated, the dose of 24 mg daily was given. Treatment duration ranged from 4 weeks to 20 months. Follow-up included regular biochemical tests, cardiological evaluation and CT or MRI.

Results: 4 of the patients discontinued treatment due to side effects, in 2 the dose of lenvatinib decreased significantly. Three showed significant proteinuria (9.7gr/24h, 5.8gr/24h and 3gr/24h) with normal serum creatinine at 4, 8 and 16 weeks after starting treatment. Proteinuria was persistent and required 4-8 month of lenvatinib discontinuation to decrease to <1gr/24h. In addition, one patient presented acute heart failure with ejection fraction <30% and QTc prolongation at 520msec. Other side effects were diarrhea (20%), stomatitis (20%), mouth ulcers (20%), anorexia-weight loss (20%) and fatigue (40%). Most patients needed an increase in daily thyroxine due to increase in TSH.

Conclusions: Lenvatinib, may be associated with serious and life-threatening adverse events from the first few weeks of its administration. It is important that patients are closely monitored and undergo regular cardiac assessment and renal function testing not only by measuring serum urea and creatinine but also by measuring 24-hour urine protein.

Diagnosis 2

P3-05-210

LONGITUDINAL CHANGES IN THYROID HORMONES AND BODY COMPOSITIONS IN EUTHYROID SUBJECTS

Ji-Eun Jun[1], *Seung-Eun Lee*[2], *In-Kyung Jeong*[3], *You-Cheol Hwang*[4], *Kyu Jeung Ahn*[3], *Ho Yeon Chung* [5], *Tae Hyuk Kim*[6]

[1]Kyung Hee University Hospital at Gang-Dong, Endocrinology, Seoul, Rep. of South Korea; [2]Konkuk University Medical Center, Seoul, Rep. of South Korea; [3]Kyung Hee University Hospital at Gangdong, Seoul, Rep. of South Korea; [4]Kyung Hee University Hospital at Gangdong, Seoul, Rep. of South Korea; [5]Kyung Hee University Hospital at Gangdong, Seoul, Rep. of South Korea; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Rep. of South Korea

Objective: Thyroid hormones determine energy expenditure and consequently affect body composition. However, it is not clear whether long-term change in thyroid hormones within reference range has clinical effects on body composition. We investigated the association between change in thyroid hormones and change in body composition together with insulin resistance in euthyroid population.

Methods: This longitudinal study included 30,146 subjects (aged 50.6 ± 8.5 years, 61.0% of men) without any history of thyroid disorders, who have sustained euthyroid status during the 3.8 years of mean follow-up. Change in variables was determined by subtracting the baseline value from the final value, divided by the observation period. Body fat percentage (BFP, %) was calculated as body fat mass/weight x 100, and skeletal muscle mass index (SMI, %) as lean mass/weight x 100, which were measured by segmental bioelectric impedance. Linear regression analyses were performed to evaluate the associations between thyroid hormone levels and body composition parameters.

Results: In multivariate linear analyses adjusting for age, SBP, LDL-cholesterol, diabetes prevalence, smoking status, and frequent exercise, baseline serum total triiodothyronine (TT3) was inversely associated with SMI, while it was positively associated with waist circumference (WC), BFP, and HOMA-IR in both men and women. Baseline free thyroxine (FT4) was inversely associated with BMI and HOMA-IR in men and women. Baseline serum thyroid-stimulating hormone (TSH) levels had modest positive correlation with HOMA-IR only in men. Change in TT3 exhibited an inverse association with change in SMI and positive associations with WC, BFP, and HOMA-IR among both men and women, even after additional adjustment for baseline level. Change in FT4 was inversely associated with BMI, BFP, and HOMA-IR. The association between change in TSH and body composition showed inconsistent results in men and women. Serum TT3 prominantly increased in euthyroid subjects with decreasing SMI and increasing BFP, compared to those with increasing SMI and decreasing BFP (1.41 vs. 0.62 ng/dL/year, P = 0.001).

Conclusion: Subtle change in TT3 over time had a significantly inverse association with change in muscle mass, whereas change in TSH and FT4 appeared to have little or no association. TT3 and FT4 showed the paradoxical opposing relationships with BMI, body fat, and insulin resistance in euthyroid population.

P3-05-211

CHANGES IN BODY COMPOSITION DURING RESOLUTION OF SHORT TERM SEVERE HYPOTHYROIDISM

Marin Gergics[1], *Greta Pham-Dobor*[1], *Orsolya Nemes*[2], *Beata Bodis*[2], *Karoly Rucz*[2], *Emese Mezosi*[1], *Laszlo Bajnok*[1]

[1]University of Pécs, Medical School, 1st Department of Medicine, University of Pécs, Szentágothai Research Centre, Pécs, Hungary; [2]University of Pécs, Medical School, 1st Department of Medicine, Pécs, Hungary

Introduction: Hypothyroidism related changes in body composition have not been fully elucidated. Short term iatrogenic severe hypothyroidism in differentiated thyroid cancer (DTC) patients before radioiodine (RAI) therapy is a special model in this respect. Our aim was to investigate changes in body composition during the treatment of this condition.

Methods: In 33 DTC patients (10 male, 23 female, mean age 49,5 ± 2,5 ys) whom DTC was not advanced (ECOG: 0) body composition was measured on the day of RAI and 10-12 weeks later using Bodystat Quadscan 4000. Statistical analyses were performed using SPSS 22.0 and MedCalc 13.3.3.0.

Results: The body weight (BW) was significantly lower after reaching euthyroidism than at hypothyroidism (84,1 ± 3,5 vs. 82,3 ± 3,5 kg). This reduction was mostly related to the decrease of fat mass (FM; -1,65 ± 0,42 kg). According to this, waist circumference lowered significantly, too (92,0±2,3 vs. 91,5 ± 2,3 cm). However, meantime the dry lean weight (DLW) reduced, as well (-0,31 ± 0,07 kg). Both extracellular and intracellular volumes (ECV, ICV, respectively) diminished also (-0,44 ± 0,25 and -0,20 [-0,85;1,55] L), but their degrees did not reach statistical significance. In a regression model during multivariate analyses, all the 4 major constituents of body composition, i.e. FM, DLW, ECV, ICV, contributed independently to the BW changes of which the variance of DLW had the highest power.

Conclusion: In hypothyroidism, at least in its short term severe form, not only the fat mass and extracellular volume are increased, but dry lean weight and intracellular volume as well. Further studies are required to confirm these hypothyroidism related changes in body composition and to clarify the underlying pathomechanisms.

P3-05-212

HIGH NORMAL RANGE OF FREE THYROXINE IS ASSOCIATED WITH DECREASED TRIGLYCERIDES BASED ON POPULATION REPRESENTATIVE DATA

Jeongmin Lee[1], *Chaiho Jeong*[2], *Jeonghoon Ha*[2], *Kwanhoon Jo*[3], *Dong Jun Lim*[2], *Jung-Min Lee*[1], *Sang-Ah Chang*[1], *Moo-il Kang*[2], *Min Hee Kim*[1]

[1]College of Medicine, The Catholic University of Korea, Enpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Rep. of South Korea; [2]College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Rep. of South Korea; [3]College of Medicine, The Catholic University of Korea, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Rep. of South Korea

Background: Thyroid hormone is involved in the most of lipid metabolism processes occurred in the liver, adipose tissue, intestine, and muscle. Thus, in overt thyroid dysfunctions, especially in hypothyroidism, noticeable changes in lipid profiles are observed. However, it is not conclusive whether subtle changes of thyroid function with in normal range could cause significant changes in lipid profiles. The aim of this study is to evaluate the association of thyroid hormone (free thyroxine, free T4) with lipid profiles in nationally representative data.

Methods: This study was based on the survey date from the Sixth Korea National Health and Nutrition Examination Survey (KNHANES VI), 2013 to 2015, a cross-sectional survey. We selected subjects who were older than 19 years old, underwent thyroid function tests and lipid profile. Subjects with history of thyroid disease or beyond normal serum FT4 and thyrotropin (TSH) ranges and those on medication for dyslipidemia and/or cardiovascular disease were excluded. Finally, a total of 3548 subjects were included.

Results: There was a significant decrease in serum triglyceride levels with increasing free T4 quartiles after adjustment of confound factors (p for trend = 0.001). Conversely, as free T4 quartiles increased, a significant increase in serum high-density lipoprotein (HDL) cholesterol was observed (p for trend = 0.014). However, there were no significant changes in other lipid profiles such as total cholesterol, low-density lipoprotein (LDL)-cholesterol, and non-HDL-cholesterol according to free T4 quartiles. Risk of hypertriglyceridemia (>150mg/dL) significantly decreased as free quartiles increased (p for trend <0.05). Though some significant associations between free T4 quartiles and risk of dyslipidemia, high LDL-cholesterol, and non-HDL cholesterol were found, no consistent results were observed according to adjustment of confounders.

Conclusion: We found that there was a positive correlation between serum free T4 and triglyceride in subjects with normal thyroid function. Incidence of hypertriglyceridemia, one of unfavorable lipid profiles, tended to be low in the higher FT4 quartiles. Therefore, a close surveillance in terms of lipid profiles could be considered in subjects with low normal serum FT4 levels.

P3-05-213

THYROID ULTRASONOGRAPHY AS A PREDICTIVE TOOL OF RECURRENT LARYNGEAL NERVE ANOMALY

Dávid Molnár[1], *Ákos Reményi*[1], *Éva Átol*[2], *Frigyes Helfferich*[1]
[1]Department of Otorhinolaryngology and Head and Neck Surgery, Medical Centre Hungarian Defence Forces, Budapest, Hungary; [2]Department of Radiology, Medical Centre Hungarian Defence Forces, Budapest, Hungary

Background: The goals of thyroidectomy are eradicating the diseased gland matter and the preservation of laryngeal innervation with a special focus on the recurrent laryngeal nerves (RLN). The spectrum of RLN injury can vary from unilateral vocal fold mobility impairment to bilateral paralysis which is an airway emergency. Any alterations in the course of the RLNs can increase the risk of nerve damage.

A common variation is the right non-recurrent inferior laryngeal nerve (NRLN) with a concomitant lusorian artery (LA). In such a case the brachiocephalic trunk (BCT) is missing. The right subclavian artery emerges directly from the aortic arch, encircles the oesophagus or passes in between the trachea and the oesophagus -this is why it is called lusorian artery.

In most of the cases, thyroid ultrasonography (TUS) is the only imaging study available and required when a patient is referred for thyroidectomy. It is easy-to-access, often done by endocrinologists and has no radiation harm. TUS describes the spatial attributes and parenchymal characteristics however, it is not informative on RLN anatomy.

Case report: The aim of this poster is to call physicians' attention on the LA and the anomaly of the BCT to be used as surrogate markers of a right NRLN. We demonstrate how the assessment can be carried out during routine TUS via the case of a 63-year-old woman who underwent total thyroidectomy for Hürthle cell carcinoma.

Conclusions: We propose, the assessment of the highlighted vessels should be performed and documented during routine TUS. Due to the increasing number of elective thyroidectomies, awareness of an NRLN and an LA could help the surgeon to minimize the chance of a nerve injury. Nevertheless, surgical approach of the carotid artery, the spine and the eosophagus could be planned properly.

P3-05-214

TRIAMCINOLONE INJECTION AND ORAL STEROID MEDICATION IN THYROHYOID SYNDROME

Giljoon Lee[1], *Nayeon Choi*[2]
[1]Kyungpook National University, Daegu, Rep. of South Korea; [2]Samsung Medical Center, Seoul, Rep. of South Korea

Background: Thyrohyoid syndrome is rare disease characterized by unilateral chronic neck pain on hyoid area. Currently, local triamcinolone injection was widely used, but oral steroid treatment was rare tried. We compared the oral steroid and triamcinolone injection for the thyrohyoid syndrome.

Methods: The patients who had unilateral pain and tenderness at thyrohyoid membrane were enrolled and other disease such as gastroesophageal reflux disease were excluded by physical exam and history taking. The patients were treated by oral steroid (n = 5) and triamcinolone injection (n = 5) and pretreatment and posttreatment numeric rating scale (NRS)-11 score were compared in both groups.

Results: The patients with thyrohyoid syndrome were comorbid with globus, sore throat and odynophagia. Pretreatment pain score and posttreatment pain score were not significantly different between two groups. In oral steroid group, posttreatment pain score (8.4 ± 1.1) was significantly improved ($p = 0.043$) than pretreatment pain score (3.2 ± 2.2). In the triamcinolone injection group, posttreatment pain score (7.2 ± 1.1) was also significantly improved ($p = 0.041$) than pretreatment score (1.6 ± 1.5). None of patient revealed treatment related complications.

Conclusion: Oral steroid treatment could be easily performed and comparable with triamcinolone injection for the patients with thyrohyoid syndrome.

P3-05-215

TOLOSA-HUNT SYNDROME ASSOCIATED WITH HYPOPHYSITIS AND TRANSIENT HYPOPITUITARISM: A CASE REPORT

Radoslav Borisov[1], *Lachezar Lozanov*[1], *Ivan Plachkov*[2], *Bojan S. Lozanov*[1]
[1]Endocrine Dept, Acibadem City Clinic Tokuda Hospital Sofia, Sofia, Bulgaria; [2]Radiology Dept, Acibadem City Clinic Tokuda Hospital Sofia, Sofia, Bulgaria

Tolosa-Hunt syndrome (THS) is a rare disease related to autoimmune granulomatous inflammation of the cavernous sinuses unusually associated with a pituitary involvement. Herein we describe a 36 year-old man presented with left painful ophthalmoplegia and eyelid ptosis. MRI demonstrated the infiltration of both cavernous sinuses and enlargement of the pituitary gland without changes of the intraorbital structures. Laboratory tests established a central hypothyroidism and a hypogonadism, negative TPO-Ab, TSHR-Ab, DNA, a normal thyroid US imaging. The treatment with pulses methylprednisolon (MPS) 500 mg i.v for 3 consecutive days was applied followed by smaller doses MPS up to 5.5 gr cummulative dose for 2 months which resulted to significant amelioration of eye symptoms and signs. The control MRI showed normalization of pituitary size concomitantly with a resolvement of hypopituitarism. Nevertheless the infiltration of the left cavernous sinus and the orbital pains persisted which required the corticosteroid therapy to be continued by MPS 30 mg/24h i.m.until 6th month after beginning of therapy. The side effects occurred such as steroid diabetes, insulin resistance and weight gain more than 10 kg. On these reasons we applied Infliximab 300 mg (4 mg/kg) by a single infusion which resulted to a successful control of all symptoms, dramatic disappearance of pains and diplopia without any side effects. The rapid improvement allowed the corticosteroid therapy to be discontinued followed by beneficial effects on diabetes and body weight. The successful treatment of Tolosa-Hunt syndrome by Infliximab as a TNF-alpha antibody inducing proinflammatory cytokines confirms the concept of autoimmunne pathogenesis of this syndrome which appeared in combination with autoimmune hypophysitis in the case described.

P3-05-216

CERVICAL TRAUMA WITH THYROID FRACTURE

Filipa Bastos[1], *Ana Ferreira*[1], *Isabel Manita*[1], *Maria Carlos Cordeiro*[1], *Jorge Portugal*[1]
[1]Hospital Garcia de Orta

Cervical trauma is common in many types of accidents. However, the lesion of the thyroid gland is poorly reported. The approach may be surgical or conservative. It is necessary to keep these patients under surveillance because of the risk of thyrotoxic crisis.

We present the case of a male child, 11 years old, with no relevant personal history.

He was sent to the emergency department after a bicycle fall with cervical trauma, with cervical edema, local pain and dysphagia. At palpation, painful left cervical swelling with inflammatory signs. Normal thyroid function. Cervical ultrasound showed a discontinuity of the thyroid gland in the left lobe, suggestive of transfixive laceration/thyroid fracture, with marked locoregional hematoma, without airway compromise. He was hospitalized for monitoring and surveillance for 24 hours with no complications.

One week later, resolution of the cervical hematoma and of pain and compressive symptoms, without complaints suggestive of thyroid dysfunction. He maintained normal thyroid function with negative antithyroid antibodies.

Five months later, cervical ultrasound showed resolution of thyroid fracture, but smaller left lobe and heterogeneous echoestructure.

Over this period, there was a progressive increase in thyroid stimulating hormone (TSH), with stable triiodothyronine (T3) and thyroxine (T4) levels (TSH rose from 4.43 to 7.67 mU/L, higher than the normal range for age). It was admitted subclinical hypothyroidism and started therapy with levothyroxine, 25 mcg per day.

Thyroid fracture or injury is infrequent. Despite the presence of thyroid imaging prior to the trauma, there seems to have been a change in the thyroid

structure with a slight decrease in the size of the left lobe, which may have led to a change in thyroid function. This case shows that it is important to keep long-term surveillance of these patients with evaluation of thyroid function, because of the risk of later complications.

P3-05-217
WITHDRAWN

P3-05-218
WHAT IS GROWING ON MY NECK?

Gergő Csitári[1], *Pál Zsuzsa*[2], *Alföldi Sándor*[2], *Simonyi Gábor*[2]
[1]Szent Imre Teaching Hospital, Budapest, Hungary; [2]Szent Imre Teaching Hospital, Metabolic Department, Budapest, Hungary

Introduction: Our patient came to the hospital with cervical lymphadenopathy and thyroid nodules certified by ultrasound. We made fine needle biopsy from the biggest nodule and lymph node. Cytology verified the former a non-malignant goiter nodule and in the latter reactive lymphadenitis. CT scan marked generalized lymphadenopathy with pathological lymph nodes of the submandibular, axillary, mediastinal, subdiaphragmatic, portal and ileocecal regions as well as lytic bone lesions in the vertebrae and in the bones of pelvic girdle. Core biopsy from the lymph node also showed reactivity and inflammation, there were no histological sign of lymphoma or metastasis in the specimen examined by several expert pathologists. I would like to present this case, which set in a benign, very rare diagnosis called Rosai Dorfman disease.

Case report: After the CT findings we made serology test for every possible infections (EBV, CMV, HIV, brucellosis, bartonellosis, melioidosis etc.), and we only found an EBV seropositivity, although in IgM and IgG immunoglobulin types as well. Other laboratory test results showed inflammation, elevated CRP level, accelerated sedimentation rate, anemia, thrombocytosis, hyperglycemia and mild proteinuria. By the effect of the repeatedly used antibiotic therapies the cervical lymphadenitis was transitionally ameliorated, although never cured. We started an extensive search for malignancy (mammography, gastroscopy, colonoscopy, gynecological and ORL examinations) with a result of only a benign colon polyp. For the bone lesions we made scintiscan and MRI, which also suggested metastatic disease. On her face, scalp and chest there were appeared small granulomas, one was excised and histology confirmed skin granuloma. Tuberculosis, other mycobacteriosis and sarcoidosis was ruled out clinically and serologically. As a final solution we made a lymph node biopsy from the axillary region for the adequate diagnosis. The histological findings showed marked histocytosis, so the rare diagnosis of Rosai Dorfman disease - also known as Sinus Histiocytosis with Massive Lymphadenopathy (SHML) - was established.

Conclusions: Lymphadenitis is often presented in the cervical region, which can frequently join to thyroid disorders, even the localized forms to malignancies. However generalized lymphadenopathy is caused most commonly by infections, malignancy or lymphomas, thus clinicians always has to make broad differential diagnostic steps to find the correct diagnosis. I would like to show these steps in my presentation, as well as the nature of Rosai Dorfman disease, that we treat now effectively by steroids.

P3-05-219
A CASE OF AN ABNORMAL NEWBORN THYROID SCREEN AND BRAIN ARTERIOVENOUS MALFORMATION

Michael Yafi[1]
[1]The University of Texas, Pediatrics, Endocrinology and Diabetes, Houston, USA

Case Report:

Method: We present a case of a newborn with an abnormal newborn thyroid screen which lead to the diagnosis of secondary hypothyroidism and brain arteriovenous malformation.

The Case: A five –week old female referred to pediatric endocrinology for an abnormal newborn thyroid test screen. The infant was asymptomatic and was growing well while breastfed. The infant was born at full term with birthweight of 3.4 kg. Laboratory tests showed normal TSH of 1.4 mIU/L (normal range 1-3- 16 mIU/L), normal T4 of 60.2 nmol/L (58- 161 nmol/L) and low Free T4 of 7.5 pmol/L (11-33 pmol/L). Based on this, secondary (pituitary origin) hypothyroidism was confirmed, a low dose synthetic ACTH stimulation test was performed which ruled out secondary hypoadrenalism and therapy with Levothyroxine was started. An MRI of the brain and pituitary gland was obtained and showed normal anatomy of the pituitary gland with arteriovenous malformation in the left parietal lobe. The patient remained under Levothyroxine therapy with monthly monitoring of the thyroid test until the lesion was successfully resected by surgery at the age of four months. Thereafter, Free T4 levels started increasing and therapy was discontinued. The patient remained euthyroid post -surgery without Levothyroxine therapy.

Discussion: Pituitary hormonal abnormalities should lead to investigation of the anatomy of the gland as well as the central nervous system. Increased intracranial pressure by itself can lead to pituitary hormonal abnormalities.

Conclusion: Pituitary hormonal abnormalities may be a result of anatomical malformations not only in the gland itself but also in the brain. This connection is of a great importance during the newborn period since it may be the first key to diagnose congenital brain malformation.

P3-05-220
RECORD-HOLDER OF SERUM FREE THYROXINE (SE FT4) LEVEL AT OUR DEPARTMENT

Gergő Csitári[1], *Alföldi Sándor*[2], *Simonyi Gábor*[2]
[1]Szent Imre Teaching Hospital, Budapest, Hungary; [2]Szent Imre Teaching Hospital, Metabolic Department, Budapest, Hungary

Introduction: We would like to present the case of our patient with repeatedly higher than 100 pmol/l fT4-levels. In his medicine history there were amiodarone and tyrosine-kinase inhibitor – sunitib – medications.

Case report: Our 63 years old patient was operated and had active radio-chemotherapy because of a malignant meningioma, but had a recurrent disease, therefore his oncologist started sunitinib therapy. He had paroxysmal atrial fibrillation, but rhythm control was achieved with amiodarone. Sunitinib proved to be ineffective, so it was stopped. We admitted the patient to our Metabolic Department in a state of disorientation, confusion, apathetic impression, anorexia and severe desiccation. His thyroid panel showed severe hyperthyroidism, although clinically we saw an apathetic form of his disease. Acute scalp CT scan and MRI ruled out progression in his underlying condition. Ultrasound findings, auto-antibodies and serum thyroglobuline levels verified a destructive thyroiditis. We managed him with methylprednisolon, gradually reduced dose of methimazole, propranolol, infusions, anxiolytics and antipsychotics, meanwhile we skipped amiodarone remedy. He leaved our Department in a significantly improved condition, and since than we regularly control him at our outpatient clinic.

Conclusions: According to our findings his disease could be a type II amiodarone-induced hyperthyroidism, although he was treated by this medication for several years. Maybe sunitinib made an interaction with amiodarone, but tyrosine-kinase inhibitors rather cause autoimmune thyroidites according to recent data. We would like to discuss this case and the role of these drugs on the thyroid gland.

P3-05-221

THE EXTERNAL JUGULAR VEIN THROMBOSIS- A RARE PATHOLOGY IN THE DIFFERENTIAL DIAGNOSE OF THE LATERAL NECK SWELLINGS

Nikolay Raykov[1], *Tonya Dragneva*[2], *Asya Raykova*[3], *Boyan Nonchev*[4], *Snezhinka Vicheva*[5], *Angel Angelov*[6], *Tsvetomir Kachovski*[7], *Milena Avdzhiyska*[8]

[1]Medical Complex „plus";varna,Bulgaria, Medical Complex „plus";varna,Bulgaria, Varna, Bulgaria; [2]Medical Center "Chaika"; Vascular Surgery, Varna, Bulgaria; [3]Mbal Dobrich Ad, First Department of Internal Diseases, Dobrich, Bulgaria; [4]Medical University - Plovdiv, Clinic of Endocrinology, Endocrinology, Plovdiv, Bulgaria; [5]Oncological Dispensary" Marko Markov";department of Clinical Pathology, Varna, Bulgaria; [6]St. Marina Hospital" Varna, Vascular Surgery, Varna, Bulgaria; [7]Medical University- Varna, Varna, Bulgaria; [8]Medical University-Varna, Varna, Bulgaria

Introduction: The external jugular vein/ejv/receives blood from the cranium and the face. It is formed in the parotid gland by the junction of the retromandibular and posterior auricular veins. It runs perpendicularly down the neck, superficial to m. sternocleidomastoideus, draining into the subclavian vein.

The EJV thrombosis is extremely rare. It often follows venous access punction, trauma, infection. It cannot be found in healthy patients, exept in cases with acute dehidratation, caused by physical exercises. The risc factors are overweight, lack of physical activity, older age, smoking, immobilization, hormonal changes, hormonal contraception and substitution. The thrombophilia should be evaluated. The simptoms of the thrombosis are classical: tumor, dolor, rubor, calor. The most common symptom is the neck swelling, which should be differentiated from the possible methastatic lymph nodes/ from squamous cell carcinoma/.

Case report: We had a chance to diagnose two JVT. They were present in women: 46 and 69 y/o. The patients were asymptomatic. No risk factors were known. The masses were on the left, about 3 cm in size, smooth, oval, moderately hard. They were located on the sternocleidomastiodeus muscle. The skin of the node looked slightly cyanotic. The ultrasound images showed an ovoid shape and smooth borders. They looked different: predominantly solid and predominantly cystic, mildly hypoechoic and hypoechoic. They had no vascularity on Doppler check and were elastic on strain elastography. The FNA result was benign. After vascular surgeon consult anticoagulant were prescribed and the masses disappeared.

Conclusion: The thrombosis of external branch of vena jugularis is very rare. A lateral neck lamb, situated on the middle third of sternocleidomastoideus muscle, with smooth surface and moderate stiffness, with mixed ultrasound structure, should be considered to be ejv thrombosis and consulted with vascular surgeon. These masses should not be biopsied.

This thrombosis is treated successfully, but could hide serious health problems.

Surgery

P3-06-222

A PROSPECTIVE, RANDOMIZED, MULTI-CENTER STUDY BETWEEN THUNDERBEAT AND HARMONIC SCARPEL IN OPEN THYROIDECTOMY

Suhwan Kang[1], *Wan Wook Kim*[2], *Jihyoung Cho*[3], *Young San Jeon*[4], *Young Ju Jeong*[5], *Jeungeun Choi*[6], *Moo Hyun Lee*[7]

[1]Departement of Surgery, Yeungnam University, School of Medicine, Daegu, Rep. of South Korea; [2]Depargment of Surgery, Kyungpook National University, School of Medicine; [3]Department of Surgery, Keimyung University, School of Medicine, Rep. of South Korea; [4]Department of Surgery, Goo Hospital; [5]Department of Surgery, Catholic University of Daegu; [6]Department of Surgery, Yeungnam Universiy, School of Medicine; [7]Department of Surgery, Keimyung University, School of Medicine

Background: Thunderbeat® that integrates ultrasonic energy and advanced bipolar energy was recently developed and applied to thyroid surgery. The purpose of this study was to compare the efficacy and safety of Thunderbeat® with Harmonic scalpel® using ultrasonic system in open thyroidectomy.

Materials and Methods: A total of 200 patients were enrolled in this prospective, randomized, multicenter study from April to September 2017. All patients were randomly assigned to the Harmonic group (n = 101) or the Thunderbeat group (n = 99). The parameters including operation time, intraoperative amount of bleeding, hospital stay, complications including recurrent laryngeal nerve (RLN) palsy, hypocalcemia, bleeding, seroma, and postoperative laboratory data including serum calcium, parathyroid hormone (PTH), thyroglobulin were analyzed.

Results: There was no statistical difference in the operation time, 54.2 ± 25.2 min in the Harmonic group and 50.2 ± 21.6 min in the Thunderbeat group. Hospital stay, postoperative complications including RLN palsy, hypocalcemia, calcium supplement, postoperative calcium, PTH and thyroglobulin level were not differed between the two groups. The total amount of bleeding was significantly lower in the Thunderbeat group (13.0 ± 17.7 mg) compared to the Harmonic group (8.6 ± 11.5 mg) ($p = 0.042$).

Conclusions: Our study showed that there was no significant difference between the two groups in postoperative surgical results and morbidity. Notably, total amount of bleeding was significantly lower in the Thunderbeat group. Our results suggest that Thunderbeat® is comparable to Harmonic scalpel® in thyroid surgery in the efficacy and safety.

P3-06-223

VOICE QUALITY AFTER TRANSORAL ENDOSCOPIC THYROIDECTOMY VESTIBULAR APPROACH

Hyun Bum Kim[1], *Dong-Il Sun*[1], *Min-Sik Kim*[1], *Jun-Ook Park*[1]

[1]Department of Otolaryngology-Head and Neck Surgery, Catholic University College of Medicine, Seoul, Rep. of South Korea

Background: Despite the widespread adoption of the transoral endoscopic thyroidectomy vestibular approach (TOETVA), there have been no previous reports on functional voice outcomes after TOETVA. Therefore, this study was designed to assess functional voice outcomes after TOETVA.

Methods: The voice functional outcomes of 34 patients who underwent TOETVA (TOETVA group) and 54 patients after open thyroidectomy (Open group) were analyzed. Thyroidectomy-related voice questionnaire (TVQ), auditory perceptual voice analysis, videolaryngostroboscopy, and objective acoustic voice analysis were carried out before and 1 month after surgery. The changes in these values after the operation, and the differences between the TOETVA and Open groups, were analyzed.

Results: There were no significant changes in perceptual evaluation or TVQ score, nor in a number of parameters of acoustic voice analysis (fundamental frequency, shimmer, noise to harmonic ratio, pitch range), after surgery in either group. The value of speech fundamental frequency (SFF) was significantly decreased after surgery in the Open group (P = 0.001*)

but no significant change was observed after surgery in the TOETVA group (P = 0.074). The value of jitter was significantly increased after surgery in the Open group (P = 0.038*) but no significant change was observed after surgery in the TOETVA group (P = 0.248). After surgery, clinically significant changes in voice pitch (ΔSFF > 12) were evident in 4 (11.76%) and 19 (35.18%) patients in the TOETVA and Open groups, respectively, and the group difference was statistically significant (P = 0.015*) (Figure 1).

Conclusions: The results indicated good subjective and objective postoperative voice outcomes in patients undergoing TOETVA. TOETVA is a promising new surgical option for thyroidectomy that provides excellent functional voice and esthetic outcomes.

P3-06-224

ROBOTIC ASSISTED TRANSAXILLARY THYROIDECTOMY (RATT) THROUGH SINGLE ACCESS: EUROPEAN EXPERIENCE ON MORE THAN 400 CASES

Gabriele Materazzi[1], *Piermarco Papini*[2], *Luigi De Napoli*[2], *Lorenzo Fregoli*[3]

[1]University of Pisa, Department of Surgical, Medical, Molecular Pathology and Critical Area, University Hospital of Pisa, Pisa, San Giuiano Terme, Italy; [2]Department of Surgical, Medical, Molecular Pathology and Critical Area, Unit of Endocrine Surgery, University Hospital of Pisa, Department of Surgery, Pisa, Italy; [3]Department of Surgery, Pisa, Italy

Background: Robotic Assisted Transaxillary Thyroidectomy (RATT) has become widely accepted in Eastern countries, but, in Europe it is performed in few centers and only small series of patients have been reported. We describe our experience on 420 patients undergoing RATT, aiming of evaluate feasibility, safety and effectiveness in a European country.

Methods: A retrospective analysis of the charts of 420 patients undergoing RATT at the Department of Surgery of Pisa was performed. Thyroid volume, nodule diameter, preoperative and postoperative diagnosis, operating time, complications, postoperative stay length, conversion rate and post-operative pain were collected. Postoperative neck ultrasound and postoperative TSH, AbTg and thyroglobulin were evaluated in order to compare completeness at thyroid bed level with group undergoing cervicotomy (CT). RATT was always performed through a single transaxillary access using three robotic arms, Da Vinci Intuitive System was used.

Results: From February 2012 to February 2019, 420 patients underwent RATT. There were 415 females and 5 males. Mean age was 37.6 (16-73). Mean BMI was 21 (18-25) Mean thyroid volume was 25.34±10.73 ml, mean nodule diameter was 27,6 (5-60) mm. 212 patients underwent hemithyroidectomy (HT) and 208 total thyroidectomy (TT). Preoperative diagnosis was: low-risk papillary carcinoma (18%), multinodular goiter (30%), undeterminated nodules (47%) and toxic adenoma (4%). Mean operative time for HT was 73,8 min (range 27-175) and 90,3 min (range 65-180) for TT. There were no significant differences between RATT and CT postoperatively values of TSH (3.44±5.29 and 3.21±3.78 microUI/ml), AbTg (83.66±128.19 and 58.11±84.94 UI/ml) and Tg levels (1.28±1.73 and 1.22±2.56 pg/ml) respectively. The postoperative remnant volume (before radioiodine ablation, when it occurred) was not significantly different between RATT (0.351±0.28 ml) and CT (0.45±0.68 ml). Also same side versus contralateral remnant volume in RATT resulted similar (0.12±0.18 and 0.22±0.24 ml respectively). One procedure was converted to cervicotomy due to finding of advanced carcinoma. There was one definitive nerve palsy in the entire series. Among patients undergoing TT, 3 cases of transient hypoparathyroidism were collected. We experienced 3 post-operative hematoma: two were conservatively treated and one was controlled by endoscopic transaxillary access. One delayed tracheal leakage occurred one month after RATT and was conservatively treated. VAS postoperative mean score was 1.79. Mean post-operative stay for HT was 1.6 days (range 1-2) and for TT was 1.9 days (range 1-4).

Conclusions: In our experience, RATT is safe and feasible and it might represent a valid treatment option in selected cases.

P3-06-225

THE IMPACT OF POST-THYROIDECTOMY PARESIS ON QUALITY OF LIFE IN PATIENTS WITH NODULAR THYROID DISEASE

Jesper Roed Sørensen[1], *Trine Printz*[2], *Jenny Iwarsson*[3], *Ågot Møller Grøntved*[2], *Helle Døssing*[2], *Laszlo Hegedüs*[4], *Steen Joop Bonnema* [5], *Christian Godballe*[6], *Camilla Slot Mehlum*[2]

[1]Department of ORL Head and Neck Surgery, Odense University Hospital, Odense, Denmark; [2]Department of ORL Head & Neck Surgery and Audiology, Odense University Hospital, Denmark; [3]Department of Scandinavian Studies and Linguistics, Copenhagen University, Denmark; [4]Dept. Endocrinol. Odense Uni. Hosp., Odense University, Odense University Hospital, Odense, Denmark; [5]Odense University Hospital, Department of Endocrinology, Odense, Denmark; [6]Dept. of ORL - Head & Neck Surgery A, Odense University Hospital, Odense, Denmark

Objective: To investigate the impact of post-operative paresis on disease specific quality of life (DSQoL) after thyroidectomy in patients with benign nodular thyroid disease.

Study design: Observational study

Setting: University hospital

Subjects and Methods: Patients were evaluated before and three weeks, and six months after surgery in an individual prospective cohort study. Videolaryngostroboscopy (VLS), voice-range-profile, voice-handicap-index (VHI), multidimensional-voice-program (MDVP), maximum-phonation-time (MPT), and auditory-perceptual-evaluation. Changes in DSQoL were assessed by the Thyroid-specific Patient-Reported Outcome (ThyPRO). Cohen's effect size (ES) was used to evaluate changes.

Results: Sixty-two patients were included, 55 of whom completed all examinations. Three weeks after surgery, a blinded VLS examination showed signs of paresis of either the recurrent laryngeal nerve- or the external branch of the superior laryngeal nerve (RLN/EBSLN) in 13 patients (24%). A paresis corresponded to a 12±28 point increase in VHI (p = 0.002) and was associated with a significant 4.3±7.5 semitone (ST) decrease in the maximum fundamental frequency (p<0.001) and a 5.3±8.2 dB reduction in maximum intensity. Further it was associated with a 4.5±11.2 seconds reduction in MPT (p = 0.001), and a 0.40±1.19 increase in grade, 0.42±1.41 in roughness, and 0.36±1.11 in breathiness. Signs of postoperative RLN/EBSLN paresis correlated with an 11.0 point (p = 0.02) poorer improvement in Goiter symptoms, at both three weeks and six months after surgery.

Conclusion: Signs of RLN/EBSLN paresis after thyroidectomy were associated with less pronounced improvement in Goiter Symptoms in patients with thyroid nodular disease. However, thyroidectomy was associated with an overall improved DSQoL by six month after surgery.

P3-06-226

METODS OF PREVENTION AND TREATMENT OF SUPERIOR LARINGEAL NERVE INJURIES IN THYROID SURGERY

Volodymyr Voitenko[1], *Oleksander Tovkay*[1], *Volodymyr Palamarchuk*[1], *Oleh Mazur*[1], *Sergii Tarasenko*[1], *Olena Yefimova*[1]

[1]Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of Moh of Ukraine, Kyiv, Ukraine

Objectives: The prophylaxis of dysphonic syndrome in thyroid surgery patients by the intra-operative identification of external branches of superior laryngeal nerve (EBSLN) and detection of its damage and the development of post-op therapeutic measures.

Materials: The study is based on the test results, treatment and post-surgery examination of 815 patients with benign and malignant thyroid tumors who were operated in the period from 2014 to 2018 inclusive. The retrospective group consisted of 110 patients who were tested on voice acoustic signal during the post-op period in 2012-2014. The result of this study was to determine the characteristic changes in terms of spectral analysis and voice fiberoptic laryngoscopy (FLS) in the following prospective study. The prospective group included 585 patients operated on thyroid, for whom the determination

of the acoustic signal was carried out at pre-and post operative stages. The control group consisted of 120 patients with thyroid surgical pathology and the absence of any laryngeal disease or tracheal intubations in anamnesis, who according to the preoperative survey demonstrated normal levels of spectral analysis of voice.

Results: It has been revealed that FLS of the larynx is a very effective method for diagnosing postoperative motility disorders in the visible elements of the larynx. FLS can help detect the characteristic visual distinction of EBSLN injury. Diagnostic test-effectiveness of the method was 85,91%. The use of voice spectrum analysis in the diagnosis of the laryngeal functional disorders at pre- and post op stages of examination can detect different types of characteristic pathology of the larynx changes and identify the normal levels of human voice in different age and sex groups. Its effectiveness was 98,68%. According to the research of the peculiarities of electrophysiological response of the cricothyroid muscle to electrical stimulation of EBSLN during thyroid operations, we developed a technique of intra-operative electroneurostimulation of EBSLN the use of which has reduced the incidence of EBSLN injury from 24.3% to 2.17%. The use of a combination of drugs - choline alfoscerate with lysine in multiple treatment of dysphonic syndrome improves the indicators of voice spectral analysis. The effectiveness of the method was 89.36%. The effectiveness of treatment with neuro-muscular electro-phonopedic stimulation in patients with post-operative dysphonia is higher than such of traditional conservative therapy.

Conclusions: The effectiveness of the method was 89.1%. There has been developed and implemented the algorithms for diagnosis and treatment of dysphonia syndrome related to intra-operative as well as combined injury of EBSLN and also inferiior laryngeal nerve.

P3-06-227

PREDICTIVE FACTORS FOR DIFFICULT THYROIDECTOMYIN TRANSORAL ROBOTIC THYROIDECTOMY: EVALUATION OF 200 CONSECUTIVE PAPILLARY THYROID CARCINOMA PATIENTS

Dawon Park[1], *Hoon Yub Kim*[1], *Ji Young You*[1], *Hong Kyu Kim*[2]
[1]Korea University School of Medicine; [2]Seoul National University Hospital

Introduction: As a novel method for minimally invasive thyroidectomy, Transoral Robotic Thyroidectomy(TORT) has gained growing popularity. Unlike the previous "minimally invasive" methods, this procedure requires less flap dissection and produce no cutaneous postoperative scars. Nonetheless, application of TORT to wide range of patient group still brings concerns regarding its confined approach access and technical difficulty. The purpose of this study was to evaluate outcomes in patients with papillary thyroid carcinoma (PTC) who underwent TORT and analyze possible predictive factors for difficult thyroidectomy in TORT.

Methods: 200 patients with PTC, who underwent TORT at a single center between March 2016 and February 2018, were retrospectively analyzed.

Results: There were 170 women and 30 men with mean age of 40± 10.4. There were 182 lobectomy and 13 total thyroidectomy cases. The mean operative time for lobectomy was 200.6 ± 31.2 minutes and 265.7 ± 63.0 minutes for total thyroidectomy. 160 patients had the average tumor size less than 1cm while 40 patients had tumor size bigger than 1cm. Mean of 5.6 ± 34.5 lymph nodes were retrieved per patient. There were 12 perioperative morbidity cases, but no conversion to endoscopic or conventional open surgery. In a subgroup analysis, patient sex was the only factor showing significant difference between difficult and non-difficult thyroidectomy groups.

Conclusion: TORT can be performed safely in patients with PTC without serious complications. Patient sex was the only predictive factor for difficulty thyroidectomy in TORT while BMI and operation side did not show any significant influence. Transoral Robotic Thyroidectomy could be considered as an alternative approach for remote access thyroidectomy.

P3-06-228

THE INTRAOPERATIVE IDENTIFICATION OF THE SUPERIOR LARINGEAL NERVE EXTERNAL BRANCH (SLNEB)

Volodymyr Palamarchuk[1], *Oleksander Tovkay*[1], *Volodymyr Voitenko*[1], *Pavlo Lishchynskyi*[1], *Oleh Mazur*[1], *Victor Smolyar*[1], *Sergii Tarasenko*[1]
[1]Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of Moh of Ukraine, Kyiv, Ukraine

Objectives: The modification of intraoperative identification of the superior laryngeal nerve external branch (SLNEB).

Materials: The research was conducted during thyroid surgery with involving the 80 patients with nodular thyroid pathology, who were divided into 2 groups: the first group (n = 40) consisted of patients who underwent intraoperative identification of SLNEB by using an electroneurostimulator. The second group (n = 40) consisted of patients in which the identification was carried out under visual control with phase by phase selection and ligation of vessels of the upper pole of the thyroid gland. Prevoiusly, all patients were obligatorily examined at all stages of treatment by laryngologist by using video laryngoskope and nothing abnormal about larynx was detected. The acoustic voice analysis and voice assessment were performed by using subjective scales of voice quality in the both groups. In the first group, the SLNEB has been identified by using the involves stimulation method of certain tissues in the operating field as the cricothyroid muscle contraction. After identification of SLNEN the upper pole vessels of thyroid part were transected without damaging thyroid body itself.

Results: In the first group, where the identification of SLNEB at the intra-op time was performed by electroneurostimulator, the damage signes of SLNEB were found in 1 (2,5%) patients out of total number. In the second group with visual control the total number of the damage signs of SLNEB was detected in 7 patients (17.5%), significant difference between groups, p = 0,0238.

Conclusions: Application of intraoperative identification methods of SLNEB allows to recognise the tissue structures in operating field while transecting the upper pole of thyroid and significantly decreased the the incidence of surgical post-op complications. The method is simple in its application, does not require special skills.

P3-06-229

ISTHMUS PRESERVATION; A STRATEGY TO PREVENT POSTOPERATIVE HYPOTHYROIDISM IN THYROID LOBECTOMY

Abdulwahid Salih[1]
[1]University of Sulaimani, Sulaimani, Iraq

Objective: To demonstrate the prevalence of postoperative hypothyroidism in cases of isthmus-preserved thyroid lobectomy.

Methods: A prospective, single group cohort study included those patients underwent thyroid lobectomy with isthmus preservation. Patients with preoperative hypothyroidism were excluded. Neck ultrasound was performed in all patients. Intraoperatively, the isthmus was reversed onto the contralateral lobe to prevent future extension into the lobectomized bed. The patients were followed for 3 years.

Results: Out of 250 cases included in the study, 170 patients (68%) were female, 80 (32%) were male, the mean age was 41 years ranging from 1 to 79 years. Thyroid swelling was the sole indication for the lobectomy in 210 (84%) cases. The final diagnoses after histopathological examination of the specimen comprised benign lesion in 222 cases (88.8%), malignancy (papillary thyroid carcinoma and follicular carcinoma) in 17 patients (6.8%) and thyroiditis in 11 patients (4.4%). During the 3-year post-operation follow-up, 248 cases (99.2%) were euthyroid and two cases (0.8%) had hypothyroidism and received thyroxin tablet.

Conclusion: Isthmus preservation might be a preventive factor for postoperative hypothyroidism following thyroid lobectomy. Reversing the isthmus on the contralateral lobe theoretically precludes isthmus extension into the lobectomized thyroid bed.

P3-06-230

BILATERAL AXILLOBREAST APPROACH ENDOSCOPIC THYROIDECTOMY FOR HUGE BENIGN GOITER LARGER THAN 5CM: EFFECTIVENESS AND TECHNICAL ASPECTS

Min Jhi Kim[1], *Jung-Han Kim*[2], *Jee Soo Kim*[3], *Jun-Ho Choe*[3]
[1]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Rep. of South Korea; [2]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Rep. of South Korea; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Department of Surgery, Samsung Medical Center, Rep. of South Korea

Background: Bilateral axillobreast approach (BABA) endoscopic thyroidectomy can be a good option for huge benign thyroid goiter larger than 5 cm. This study aimed to describe the effectiveness and technical aspects for Bilateral axillobreast approach (BABA) endoscopic thyroidectomy in detail.

Methods: Between January 2008 and October 2017, 30 patients with a benign thyroid goiter larger than 5 cm or Graves' disease underwent BABA endoscopic thyroidectomy. Parathyroid hormone was measured at postoperative day 1 in all patients.

Results: The bilateral axillo-breast approach endoscopic thyroidectomy was successful in all patients, was performed by a single surgeon, and none required conversion to open surgery. The operation types were lobectomy (n = 20), subtotal thyroidectomy (n = 2), near total thyroidectomy (n = 3), and total thyroidectomy (n = 5). There was no postoperative vocal cord paralysis or postoperative bleeding. Postoperative transient hypocalcemia occurred in 3 patients (10.0 %), but permanent hypocalcemia occurred in only 1 patient (3.3 %).

Conclusions: BABA endoscopic thyroidectomy can be safely performed in patients with a thyroid goiter larger than 5 cm, and it showed excellent clinical and cosmetic outcomes.

P3-06-231

GASELESS TRANSORAL ENDOSCOPIC THYROIDECTOMY

Jun-Ook Park[1], *Hyun Bum Kim*[1]
[1]Department of Otolaryngology-Head and Neck Surgery, Catholic University College of Medicine, Seoul, Rep. of South Korea

Background: The transoral endoscopic thyroidectomy vestibular approach (TOETVA) has been the subject of increasing interest from several institutions around the world over the last 2 years. The possibility of CO_2 gas-related complications is an obstacle that must be overcome for TOETVA to become a more widely used thyroid treatment. Recently, we successfully performed TOETVA in live human patients without CO_2 gas using our newly designed retractable blade.

Methods: We reviewed the medical records of 15 consecutive patients who underwent gasless TOETVA using a self-retaining retractor.

Results: We successfully performed 13 thyroid lobectomies and 2 total thyroidectomy in 15 patients. No patient exhibited serious postoperative complication such as recurrent laryngeal nerve palsy and permanent hypocalcemia. One patient developed transient hypocalcemia but recovered within 2 months. No patient developed a wound infection; furthermore, no visible scar or dimpling was evident on the neck of any patient, and no patient developed any CO_2-related complication.

Conclusion: The main advantage of gasless TOETVA is the lack of any risk of CO2 gas-related complications. It has several other minor advantages compared to conventional TOETVA. Therefore, the operation could be performed with better visibility in a more stable environment. Gasless TOETVA seems to be a safe and feasible technique for thyroid surgery.

P3-06-232

EFFECTIVENESS OF A PROTOCOL FOR THE CORRECTION OF SEVERE HYPOCALCEMIA IN PATIENTS WHO ARE IN POSTOPERATIVE THYROIDECTOMY AND PARATHYROIDECTOMY AT A REFERENCE HOSPITAL IN MEDELLIN. COLOMBIA

Maria Pizza[1], *Jeronimo Buritica*[1], *Cesar Arias*[1], *Nayade Buitrago*[1], *Nicolas Coronel*[1], *Ana Betancur*[1], *Johan Muñoz*[1], *Natalia Aristizabal*[1]
[1]Universidad Pontificia Bolivariana, Clínica Universitaria Bolivariana, Medellin, Colombia

Background: Thyroidectomy and parathyroidectomy are two of the most common surgeries in the world. Transient postoperative (POP) hypocalcemia is the most frequent complication in the postoperative period. It occurs in up to 68% and 30% of patients. Regarding treatment, recommendations have been described for the management of severe symptomatic hypocalcemia with administration of parenteral calcium. However, adjustment is not standardized, and many protocols exist in clinical practice, in relation to the start of treatment with calcium supplements, dosage and route of administration. The aim of this study is to highlight the experience of a reference center in Medellin, Colombia, since 2015 in the management of patients with severe postoperative hypocalcemia of thyroidectomy and parathyroidectomy that required intervention and management in the intensive care unit, with the implementation of a parenteral calcium replacement protocol.

Methods: Observational, retrospective study conducted in a single center from December 2015 to December 2017, 27 patients with postoperative hypocalcemia who required parenteral calcium management were included: Ca lower than 7.5 mg/dL or 8 mg/dL with symptoms. The following factors were analyzed: pre-operative and post-operative biochemical blood parameters, clinical effects and factors related to surgery, the patient, and the disease.

Results: The mean age of the patients with symptomatic acute hypocalcemia who required calcium infusion was 53 years (SD 16), 78% were women. For us 56% of postoperative hypocalcemia were secondary to total thyroidectomies and 44% to parathyroidectomies. The median duration of calcium infusion was 11 hours, (DS 27) therefore most patients resolved their hypocalcemia in less than 12 hours with the protocol. In 22.2% of patients it was necessary to restart the infusion. The serum total calcium values at 48 hours of POP were around 8.2 mg/dL, finding the lowest values of calcium reported at 12 and 36 hours postoperatively (median 7.8 DS1.2 and 0.9 respectively). The percentage of patients with hypomagnesia (<1.6 mg/dL) was 15%; hungry bone syndrome was present in one of the patients with POP hypocalcemia of parathyroidectomy. The oral substitution was carried out in 81.5% with calcium carbonate, 11% calcium carbonate plus vitamin D and in 7.4% calcium citrate. On average, they required 3.8 grams of elemental calcium each day. (DS10) and 0.76 mcg calcitriol (DS0.4).

Conclusion: the use of a parenteral calcium replacement protocol succeeded in correcting postoperative hypocalcemia in a period of less than 12 hours.

P3-06-233

DO OR NOT DO THE TRACHEA INTUBATION IN PRIMARY HYPERPARATHYROIDISM PATIENTS UNDER SURGICAL TREATMEANT

Vasylina Rudenko[1], *Oleksander Tovkay*[1], *Sergii Tarasenko*[1], *Volodymyr Palamarchuk*[1], *Pavlo Lishchynskyi*[1]
[1]Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of Moh of Ukraine, Kyiv, Ukraine

Objectives: To analyze the anesthesia peculiarities with either the trachea intubation or the laryngeal mask using in primary hyperparathyreosis (PGPT) patients.

Materials: 39 patients were included in the study. In the first group (n = 25), Sevoflurane - Trachea Intubation (S-TI), combined general anesthesia, such as the trachea intubation with the myorelaxates introduction, maintenance as low flow sevoflurane anesthesia and bilateral cervical superficial plexus blockade (BCSPB) was performed for the single parathyroid adenoma ectomy. The second group, Propofol-Laryngeal Mask (P-LM) n = 14,

combined anesthesia BCPSPB and IV propofol was performed by using a laryngeal mask without the myorelaxates introduction.

The age of patients was (M±σ) 55.9±14.8 and 55.6±14.6 years, BMI (M±σ) was 28.5±7.1 and 28.6±7.6 kg/m2 in the S-IT and P-LM respectively (p> 0.05, Wilcoxon criterion).

Results: The operation duration was 38.2±14.4 and 33.62±12.6 min (p = 0.314, NS), the anesthesia duration was 60.8±18.5 min and 48,1±16.5 min (p = 0.024, difference is significant) in S-TI and P-LM respectively. The time from the operation ending till the eyes opening was 15.4±3.6 min in the S-TI group, in the P-LM group was 11.2±2.6 min (p = 0.028, difference is significant). Desaturation (SpO2 below 92%) due to residual sedation and the effect of myorelaxants was observed in 12 (48%) patients in the S-TI group during the first 30 minutes postoperatively, compared to 2 cases (14.3%) in the P-LM group (difference is significant, Pearson's chi square test). The dose of intra-op fentanyl was 256.5±86.9 mcg and 228.6±46.1 mcg in S-TI and P-LM respectively (p = 0.168, NS).

Conclusions: Under ectomy of single parathyroid adenoma the using of propofol and BSCPB with laryngeal mask without myorelaxants seems more preferable compare to sevoflurane anesthesia with BBSCP and tracheal intubation due to the shorter anesthesia duration, time to eye opening after surgery, lower desaturation frequency.

Thyroid Gland

P3-07-234

HIPPO SIGNALING-TGFBETA CROSSTALK CONTROLS TAZ-PAX8 INTERPLAY TO REGULATE NIS EXPRESSION

Celia Fernández Méndez[1], *Pilar Santisteban*[2]
[1]Instituto de Investigaciones Biomédicas (CSIC-UAM), Ciberonc, Instituto de Salud Carlos III, Madrid, Spain; [2]Instituto de Investigaciones Biomédicas, Universidad Autónoma de Madrid, Ciberonc, Instituto de Salud Carlos III, Madrid, Spain

TAZ is a well-known coactivator downstream of the Hippo signaling pathway. Together with its paralogous YAP and the transcription factors of the TEAD family, TAZ plays a key role in the regulation of differentiation, among other cellular processes. Little is known about the involvement of this signaling pathway in the function of the thyroid gland, although TAZ has been described as a coactivator of Pax8 on the thyroglobulin promoter. Pax8 has a predominant role in thyroid differentiation by regulating the transcription of many crucial genes, such as NIS. The aim of this work was to study the role of the Hippo pathway, and particularly its mediator TAZ, in NIS expression, and hence in thyroid differentiation.

By chromatin immunoprecipitation (ChIP) and luciferase reporter assays, we demonstrated that TAZ strongly suppresses Pax8 activation of the NIS promoter by decreasing its binding to the NIS Upstream Enhancer (NUE). In accordance to this, TAZ silencing by RNAi partially impairs TGFβ-induced NIS repression and allows NIS membrane location, improving iodine uptake. By western blot and immunofluorescence, we showed TGFβ-induced TAZ upregulation through the TGFβ effector p38, and inhibition of this kinase leads to an increase of NIS expression. RNAi assays of other Hippo effectors were performed in order to check their participation in this process. Although YAP and TEAD1 could have additive effects, TAZ seems to be the main requirement for NIS downregulation. Despite this, NIS repression was completely rescued by a mutant TAZ defective for TEAD binding. Co-Immunoprecipitation assays with this mutant shown a decrease binding to Pax8 as a side effect.

In conclusion, these data evidence a novel crosstalk between TGFβ, the cofactor TAZ and Hippo signaling in the regulation of NIS expression in thyroid follicular cells.

P3-07-235

DECREASED EXPRESSION OF SODIUM/IODIDE SYMPORTER IN THE SALIVARY GLAND ACCORDING TO AGING AND RADIOIODINE THERAPY

Ji Won Kim[1], *Jeong Mi Kim*[1], *Mi Eun Choi*[1], *Young-Mo Kim*[1], *Jeong-Seok Choi*[1]
[1]Department of Otolaryngology, College of Medicine, Inha University, Incheon, Rep. of South Korea

Background: Radioactive iodine (RI)-induced salivary gland (SG) dysfunction can be caused by physiologic iodide-uptake, mediated by the sodium iodide symporter (NIS). To understand for NIS modulation in the SGs, we investigated the NIS expression according to SG cells types, aging and RI therapy related various conditions.

Methods: NIS expression was evaluated by western blot in the human parotid ductal and acinar cell line. Histopathologic analyses, IHC studies with Aquaporin 5 (AQP5), CD31, alpha smooth muscle actin (α-SMA), Hypoxia-inducible factor 1-alpha (HIF-1α), and NIS were performed in normal and RI treated SG cells in a mouse model. Furthermore, we compared the NIS, HIF-1α expression via IHC between human normal vs. post- RI parotid gland and performed TUNEL assay. We identified the age-related of NIS expression by western blot in human SG tissue.

Results: NIS is highly expressed in the ductal cell line, yet weakly expressed in acinar cells. In an animal model, ductal dilatation and diffuse inflammation were identified in RI treated SG. RI treated mice showed weakly positive in AQP5, CD31, α-SMA, and strongly positive HIF-1α compared with normal SG. The percentage of NIS-positive cells in RI treated mice SG was statistically lesser than in normal SG, suggesting the decrease of NIS by the inflammation and ductal cell destruction during RI treatment. Post-RI therapy human parotid gland showed lower NIS, higher HIF-1α expression and more apoptotic cells than normal parotid. On western blot, NIS expression in older patients was lower than that of younger patients in both parotid and submandibular gland.

Conclusions: NIS expression in SG could be decreased during RI treatment, related to an apoptosis process. As the age increased, the expression of NIS showed the decreasing tendency in human SG. These results suggest that the modulation of NIS expression/activity is needed in the earlier staged or before RI therapy focusing the ductal cells for the prevention of RI induced sialadenitis and we should consider the age-related NIS expression pattern.

P3-07-236

MMP-9 PROMOTOR POLYMORHISMS -1562C>T SNP AND MICROSATELLITE (CA)13-25X TANDEM REPEATS ASSOCIATE WITH INCREASED MMP-9 EXPRESSION IN PAPILLARY THYROID CARCINOMA

Jelena Roncevic[1], *Sonja Selemetjev*[2], *Jelena Jankovic Miljus*[2], *Tijana Isic Dencic*[2], *Ilona Djoric*[2], *Dubravka Cvejic*[2]
[1]Belgrade, Serbia; [2]Institute for the Application of Nuclear Energy - Inep, Belgrade, Serbia

Introduction: Papillary thyroid carcinoma (PTC) comprises 80% of all thyroid carcinomas. Although this type of malignancy is generally associated with good prognosis, some patients develop more aggressive forms of the disease. Therefore, there is an urgent need to identify patients requiring a more aggressive therapy, all the while protecting the majority from overtreatment. A number of studies attempted to identify possible prognostic molecular markers in PTC, but so far not many yielded promising results. A member of the matrix metalloproteinase family, MMP-9, is involved in degradation of the extracellular matrix during physiological and pathological processes and is reported to be overexpressed in a wide range of tumors. Two functional polymorphisms, $C^{-1562}T$ and microsatellite $(CA)_{13-25x}$ in the promoter region of the MMP-9 gene are suspected to cause overexpression of MMP-9, which in turn contributes to development of aggressive phenotype. The aim of this study was to determine whether there is an association between these polymorphisms and PTC aggressive behavior.

Methods and Results: This study included 80 papillary thyroid carcinoma patients. Genotypes for $C^{-1562}T$ polymorphism were determined by polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP). Length of CA region was determined by sequencing by the method of Sanger et al. The expression of MMP9 in PTC was estimated by immunohistochemistry. Association of genotypes with MMP-9 expression and other clinicopathological features was analyzed. The presence of T allele at -1562 position and a high number of CA repeats were accompanied by elevated MMP-9 expression ($p = 0.003$ and $p = 0.013$, respectively). However, only -1562C>T, associated with clinicopathological features of PTC, including higher risk of developing extrathyroid extensions ($p = 0.008$) and high TNM stages ($p = 0.013$).

Conclusions: Our study indicates that $C^{-1562}T$, but not $(CA)_n$ polymorphism is associated with PTC aggressive behavior, and may be utilized as an ancillary genetic prognostic marker.

P3-07-237

85% PREVALENCE OF TSHR AND GNAS MUTATIONS IN 182 HOT THYROID NODULE SAMPLES

Eszlinger Markus[1], *Alexandra Stephenson*[2], *Paul Stewardson*[3], *John McIntyre*[4], *Ralf Paschke*[1]

[1]Department of Biochemistry and Molecular Biology, Medicine, Oncology and Pathology Cumming School of Medicine, University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; [2]Biochemistry and Molecular Biology, University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; [3]Medical Science, University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; [4]Translational Laboratories, Tom Baker Cancer Centre, Calgary, AB, Canada

Objectives: Constitutively activating mutations in the thyroid stimulating hormone receptor (TSHR) and the $G_s\alpha$ subunit (GNAS) are the primary cause of hot thyroid nodules (HTN). The prevalence of TSHR and Gsa mutations in HTN has been reported to vary from 8 to 82% and 8 to 75%, respectively. By using a very sensitive and comprehensive targeted Next Generation Sequencing (tNGS) method, we aimed to further improve the sensitivity and determine the real prevalence of TSHR and Gsα mutations in HTNs as well as assess the improvement in detection associated with more sensitive methods.

Methods: Samples from three previous studies that were found to be mutation negative were selected and re-evaluated using the more sensitive HRM PCR. Remaining mutation negative samples were re-analyzed using tNGS with a depth of coverage between 3000X and 10000X. Our tNGS panel consisted of the entire TSHR and hot spot coding regions in GNAS and EZH1. Library preparation and tNGS sequencing was performed according to the Ion Torrent Ampliseq protocol. Raw data output was analyzed using ThermoFisher Scientific's Ion Reporter program.

Results: Of 182 previously mutation negative samples analyzed using tNGS, 154 were mutation positive (85% prevalence of TSHR and GNAS mutations, 79% and 6% respectively). Improvement of detection of mutations varied across publications with 5%, 16% and 1% of previously WT samples having mutations detected in tNGS.

Conclusions: The higher sensitivity of tNGS has allowed us to better determine the frequency of TSHR and GNAS mutation in HTN. It is unlikely that the remaining 15% of HTNs harbour TSHR or GNAS mutations based on our depth of sequencing and our findings of 6 mutations with mutated allele frequencies of 3-5%. Additional mutations detected varied between sample sets, possible explanations include multiple samples per nodule previously analysed which allowed for increased detection in DGGE and HRM.

P3-07-238

THE PROGNOSTIC SIGNIFICANCE OF MRNA SPLICE-DELETION VARIANT (FAK-DEL33), TOTAL MRNA FAK AND PY397FAK PROTEIN EXPRESSIONS LEVELS IN PAPILLARY THYROID CARCINOMA

Sonja Selemetjev[1], *Valentina Ignjatovic*[1], *Jelena Jankovic Miljus*[1], *Jelena Roncevic*[1], *Ilona Djoric*[1], *Tijana Isic Dencic*[1], *Dubravka Cvejic*[1]

[1]Institute for the Application of Nuclear Energy – Inep, Department for Endocrinology and Radioimmunology, University of Belgrade, Belgrade, Serbia

Objective: Focal adhesion kinase (FAK) has been shown to affect cell adhesion, migration and invasion. Its overexpression has been confirmed in many types of human malignancies, as well as in thyroid tumors. There are, however, speculations about whether splice deletion mRNA FAK transcript variant may influence the level of phosphorylated FAK (pY397FAK, an active form of enzyme). We aimed to investigate possible influence of splice variant FAK-Del33 on the level of active form of FAK enzyme. Furthermore, we correlated expression levels of mRNA splice variant, total mRNA FAK and pY397FAK protein with clinicopathological parameters of papillary thyroid carcinoma patients, in order to test their prognostic capacity.

Methods and results: Thyroid tissue specimens were used for measuring expression levels of mRNA FAK-Del33 and total mRNA FAK by RT-qPCR ($n = 42$), while pY397FAK protein expression was analyzed by Western blotting and densitometry ($n = 55$). The levels of FAK-Del33 mRNA were positively correlated with the total FAK mRNA and the protein levels of pY397FAK ($p<0.05$, Spearman's correlation test). FAK-Del33 mRNA showed correlation with pT (cut off between T2 and T3), degree of tumor infiltration (cut off between C and D) and tumor agressiveness ($p<0.05$ for all, t-test). Total FAK mRNA correlated with the degree of tumor infiltration (cut off between B and C; $p<0.05$, t-test) and showed borderline significance with the degree of tumor infiltration (cut off between C and D). Elevated pY397FAK significantly correlated with pT (cut off between T2 and T3; $p = 0.008$), degree of tumor infiltration (without cut off; $p = 0.002$ and with cut off between B and C; $p = 0.001$, and C and D; $p = 0.004$), lymph node metastasis ($p = 0.013$), extrathyroid invasion ($p = 0.003$) and tumor aggressiveness ($p<0.0001$, t-test for all).

Conclusions: Correlation between mRNA FAK-Del33 and pY397FAK expression implies that this transcript may play a regulatory role for pY397FAK in PTC patients. Furthermore, elevated pY397FAK could predict aggressive tumor behavior in patients with PTC diagnosis.

P3-07-239

THYROGLOBULIN AS A BIOMARKER OF IODINE DEFICIENCY AND EXCESS IN PREGNANCY

Sandra Hunziker[1], *Andersson Maria*[2], *Stinca Sara*[1], *Fingerhut Ralph*[3], *Zimmermann Michael Bruce*[1]

[1]Human Nutrition Laboratory, ETH Zurich, Zurich, Switzerland; [2]Division of Gastroenterology and Nutrition, University Children's Hospital Zurich, Zurich, Switzerland; [3]Swiss Newborn Screening Laboratory and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland

Background: The current range of urinary iodine concentration (UIC) to define iodine sufficiency in pregnant women (PW) is uncertain. Dried blood spot (DBS) thyroglobulin (Tg) is a valid biomarker of iodine status in school age children, but its performance in PW needs further assessment.

Objectives: 1) To assess the association between UIC and Tg in pregnancy and 2) to use this relationship to reevaluate the UIC threshold of >150 µg/L for iodine sufficiency in PW.

Methods: In cross-sectional studies in 18 countries, we collected spot urine and DBS samples of pregnant women to assess the relationship of UIC and Tg. We used the Sandell-Kolthoff method to analyse UIC and a low-cost ELISA to analyse DBS-Tg.

Results: We recruited PW (n = 4779) from both high (e.g., Sweden, Switzerland) and low income countries (e.g., Kenya, Tanzania). Median UIC per country ranged from 32 to 429 µg/L and median Tg from 8.3 to 62.4 µg/L. Classified by median UIC, PW of ten countries were iodine deficient (median UIC <150 µg/L), four countries were sufficient (median UIC 150-249 µg/L) and four countries were more than adequate (median UIC 250-499 µg/L). Eleven countries had elevated Tg values (>3% above 43.5 µg/L). Median Tg did not differ by trimester in countries classified iodine sufficient according to Tg (median Tg <10 µg/L; Kruskal-Wallis, p = 0.133). The data indicate a U-shaped relationship between median UIC and median DBS-Tg, including a second-order polynomial trendline ($R^2 = 0.67$). Data of five additional countries in the UIC range in question will be available by September 2019.

Conclusion: There is a U-shaped association between UIC and Tg in pregnancy. Tg is elevated at low and more-than-adequate iodine intakes, suggesting that Tg may be a valuable functional biomarker of iodine status in PW.

P3-07-240

FOLLISTATIN-LIKE 1 (FSTL1) MARY REDUCE METASTASTIC ACTIVITY OF ANAPLASTIC THYROID CANCER BY INCREASING THYROID TRANSCRIPTION FACTOR 1 (TTF1) AND EPITHELIAL GENE MARKERS

Jisunn Nam[1], *Arim Choi*[2], *Kahui Park*[2], *JungHye Kim*[2], *Shinae Kang*[2], *Jong Suk Park*[2], *Chul Woo Ahn*[3], *Su Jeong Park*[4], *YuSik Kim*[5]

[1]Gangnam Severance Hospital, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Rep. of South Korea; [2]Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Rep. of South Korea; [3]Gangnam Severance Hospital, Seoul, Rep. of South Korea; [4]Yonsei University College of Medicine Brain Korea 21 Plus Project, Seoul, Republic of Korea; [5]Severance Institute for Vascular and Metabolic Research, Yonsei University College of Medicine, Seoul, Republic of Korea

Background: Although anaplastic thyroid cancer (ATC) is found in less than 2% of patients with thyroid cancer, it is the most advanced, aggressive and lethal. ATC is known to develop from well-differentiated thyroid cancers, such as follicular thyroid cancer, and it is undifferentiated itself. Among the thyroid-specific transcription factors that are critical for the function of thyroid, the expression of thyroid transcription factor 1 (TTF1), or NKX2.1, has been reported to correlate with the degree of differentiation, thus, its level is the lowest in ATC among thyroid cancers. TTF1 was reported to reduce invasion and metastasis in lung cancer; however, its regulatory effects on metastasis in ATC in unknown. The metastasis suppression effect of follistatin-like 1 (Fstl1) has been recently reported; however, the results are inconsistent. Herein, we investigated the effects of Fstl1 on metastasis of ATC cell line.

Methods: 8505C cell line was maintained in EMEM containing 2mM glutamine, 1% non-essential amino acids and 10% FBS. Human Fstl1 was treated at 200 ng/m for 24hr, 48hr, and 72 hr. Cell viability was measured by MTT assay. Expression of epithelial gene markers including claudin 1, claudin 4, claudin 7, and occludin and mesenchymal gene markers including vimentin and N-cadherin were confirmed by real-time quantitative PCR (qPCR). In addition, gene expression of TTF1 was also measured by qPCR. Protein expression of each marker was examined by western blot.

Results: Fstl1 did not affect cell viability. Gene expressions of claudin 1, 4 and 7 significantly increased after 24 hours compared to control while that of TTF1 significantly increased after 72 hours. However, there was no significant change in protein expression of each marker. None of mesenchymal markers were changed in response to Fstl1.

Conclusion: We demonstrated that Fstl1 increased epithelial gene markers and TTF1 in 8505C cell line. These suggest that Fstl1 can suppress metastastic activity of anaplastic thyroid cancer.

P3-07-241

UPDATE OF TSHR MUTATION DATABASE: TSH-RECEPTOR-MUTATION-DATABASE.ORG

Ralf Paschke[1], *Markus Eszlinger*[1], *Alexandra Stephenson*[2]

[1]Department of Biochemistry and Molecular Biology, Medicine, Oncology and Pathology Cumming School of Medicine, University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; [2]Biochemistry and Molecular Biology, University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada

Objectives: The clinical conditions and functional characterizations of reported human TSHR mutations are followed using the TSHR Mutation database which was established in 1999, with updates in 2003 and in 2012 and now again in 2019. The database is located at tsh-receptor-mutation-database.org

Methods: Additional entries were made based on google scholar and pub med queries using the key words "TSHR mutation", "thyrotropin receptor mutation", and "non autoimmune hyperthyroidism."

Results: Five years after the last update, the relocated and updated database now contains all clinically occurring TSHR mutations published up to August 2018. 27 novel mutations were added. Additionally, 57 further cases for known mutations were added to allow for comparisons between phenotypes of patients with the same mutation as well as for prevalence calculations for each mutation.

Thus, a total of 84 additions were made to the TSHR mutation database in the most recent update:

- 5 novel mutations and 9 new cases for previously described constitutively activating TSHR germline mutations
- 1 novel mutation and 24 cases for previously described somatic mutations
- 1 novel mutation and 3 cases for previously described somatic gain of function mutations in carcinomas
- 19 novel mutations and 22 cases for previously described cases of inactivating germline mutations

Conclusions: New additions to the webpage include a summary, and an updated prevalence page that reflects the number of cases rather than the number of publications for mutations found in nodules or in carcinoma. Currently there are 23 cases of SNAH, 34 families with FNAH, 16 cases of hot thyroid carcinomas and 146 families with hypothyroidism or TSH insensitivity with TSHR mutations. This database allows for rapid validation of patient TSHR mutations causing hyper or hypothyroidism.

Thyroid Hormone, Metabolism and Inflammation

P3-08-242

MOLECULAR ACTIVATING AND BLOCKING MECHANISMS AT THYROTROPIN RECEPTOR DECIPHERED BY POSITIVE AND NEGATIVE ALLOSTERIC MODULATORS

Patrick Marcinkowski[1], *Annika Kreuchwig*[1], *Sandro Mendieta*[1], *Inna Hoyer*[1], *Franziska Kreuchwig*[2], *Jens Furkert*[1], *Claudia Rutz*[1], *Dieter Lentz*[3], *Ralf Schülein*[1], *Gerd Krause*[1]

[1]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (Fmp), Berlin, Germany; [2]Leibniz-Forschungsinstitut für Molekulare Pharmakologie (Fmp), Max Delbrück Center for Molecular Medicine (Mdc), Berlin, Germany; [3]Institut für Chemie und Biochemie - Anorganische Chemie, Freie Universität Berlin, Germany

The thyrotropin receptor (TSHR) is activated by TSH or by stimulating immunoglobulins in autoimmune disease upon ligand binding at the large receptor ectodomain (ECD). The signal is transduced to the transmembrane domain (TMD) indirectly via an internal agonist (IA), which is located at the ECD-TMD interface. Small molecule positive and negative allosteric modulators (PAM, NAM) are supposed to act in the TMD downstream of TSH or antibodies.

In order to gain a better understanding of the intramolecular signal transduction mechanism from the ECD towards the TMD of TSHR, we employed our recently discovered highly TSHR selective NAM, S37a. We narrowed down the binding region of S37a by using stepwise N-terminal truncations and distinct constitutively active mutations (CAM) and could show that S37a probably binds close to the extracellular loops (ECL) of the TMD.

Moreover, we investigated the antagonistic effect of S37a on TSHR variants with point mutations close to IA and ECL, chosen on the basis of our model of the ECD/TMD. We observed a loss of inhibition by S37a when the two TSHR-specific residues E404 (prior IA) and H478 (in ECL1) were replaced by alanine. These data and docking of the crystal structure of S37a into our refined TSHR model confirmed a new allosteric binding site at the TMD-ECD interface, surrounded by IA, converging helix of the hinge region and ECL1.

The identified binding site of NAM S37a not only unites the particular inhibitory effects of S37a on TSH, PAM and TSHR variants but also explains the strong selectivity for TSHR compared to the gonadotropin receptors. It helped us to gain more detailed insights into the intramolecular course of TSHR activation at the ECD/TMD interface by delocalizing CH and rearranging the conformation of IA and how they, embedded between the ECL, cooperatively trigger active conformations of the TMD.

P3-08-243

THYROID FUNCTION AND PHYSICAL ACTIVITY

Oscar Roa Dueñas[1], *Chantal Koolhaas*[2], *Trudy Voortman*[2], *Oscar Franco*[3], *Arfan Ikram*[2], *Robin Peeters*[2], *Layal Chaker*[2]

[1]Erasmus MC, Rotterdam, Netherlands; [2]Erasmus MC, Netherlands; [3]Universitat Bern, Switzerland

Background: Thyroid hormones are important regulators of the metabolic system and impact muscle and cardiorespiratory function. Thyroid hormone status may therefore have profound effects on physical activity levels. However there are currently no studies evaluating the association between thyroid function and physical activity in the general population.

Methods: In a population-based-cohort-study, we assessed the cross-sectional and longitudinal association of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) with physical activity. Blood samples were taken at baseline to measure TSH and FT4, and information on physical activity was collected with a validated questionnaire (LASA questionnaire). The association of TSH and FT4 with physical activity at baseline and follow-up was examined using linear regression models, adjusted for age, sex, smoking and alcohol consumption. Additional adjustment included prevalent cardiovascular disease, body mass index and diet quality.

Results: We included 2470 participants for the cross-sectional analysis (mean age 57.31 years) and 1907 participants for the longitudinal analysis (mean age 56.88). Cross-sectionally,

TSH and FT4 (Beta [ß], 0.67, 95% confidence interval [CI]; -1.64, 2.98 and ß -0.18 CI; -0.58, 0.94,respectively). Similarly, in the longitudinal analyses we observed no association of TSH (ß 1.11, 95% CI; -1.34, 3.56) or FT4 (ß -0,58 95% CI; -1.38, 0.22) with physical activity.

Conclusion: We did not observe any cross-sectional or longitudinal association between thyroid hormones and physical activity in a population based-cohort.

P3-08-244

SERUM LEVELS OF THE SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (AGES) ARE REDUCED AND AGES INCREASED IN HASHIMOTO'S THYROIDITIS (HT)

Rosaria Ruggeri[1], *Teresa Manuela Vicchio*[2], *Maria Teresa Cristani*[3], *Salvatore Giovinazzo*[4], *Alfredo Campenni*[5], *Salvo Cannavò*[6], *Francesco Trimarchi*[7]

[1]Department of Clinical-Experimental Medicine and Pharmacology, Division of Endocrinology, University of Messina, Unit of Endocrinology, University Hospital of Messina, Messina, Italy; [2]Endocrine Unit at University Hospital of Messina, Aou Policlinico di Messina, Messina, Italy; [3]Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy; [4]Unit of Endocrinology, University Hospital of Messina, Messina, Italy; [5]Dep. of Biomedical and Dental Sciences, and Morfo-Functional Images, Nuclear Medicine Unit, University of Messina, Messina, Italy; [6]Department of Human Pathology, Endocrine Unit, University Hospital, Dep. of Human Pathology of Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy; [7]Accademia Peloritana Dei Pericolanti at University of Messina, Messina, Italy

Objective: AGEs are increased in conditions of oxidative stress and promote inflammation by interacting with their receptor (RAGE) on cell membrane. By contrast, the soluble receptor for AGE (sRAGE), that is proteolytically cleaved from cell surface receptor via matrix metalloproteinases, sequester RAGE ligands and act as a cytoprotective and anti-inflammatory agent. AGEs/sRAGE interaction play a role in the pathogenesis of several diseases related to oxidative stress. Recently, increased levels of AGEs, as specific markers of oxidative stress, have been reported in HT, but no data are available on sRAGE levels in these patients.

Materials and Methods: We enrolled 50 euthyroid HT patients (5 M e 45 F, mean age 38.5±12 yr) and 50 age- and sex-matched healthy controls. None was on LT-4 therapy. Exclusion criteria: autoimmune, inflammatory and infection comorbidities. In sera from each subject, sRAGE levels were measured by ELISA (kit sRAGE Elisa, R&D System, Minneapolis, USA; minimum detectable dose 3 pg/ml); AGEs were determined on spectrophotometric method.

Results: sRAGE levels were significantly lower in HT patients compared to controls (median 424 pg/ml, *range 307-1070 vs* 738 pg/ml, *365-1205*; P = 0.001), while AGEs levels were significantly higher in TH than in controls (median: 205 AU/g prot, range 38-463 *vs* 114 AU/g prot, range 30-325; p = 0.0001) and the two parameters were inversely correlated (r = -0.377; P = 0.016). Also, the sRAGE levels showed significantly inverse correlations with BMI and anti-thyroid antibodies positivity (r = -0.27, P = 0.001). In regression analysis models, adjusted for BMI, serum Ab-TPO were the main predictors for both AGEs (P = 0.014) and sRAGEs (P = 0.027), irrespective of TSH and/or FT4 values.

Conclusion: sRAGE levels were decreased and AGEs increased in HT patients, even when in euthyroid status. Autoimmunity *per se* seems to play a role in AGEs/sRAGE imbalance. Given the protective effects of sRAGE, HT subjects may exhibit increased susceptibility to oxidative damage.

P3-08-245

EFFECTIVENESS OF IODINE DEFICIENCY PREVENTION PROGRAMS IN WESTERN SIBERIA

Ольга Макарова[1], *Lyudmila Suplotova*[1], *Galina Sharuho*[1]
[1]Tyumen State Medical University, Tyumen, Russian Federation

Purpose: to evaluate the criteria for the effectiveness of IDD prevention programs (WHO, UNICEF, ICCIDD, 2001) in the monitoring process.

Materials and methods: In West Siberia, during IDD programs since 1997, biomedical and sanitary-hygienic monitoring was performed in accordance with the criteria of WHO, UNICEF, ICCIDD (2001). In total for the period from 1997 - 2016 18,186 children 8-12 years were examined. The frequency of goiter among children of 8-12 years was evaluated by thyroid ultrasound with a portable device - ultrasound scanner 200 Pie Medical, a sensor with a frequency of 7.5 MHz, the volume of the thyroid gland was evaluated according to WHO criteria (2008). Iodine urinary excretion was evaluated by cerium-arsenic method by calculation of the median ioduria. We analyzed parameters of neonatal thyrotrophic hormone (TSH), determined by screening for congenital hypothyroidism for the period from 1997 to 2015. (N = 370 874). The study of neonatal TSH was performed by two-way fluorometric immuno ferment assay using the reagents "Delphia neonatal TSH", DELFIA (manufactured by WALLAC, Finland). Statistical processing of the material was done using the Statistica software package (StatSoft.Inc., USA, 8.0).

Results of the study: since 1997, a program for iodine deficiency diseases prevention has been implemented in the region, with the focus on increasing the use of iodized salt by households, in the public catering system and in the food industry. As a result of increased consumption of iodized salt with nutrition in the region, urinary excretion of iodine increased. After 3 years of preventive measures the median ioduria (MY) exceeded the threshold epidemiological level of 100 μg/l and significantly increased from 71.4 μg/l in 1995 up to 142 μg/l in 2009 ($p<0,0001$). The incidence of the goiter among prepubertal children significantly decreased from 87% in 1994 to 6.8% in 2016 ($p<0.0001$). The level of neonatal hyperthyrotropinemia > 5 mU/l decreased from 44.7% in 1995 to 5.3% in 2015 ($p <0.001$), which generally characterizes the region as a territory with a slight iodine deficiency.

Thus, the implementation of preventive programs in the region has improved the situation with the consumption of iodine, but the persistent slight iodine deficiency indicates a lack of effectiveness of the voluntary model for the prevention of iodine deficiency.

P3-08-246

HYPOTHYROIDISM INDUCES NEURO-INFLAMMATION IN LINK WITH METABOLIC DYSFUNCTIONS

Lamis Chamas[1], *Isabelle Seugnet*[1], *Valérie Enderlin*[2], *Marie-Stéphanie Clerget-Froidevaux*[1]
[1]Muséum National D'histoire Naturelle, Centre National de la Recherche Scientifique, Umr 7221, Paris, France; [2]Neuroscience Paris-Saclay Institute (Neuro-Psi), Centre National de la Recherche Scientifique, Umr 9197, Orsay, France

Thyroid hormones (THs) are one of the most important regulators of metabolism through their actions in many organs, including brain, adipose tissues and liver. Indeed, hypothyroidism is characterized by low energy expenditure and a decrease in lipid and carbohydrate metabolism, and even a slight thyroid dysfunction can disrupt energy balance. Hypothyroidism also promotes neuro-inflammation and is linked with cognitive impairments. Furthermore, metabolism deregulations are known to favor neuro-inflammation (a major lesion of Alzheimer's disease) by increasing peripheral inflammation. Actually, the literature reports that metabolic disorders are considered as risk factors for neurodegenerative diseases as Alzheimer's disease (AD). In that light, we hypothesized that an altered TH status could trigger the onset of AD by disrupting metabolic homeostasis then, favoring neuro-inflammation. The objective of this study was to test this hypothesis by analyzing the impact of hypothyroidism on metabolism, peripheral and central inflammation and on cognitive functions.

To this aim, we compared wild-derived WSB/EiJ mouse strain, characterized by obesity resistance due to its high metabolic flexibility phenotype, with C57BL/6J mice which are prone to high-fat-diet induced obesity. After induction of hypothyroidism in two-month old mice by propylthiouracil treatment for seven weeks, we assessed the lipid metabolism of eu- or hypothyroid mice of each strain, by quantifying serum lipid levels and expression of key metabolic genes in the liver. Furthermore, we evaluated the peripheral and central inflammation responses by measuring circulating cytokines and microglia/astrocytes activation in the hippocampus (both gene and protein levels). Finally, we will test the cognitive consequences of hypothyroidism by assessing novelty and spatial memory functions. According to their lower sensitivity to metabolic dysregulation, WSB/EiJ mice should be protected from neuro-inflammation induced by the metabolic consequences of hypothyroidism, in contrast to the C57BL/6J mice. Our data will emphasize the importance of maintaining metabolic and thyroid homeostasis to prevent the development of neuro-inflammation development and subsequent cognitive impairment.

P3-08-247

SEAWEED ABUNDANCE AND DIETARY IODINE STATUS

Peter Smyth[1], *Robert Burns*[2], *Michael Casey*[3], *Karen Mullan*[4], *Maria Andersson*[5], *I. Munz*[5], *Colin O'Dowd*[3]
[1]University College Dublin, National University of Ireland (Galway), Dublin, Ireland; [2]University College Dublin, Ireland; [3]National University of Ireland (Galway), Ireland; [4]Royal Victoria Hospital Belfast, N. Ireland; [5]ETH, Zurich, Switzerland

Living close to the sea is usually considered beneficial in terms of iodine intake. As the source of additional iodine is unclear, this communication tests the hypothesis that gaseous iodine (I_2) released from seaweeds may, through respiration, supply a significant fraction of daily iodine requirements in coastal communities. Seaweed abundance rather than proximity to the sea may explain variable iodine levels reported from European coastal areas. Iodine intake was assessed by measuring urinary iodine (UI) excretion using a dry ashing technique with Sandell Kolthoff colorimetry. The median UI of 80 μg/L in adults derived from a national inland population was not significantly different from that of 92 μg/L living in coastal cities. However both were significantly lower that the median of 136 μg/L in populations living in a coastal area with high seaweed abundance ($p<0.02$). Perhaps the greatest difference was the % of higher (>150 μg/L) values (43%) in the seaweed rich area compared to 16% in the low seaweed coastal and 11.6% in the inland samples. Higher UI values predominated in schoolchildren in the coastal area/seaweed hotspot (45.6%) v 3.6% and 2.3% respectively in the low seaweed and inland populations ($p < 0.01$). These findings were reflected in the number of values <50 ug/L which amounted to 8.7% in coastal area/seaweed hotspot but reached 14.5% in the coastal area/ low seaweed and was highly significantly elevated (37.6%) in the inland population ($p <0.01$). Interestingly, greater numbers of higher UI values (> 150ug/L) were also observed in pregnant women in a coastal compared to an inland city (17.9% v 8.6% respectively). The findings suggest that seaweed derived gaseous iodine inspiration can make a significant contribution to iodine intake in seaweed rich coastal areas and indicate the possible importance of this factor in defining population iodine status.

P3-08-248

THE ROLE OF VITAMIN D IN THE TREATMENT OF THE PARATHYROID ADENOMA WITH AUTOIMMUNE THYROID DISEASE

Mari Ghasaboghlyan[1], *Ar Hovhanisyan*[1]
[1]Vardanants Center of Innovative Medicine, Yerevan, Armenia

Background: Autoimmune thyroid disease (AITD) is a chronic disease and the most common organ specific autoimmune disorder usually resulting in dysfunction (hyperfunction, hypofunction or both) of the thyroid gland. Primary hyperthyroidism is a rather frequent disorder characterized by high plasma parathyroid hormone (PTH) and calcium.

Objectives: The purpose of this study is to demonstrate the efficacy of the Vitamin D at primary hyperparathyroidism with AITD.

Methods: 12 patients (age 25-50, 1 male and 32 females) with parathyroid adenoma and AITD where enrolled in the study. All of them were in the AITD euthyroid stage and stage of primary hyperparathyroidism. The patients were treated with vitamin D (6000IU/daily) and calcium (1000mg/daily) for a follow-up period of 6 month. No surgical intervention was performed. The determination of serum levels of PTH, calcium (Ca), vitamin D, antibodies against thyroglobulin (anti TG Ab) and antibodies against thyroid peroxidase (anti TPO Ab), TSH, FT4, as well as neck CT scan and ultrasound were performed twice-at baseline and at the end follow-up period. All patients were informed about the potential aim of the study and expectations from the treatment with vitamin D.

Results: Eventually, follow-up was complete in all patients. The treatment was well tolerant, no serious adverse effects occurred. In 7 patients out of 12 we determined significant ($p<0.05$) reduction of the size of adenoma as well as normalization of laboratory parameters.

Conclusion: From the above mentioned, can be concluded that vitamin D and calcium can be considered as a treatment modality of parathyroid adenoma and primary hyperparathyroidism with AITD.

Eur Thyroid J 2019;8(suppl 1):1–127
DOI: 10.1159/000501012

European Thyroid Journal

Author Index

Numbers refer to abstract numbers

KARGER

E-Mail karger@karger.com
www.karger.com/etj