

**BOOK OF ABSTRACTS**

# ENDOCRINOLOGY UPDATE

Polish-Romanian-Hungarian Scientific Symposium   

Scientific and Organizational Committee  
prof. dr hab. n. med. Beata Kos-Kudła  
prof. dr hab. n. med. Renata Świątkowska-Stodulska

Honorary Committee  
prof. Ioana Zosin  
prof. dr hab. n. med. Marek Bolanowski

10<sup>TH</sup> – 11<sup>TH</sup> OCTOBER 2024

# GDANSK



SympoMed  
KONFERENCJA MEDYCZNA



# CONTENTS

---

Professor Miklós Bodor Hypophysitis: diagnostic and treatment challenges	3
Profesor Marek Bolanowski How can we improve the management of our patients with acromegaly and Cushing's disease?	4
Professor Carmen Georgescu Thyroid (auto)immunity and thyroid cancers	6
Professor Péter Igaz Recent Advances in Primary Aldosteronism	8
Prof. dr hab. n. med. Grzegorz Kamiński The last six years of experience in radioligand therapy of progressive neuroendocrine neoplasms	10
Prof. dr hab. n. med. Grzegorz Kamiński Lutetium-177 (177Lu)-dotatate - Polish experience after 2 years of reimbursement under Drug Program B.139. Polish Patient Registry	12
Prof. dr hab. n. med. Beata Kos-Kudła New insights in neuroendocrine tumors therapy	14
Professor Emese Mezósi Association of other autoimmune conditions to endocrine autoimmune disorders	16
Professor Ionela Pascanu Osteosarcopenia - approaching the musculoskeletal frailty	18
Professor Cristina Preda Coexistence of papillary thyroid carcinoma with hyperparathyroidism. Experience of a tertiary endocrinology center	20
Professor Anhelii Syrenicz Thyroid medullary carcinoma – etiopathogenesis, clinical picture, diagnosis, treatment and prognosis	22
Profesor Renata Świątkowska-Stodulska Management of adrenal incidentaloma – update	24
Professor Miklós Tóth Aggressive pituitary tumours and carcinomas	26
Professor Zsuzsanna Valkusz Hypogonadism and male health	28
Professor Mihaela Vlad X-linked hypophosphatemia - a rare cause of short stature	30
Professor Ioana Zosin Thyroid cancer and toxic adenoma	32

# Hypophysitis: diagnostic and treatment challenges

Professor Miklós Bodor



Miklós Bodor  
Department of Medicine, Division of Endocrinology  
University of Debrecen, Hungary

## Hypophysitis: diagnostic and treatment challenges

### Hypophysitis

- Hypophysitis is a heterogeneous disease that leads to the inflammation of the pituitary gland and/or suprasellar region and may present with hormonal insufficiencies and/or symptoms related to consequences of mass effects and can be primary or secondary to a local or systemic process
- A significant number of hypophysitises have an underlying autoimmune etiology but other etiologies may be present, like inflammation secondary to sellar tumors, systemic diseases, infections or drug-induced cases

### Hypophysitis

- The incidence and prevalence of hypophysitis has dramatically increased during the last decade, mainly due to increased awareness of the illness among physicians, modern imaging techniques, and a rise of certain forms like IgG4 hypophysitis (IgG4Hy), immune checkpoint inhibitor induced hypophysitis (ICIHy) or paraneoplastic pituitary-directed autoimmunity among the growing spectrum of this rare pituitary condition
- The differential diagnosis of the disease is often challenging and only a pituitary biopsy can confirm the subtype of the hypophysitis and rule out other causes, however, a presumptive diagnosis can be made in most cases without biopsy
- A detailed patient history and clinical examination are crucial and often signs of underlying etiology with systemic manifestations help in establishing the diagnosis

### Hypophysitis

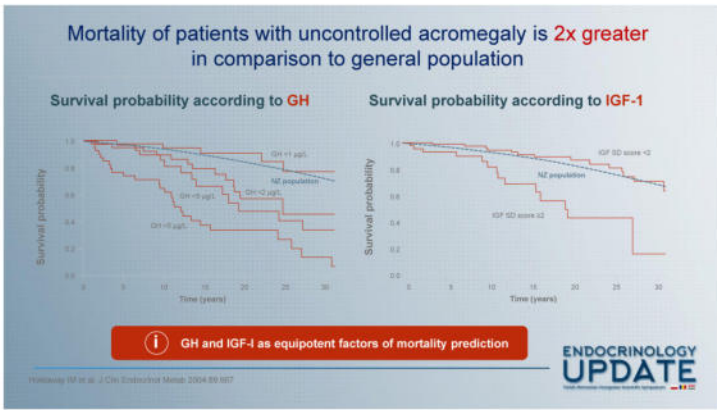
- The symptoms of hypophysitis usually include headaches, certain degree of anterior and/or posterior pituitary dysfunction associated with enlargement of the pituitary gland and/or stalk
- Imaging is not always specific; however, magnetic resonance picture usually reveals homogenous enlargement of the gland
- Careful patient observation is important in the management with imaging follow-up.
- Hormone replacement therapy and, in some carefully selected cases, high-dose glucocorticoids are indicated to reduce mass effect

### Hypophysitis

- Surgery may be necessary in few hypophysitises to relieve mass effect; in these cases a definite diagnosis can be obtained
- In resistant cases immunosuppressive therapy and radiation are sometimes also necessary in the management of the disease
- The recognition and adequate treatment are essential in hypophysitis, a disease that might develop accompanied with a wide spectrum of symptoms spreading from an unrecognizably mild presentation to severe and potentially fatal consequences

# How can we improve the management of our patients with acromegaly and Cushing's disease?

Profesor Marek Bolanowski



**Treatment goals in acromegaly**

**Restoration of expected survival**

- Hormonal normalization
- Pituitary adenoma growth reduction
- Optimal control of complications and accompanying disorders
- Quality of life improvement
- Improvement of psychosocial functions

**Introduction of modern therapies caused more efficacious disease control and elongation of the patients' survival**

**Evolution of acromegaly diagnostics and remission criteria**

Changes in recent guidelines (2023)

Year	Diagnosis	Therapeutic efficacy target
2000	1st Acromegaly consensus [3] IGF-1 elevated for age and sex Confirm with random GH ≥ 0.4 µg/L or IGF-1 elevated for age and sex Confirm with GH > 1 µg/L during OGTT	IGF-1 normalized for age and sex GH < 1 µg/L during OGTT
2010	7th Acromegaly consensus [4] Random GH elevated Confirm with GH > 1 µg/L during OGTT	Random GH < 1 µg/L GH < 0.4 µg/L during OGTT
2014	Endocrine society guidelines [5] IGF-1 elevated for age Confirm with GH > 1 µg/L during OGTT	IGF-1 normalized for age Random GH < 1 µg/L
2023	14th Acromegaly consensus (this publication) IGF-1 > 1.3 x ULN for age and sex Characteristic clinical signs of disease For equivocal results, IGF-1 measurements can be repeated, and OGTT might additionally be useful	IGF-1 normalized for age and sex

**Individual choice of somatostatin analogue**

**T2-weighted MRI signal**

- hyperintensity
  - pasireotide test?
  - treatment with II generation SSA (pasireotide)
- hypointensity
  - octreotide test?
  - treatment with I generation SSA (octreotide/lanreotide)

**T2-weighted MRI signal predicts hormone and tumor response to somatostatin analogs in acromegaly**

# How can we improve the management of our patients with acromegaly and Cushing's disease?

Profesor Marek Bolanowski

### Individual choice of somatostatin analogue

**Morphological and genetical assessment**

- granulation - sparse
- E-cadherine - low
- receptors - 5 > 2
- Ki-67 - high
- AIP - low

**Pasireotide in the Personalized Treatment of Acromegaly**

**ENDOCRINOLOGY UPDATE**

### Medical therapy of acromegaly in Poland

**1<sup>st</sup> choice medical therapy**  
long acting I generation SSA

**2<sup>nd</sup> choice medical therapy**  
long acting II generation SSA (PAS) and GH receptor antagonist (PEG)

**Early decision on pasireotide or pegvisomant therapy enhances opportunity for good disease control, complications avoiding, quality of life improvement and survival elongation**

**ENDOCRINOLOGY UPDATE**

### Metabolic disturbances and complications in Cushing's

- Prediabetes, diabetes
- Hypertension, cardiomyopathy, heart failure
- Hypercoagulability
- Dyselectrolitaemia
- Loss of immunity
- Fractures
- Psychosis
- Low QoL

**Increased mortality**  
Cardio-vascular disease  
Suicides  
Infections

**ENDOCRINOLOGY UPDATE**

### Cushing's disease - most common form of endogenous Cushing's syndrome

**Corticotropinoma**

- usually microadenoma
- difficult to visualize
- sinus petrosus inferior sampling necessary
- surgery efficacy ≈ 60%
- risk of recurrence

**Need for effective medical treatment**  
Radiotherapy  
Bilateral adrenalectomy?

**Increased mortality persists after treatment of Cushing's disease**

**ENDOCRINOLOGY UPDATE**

### Medical treatment of Cushing's disease

**Medical Treatment of Cushing's Disease: An Overview of the Current and Recent Clinical Trials**

**ENDOCRINOLOGY UPDATE**

### Medical treatment of Cushing's disease

**Disease control**

- A - cabergoline - 35%
- B - ketoconazole - 41%
- C - metyrapone - 66%
- D - pasireotide - 44%
- osilodrostat - 72%**

Long-term efficacy and safety of osilodrostat in patients with Cushing's disease: results from the LINC 4 study extension

**ENDOCRINOLOGY UPDATE**

# Thyroid (auto)immunity and thyroid cancers

Professor Carmen Georgescu

**ENDOCRINOLOGY UPDATE**  
Polish-Romanian-Hungarian Scientific Symposium  
Scientific and Organizational Committee: prof. dr hab. n. med. Senta Kovacs, prof. dr hab. n. med. Daniela Savașcoiu-Stoiciu  
Honorary Committee: prof. dr hab. n. med. Maria Balazs, prof. dr hab. n. med. Maria Balazs  
10<sup>th</sup>-11<sup>th</sup> October 2024 GDAŃSK  
**THYROID (AUTO)IMMUNITY AND THYROID CANCERS**  
CARMEN GEORGESCU M.D., Ph.D., Dr. habil ENDOCRINOLOGY DEPARTMENT, IULIU HATIEGANU UNIVERSITY OF MEDICINE AND PHARMACY CLUJ-NAPOCA, ROMANIA

### Thyroid Cancers (TCs) are Not Always Indolent

5-10% of TCs exhibit an "aggressive" behaviour

- histological aggressiveness
  - eg. diffuse sclerosing, tall cell, insular variants of papillary TC (PTC)
- poorly differentiated TC (PDTC)
- anaplastic TC (ATC)

radioiodine-refractory disease

- advanced, metastatic DTC – 30% have radioiodine-refractory disease
  - dedifferentiation (ie loss of NIS expression) of even PTC has been demonstrated in single-cell transcriptomics experiments
- oncocytic carcinoma of the thyroid

4% of TCs are medullary, with about 50% residual or recurrent disease

Peirasa M, Georgescu CE, Nemes-Majer R et al. Cancer Treat Rev 2016; 707-73, Lu L, Gao R et al. J Clin Invest. 2023; 133: 11 e15965

### WHO 2022 Classification of Thyroid Tumors

**Low-risk Neoplasms**

- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
- Follicular thyroid tumor of uncertain malignant potential (FTUMP)
- Well-differentiated thyroid tumor of uncertain malignant potential (WD-UMP)
- Hydrating medullary thyroid tumor (HMT)

**Malignant Thyroid Neoplasms**

- Follicular thyroid carcinoma (FTC)**
  - mi, esi, wt
- Invasive encapsulated follicular variant papillary thyroid carcinoma (EIPV-PTC)**
  - mi, esi, wt
- Papillary thyroid carcinoma (PTC)**
  - Subtypes:
    - Infiltrative follicular
    - Solid follicular
    - Tall cell
    - Columnar cell
    - Hidradial
    - Oncocytic
  - Diffuse sclerosing
  - Warthin-like
- Oncocytic carcinoma of the thyroid (OCT)**
  - mi, esi, wt
- Differentiated high-grade thyroid carcinoma (DHGTC)**
  - Papillary, follicular or solid growth
    - invasive features
    - Any nuclear cytology
    - At least one of:
      - Mitotic count  $\geq 2$  mm<sup>2</sup>
      - Necrosis
  - Solid, trabecular or insular growth
    - invasive features
    - At least one of:
      - Mitotic count  $\geq 2$  mm<sup>2</sup>
      - Necrosis
      - Convulsed nuclei
- Anaplastic thyroid carcinoma (ATC)**
  - Anaplastic features
  - Undifferentiated phenotype

WHO, 2022

- Delineation of FT-UMP and NIFTP
- Characterization of the histological PTC subtype
- "Hürthle cell carcinoma" not to be used
- Characterization of differentiated high-grade thyroid carcinoma (DHGTC)

Johns CC, Miah C, Zubair S. Endocrinol-Pat Cancer 2022; 30: 2 e120263

### Overall and "Clinically Relevant" Thyroid Cancer (TC) Incidence Rate

Sex- and Age-adjusted Incidence Rates 1935-2018 Mayo Clinic

after: Genere N, Sitar JP et al. Mayo Clin Proc 2021; 2823-30

### Autoimmune Thyroiditis (AIT) and PTC: A Shift of The Paradigm

- Co-occurrence of autoimmune thyroiditis and PTC is prevalent (8-36.4%)
- In children, AIT is associated with increased risk of PTC [OR 2.19, 95%CI 1.32-3.62] and the risk is doubled for diffuse sclerosing (DS)PTC [OR4.74, 95%CI 1.33-16.9]
- No evidence that PTC and AIT coexistence is associated with increased invasiveness or mortality, not even for DSPTC
- No shorter recurrence-free survival of PTC in patient with AIT than without AIT
- Less structural recurrence with total thyroidectomy than lobectomy in Hashimoto Thyroiditis

Wang J, Wang Y, Sun L, et al. Endocrinol 2020; 264: 71, Healy O, Gleason AJ et al. Thyroid. 2022; 15(9-17), Xu S, Liu J et al. JAMA Network Open. 2021; 4(6): e2118026

### The Inflammatory Tumour Microenvironment in Non-Medullary TC

IL-1 $\beta$  production increases after LPS stimulation in non-medullary TC cell lines

Expression of CXCL8, CCL20 chemokines is higher in PTC samples independent of thyroiditis

NF- $\kappa$ B staining is intense in neoplastic thyroid cells but not in peritumoral thyrocytes and related to TIL infiltrate and lymph node invasion

Wang J, Wang Y, Sun L, et al. Endocrinol 2020; 264: 71, Skusa M, Figaszewska L, et al. Clin Endocrinol. 2010; 73: 6, Paskovalic D, Flamigni G et al. J Clin Invest. 2023; 6817

# Thyroid (auto)immunity and thyroid cancers

Professor Carmen Georgescu

### The Immunosuppressive Tumor-associated Microenvironment

**RET/PTC, RAS, BRAF, NTRK**  
miRNAs  
chronic extrinsic inflammation  
radiation

MAPK, P3K/Akt/mTOR  
NF- $\kappa$ B, JAK-STAT, WNT

**CDS+T cells**  
immunosuppressive TME  
protective in PTC  
BRAFV600E, ICID8+FoxP3, TPD-3

**NK**  
cytotoxic

**TAN**  
proinflammatory neutrophil  
status induced by TC  
NLRB and neutrophil density  
relate to TC size

**DC**  
immature phenotype  
IL-10, TGF- $\beta$

**Treg**  
tumor aggressiveness

**B lymphocyte**  
anti-tumor response

**M2DC**  
immunosuppressive  
monocyte phenotype in  
blood and the bone marrow

**TAM**  
inflammation, angiogenesis,  
progression, low survival rate  
CXCL8, CSF-1, IL-1 $\alpha$ , NF- $\kappa$ B, VEGF,  
IDO1, ARG1

**TAMC**  
tumor growth  
and invasiveness  
CXCL8, VEGF-A

T cells, B cells, Treg, NK = tumor infiltrating lymphocytes (TIL)

M2DC = myeloid-derived suppressor cells  
TAM = Tumor-associated macrophages (M2)  
TAMC = Tumor-associated mast cells  
DC = Dendritic cells  
TAN = Tumor-associated neutrophils

cytokines & growth factors: ILs, TNF, IFN- $\gamma$ , TGF- $\beta$   
chemokines: CXCL8, IL-1 $\alpha$ , IL-1 $\beta$   
enzymes: ARG1, IDO1  
angiogenic factors: VEGF, adipothens

**ENDOCRINOLOGY UPDATE**

Stegh H, Liberman V, Georgescu CB, Stegh A et al. Int J Mol Sci. 2022; 23: 3470.

### DTC vs ATC: not the same Tumour Microenvironment

**DTC**

- differentiated thyroid cancer cell population
- abundant TIL infiltrate
- low TAM and MDSC infiltrate
- PD-L1: 6.1-82.5%, low membranous
- low tumour mutation burden (TMB)

**ATC**

- undifferentiated thyroid cancer cell population
- scarce TIL infiltrate
- important TAM infiltrate
- PD-L1: 22-81%, high membranous
- high TMB

**ENDOCRINOLOGY UPDATE**

Adapted from Garcia-Perez A, Caporaso J et al. Front Endocrinol. 2022; 1-12.

### Second-line Management Strategies of Radio-refractory Advanced/Metastatic TC

**Single targeted TKIs** (vemurafenib, dabrafenib, everolimus)

**Salvage therapy after first-line TKIs failure** (cabozantinib, sunitinib)

**Combinatorial therapy with MAPK, PI3K/Akt, NF- $\kappa$ B, MKIs**

**Targeting alternative pathways** (HER, JAK/STAT, eIF4F, RBM)

**Targeting gene fusions** (RET/PTC, PAX8/PPAR $\gamma$ , EML4/ALK)

**Immunotherapy** (CTLA-4, PD-1, B7/HLA inhibitors, Anti-CD19)

**Redifferentiation Therapy** (retinoic acid, HDAC inhibitors, PPAR $\gamma$  agonists, TKIs)

**Overcoming tumor escape from MAPK, PI3K/Akt inhibitors** (HER2/HDAC/EGFR inhibitors)

**ENDOCRINOLOGY UPDATE**

Stegh H, Liberman V, Georgescu CB, Stegh A et al. Int J Mol Sci. 2022; 23: 3470.

### Immunotherapeutic Approach of Thyroid Cancers

**Immune Checkpoint Inhibitors (ICI)**

- PD-1 antagonist pembrolizumab, camrelizumab
- CTLA-4 antagonist nivolumab, ipilimumab, tremelimumab
- PD-L1 inhibitors spartalizumab, durvalumab, atezolizumab
- CD27, -47, 70 inhibitors

mono+ICI, TKI, chemo, radiotherapy

**Tumour-specific immunotherapies**

- NK cells-based immunotherapy – effective in ATC lung metastases in animal models
- CAR-T – modified T cells that express synthetic receptors and Ag that target predefined tumour expression
- vaccines

**Oncolytic viruses**

- d922-947, poxvirus, Newcastle virus
- results in ATC animal models

**Inhibition of TAMs recruitment**

- CSF-1/CSF-1R blocker
- CCL2/CCR blocker

**ENDOCRINOLOGY UPDATE**

Gao X, Zeng X. Front Oncol. 2023; 13.

# Recent Advances in Primary Aldosteronism

Professor Péter Igaz

**ENDOCRINOLOGY UPDATE**  
Polish-Romanian-Hungarian Scientific Symposium  
Scientific and Organizational Committee: prof. dr hab. n. med. Beata Fijałkiewicz, prof. dr hab. n. med. Danuta Świątkiewicz-Stasińska  
Honorary Committee: prof. dr hab. n. med. Andrzej Gąsior, prof. dr hab. n. med. Marek Rutkowski  
10<sup>th</sup>-11<sup>th</sup> October 2024 GDAŃSK  
**RECENT ADVANCES IN PRIMARY ALDOSTERONISM**  
Prof. Peter Igaz  
(Dept. Endocrinology, Semmelweis Univ., Budapest, Hungary)

### Physiological relevance of aldosterone

- The relevance of aldosterone in the evolution began with the appearance of life on drylands
- In contrast to the sea, continental herbivores consumed much more potassium than sodium.
- 1 kg grass forage contains 20-40 mg sodium and 4000-15000 mg potassium.
- Aldosterone increases the excretion of potassium and hydrogen ions in the kidney whereas increases sodium resorption.
- In developed industrial societies, the daily sodium ingestion is over 3500-4000 mg and the intake of potassium is <2500 mg!

### Primary aldosteronism

Autonomous overproduction of aldosterone, suppressed renin resulting in hypertension (hypokalemia) and metabolic alkalosis.

**5-10 % of all hypertension cases – most common cause of secondary hypertension!!**

Diagnosing primary aldosteronism is important, as its treatment is fully different from essential hypertension, and it can not only be treated, but can be healed!

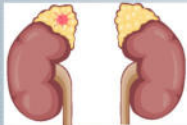
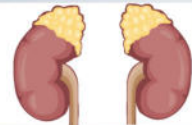
### Indications for screening primary aldosteronism

- Resistant hypertension
- Hypertension with spontaneous or diuretics-induced hypokalemia
- Hypertension with adrenal incidentaloma
- Hypertension and sleep apnea
- Hypertension in the young (<40 years)
- Cerebrovascular event (stroke in the young)
- Family history of primary aldosteronism
- Type 2 diabetes mellitus diagnosed in hypertensive patients (prevalence of 19 %!) (Yuhang Hu et al., Endocr Metab, 2020)
- Hypertension and atrial fibrillation

### Background

**Primary Aldosteronism (PA):**

- 5-10 % of secondary hypertension
- Uni- or bilateral
- Gold standard differentiaton: AVS

UPA (Unilateral PA)	BAH (Bilateral adrenal hyperplasia)
	
<ul style="list-style-type: none"><li>• Multiple pathologies</li><li>• Surgical treatment</li></ul>	<ul style="list-style-type: none"><li>• Less understood</li><li>• Pharmacological treatment</li></ul>

### Pathological classification of unilateral adenoma (HISTALDO)

- Aldosterone producing adenoma (APA)
- Aldosterone producing nodule (APN)
- Aldosterone producing micronodule (APM)
- Multiple aldosterone producing nodules (MAPNs)
- Aldosterone producing diffuse hyperplasia



# Recent Advances in Primary Aldosteronism

Professor Péter Igaz

## Problems of diagnosis

- Aldosterone-renin ratio influenced by many different drugs
- Different hormone reference ranges among centers
- Sodium restriction can increase renin itself and can mask milder cases of primary aldosteronism (Baudrand et al., JCEM, 2016)
- Need for confirmatory testing except for florid cases with hypokalemia (saline infusion test, oral sodium loading test, captopril test, fludrocortisone test) – all having limitations

ENDOCRINOLOGY  
UPDATE

## Problems of differentiating uni- and bilateral disease

ENDOCRINOLOGY  
UPDATE

## Problems with Adrenal Venous Sampling

- Limited availability, invasive technique
- Expertise needed – cannulating the right adrenal vein is difficult
- Protocol is not uniform – with or without ACTH-stimulation
- Interpretation can be difficult (various indices)
- Co-secretion of cortisol from adrenal adenomas can be confounding – need for low dose dexamethasone test in case of adenoma suspicion
- Asymmetrical bilateral hyperplasia cannot be differentiated from unilateral disease

ENDOCRINOLOGY  
UPDATE

## Nuclear medicine

- Norcholesterol
- <sup>11</sup>C metomidate PET-CT
  - MATCH Study, Wu et al., Nat Medicine, 2023) – accuracy of MTO vs. AVS in predicting biochemical success: 72.7 % vs. 65.4, clinical success: 65.4 vs. 61.4) – MTO might be superior over AVS
- 18F-CETO
- CXCR4 – sensitivity ranging (88.9-100 %), specificity (78.6-87.2 %)

ENDOCRINOLOGY  
UPDATE

## Alternative methods

- Steroid fingerprinting
- Machine learning-based approaches of clinical data
- Other molecular markers – e.g. circulating microRNAs

ENDOCRINOLOGY  
UPDATE

## Treatment of primary aldosteronism

- Unilateral (lateralizing PA)
  - Surgical – unilateral adrenalectomy – Success to be judged by the PASO criteria
  - Novel approaches – e.g. thermal ablation
- Bilateral – non-lateralizing PA
  - Drug treatment
    - Mineralocorticoid antagonists (spironolactone, eplerenone)
    - Dietary sodium restriction
    - Potassium sparing diuretics
    - CYP11B2 inhibitor - investigated
  - Treatment optimization
    - Blood pressure control
    - Potassium control - preferably without supplementation
    - Increase in renin

ENDOCRINOLOGY  
UPDATE

# The last six years of experience in radioligand therapy of progressive neuroendocrine neoplasms

Prof. dr hab. n. med. Grzegorz Kamiński



## The last six years of experience in RLT patients with progressive neuroendocrine neoplasms

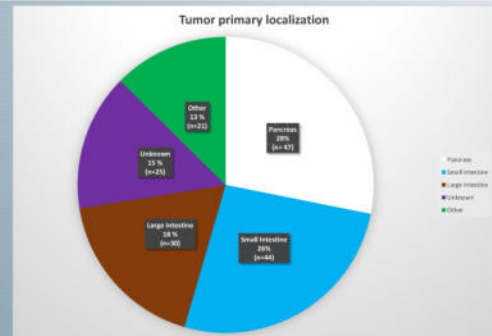
Three analysis concerning subgroups

1. 167 pts with GEP - NENs (66 months observation),
2. 51 patients with NENs of unknown origin, non-GEP-NENs and G3 NENs (36 months observation)
3. 13 pts as a RE-TREATMENT (retrospective - 8 years observation)

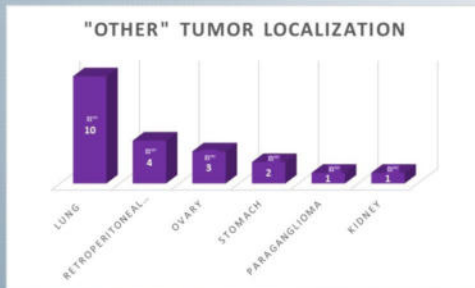


### A prospective analysis covered 66 months of observation (01.12.2017 - 30.05.2023)

- 167 patients were treated with RLT in one of Poland' highest-reference center
- 479 RLT single administrations (courses) were given.
- Standard procedure was to give four courses of [<sup>177</sup>Lu]Lu-DOTA-TATE alone or tandem therapy - [<sup>177</sup>Lu]Lu-DOTA-TATE + [<sup>90</sup>Y]Y-DOTA-TATE.
- The study was conducted by the Declaration of Helsinki and approved by the local Ethics Committee, Protocol Code 154/17; date of approval: 15 December 2017.



### "OTHER" TUMOR LOCALIZATION



### Results

Directly after the last course of RLT:

- disease stabilization was noted in 70% of patients,
- partial regression in 20% of patients,
- complete regression in 0.60%, and progression in 9.4% of patients

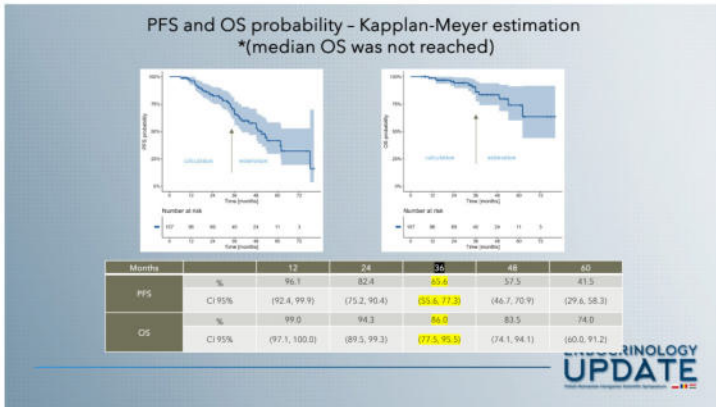
In long-term follow-up (median 36 months):

- stabilization of the disease was in 56% of patients,
- progression in 27%,
- while 18% of patients died.



# The last six years of experience in radioligand therapy of progressive neuroendocrine neoplasms

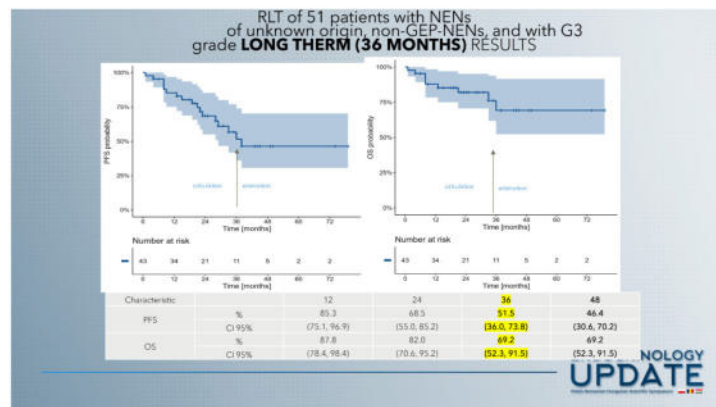
Prof. dr hab. n. med. Grzegorz Kamiński



**51 patients with NENs of unknown origin, non-GEP-NENs, and with G3 grade**

- In subgroups of patients with unknown tumor localization, the median PFS before RLT was 19 months,
- with "other localization" PFS before RLT was 31 months,
- and with NEN G3 before RLT 18 months.
- 35 pts received <sup>177</sup>Lu and 16 pts received <sup>177</sup>Lu + <sup>90</sup>Y

ENDOCRINOLOGY UPDATE



**13 pts RE-TREATMENT**  
a retrospective analysis covering years 2015-2023

- 13 pts received RLT re-treatment (5-8 courses)
- The median PFS after first cycle of RLT was 36.5 months
- Directly after second cycle of RLT disease stabilization was observed in 11/13 (85%) and progression in 2/13 (15%)
- After second cycle of RLT median observation time for the study group was 6.5 months.
- Stabilization was confirmed in 62.5 % (5/8), progression in 12.5% (1/8) and death in 25% (2/8) patients (\*status of 5 patients was unknown)

ENDOCRINOLOGY UPDATE

**13 pts RE-TREATMENT**  
a retrospective analysis covering years 2015-2023

In summary during this observation we noticed:

- statistically significant decrease of number of all lines of blood cells
- statistically, but not clinically significant increase of transaminases
- not statistically significant increase of creatinine concentration with decrease of GFR
- not statistically significant decrease of albumin concentration, and fasting glucose concentration
- not statistically significant correlation of increase of CgA concentration with progression of the disease.

ENDOCRINOLOGY UPDATE

**Conclusions**

- RLT is an effective and safe method of treating patients with progressive neuroendocrine tumors, leading to stabilization or partial regression in over 90% of patients in early assessment and over 56% of patients in three years observation;
- Repeated RLT is an effective and safe therapeutic option, especially for patients who have shown a good response to the first cycle of treatment;
- RLT in patients with neuroendocrine tumors of unknown origin, other than arising from the midgut and G3 (beyond current registration indications for Lutathera) is effective and safe, both in early and three years assessment;
- Further research is needed to evaluate the impact of the type of radioisotope and its activity on the effectiveness and safety of treating patients with neuroendocrine tumors.

ENDOCRINOLOGY UPDATE

# Lutetium-177 (<sup>177</sup>Lu)-dotatate - Polish experience after 2 years of reimbursement under Drug Program B.139. Polish Patient Registry

Prof. dr hab. n. med. Grzegorz Kamiński



Lutetium-177 (<sup>177</sup>Lu)-dotatate - Polish experience after 2 years of reimbursement under Drug Program B.139. Polish Patient Registry

prof. Grzegorz Kamiński,

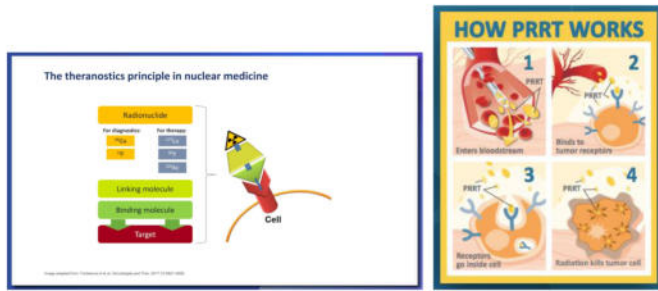
Department of Endocrinology and Radioisotope Therapy, Military Institute of Medicine - National Research Institute, Warsaw, Poland



## Oświadczenie o odpowiedzialności

Na podstawie art. 51 c Kodeksu Etyki Lekarskiej wykładowca oświadcza, że niniejszy wykład jest sponsorowany przez firmę farmaceutyczną Novartis Poland sp. z o.o.

Ponadto, wykładowca oświadcza, że treść wykładu prezentuje jego niezależne poglądy, ma przyczynić się do propagowania wiedzy medycznej oraz nie stanowi reklamy produktów leczniczych w rozumieniu ustawy Prawo farmaceutyczne i przepisów wykonawczych do tej ustawy.

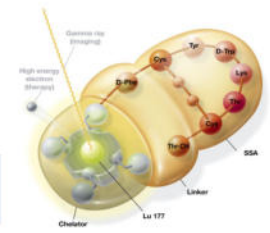


Ref: 1 Canadian Neuroendocrine Tumour Society: <https://www.cnetso.ca/what-is-cancer/what-is-diagnosis-and-treatment-of-neuroendocrine-tumors/>



## structure of the <sup>177</sup>Lu oxodotretotide<sup>1</sup>

- <sup>177</sup>Lu oxodotretotide is used in radioisotope therapy with somatostatin analogues (PRRT)
- <sup>177</sup>Lu oxodotretotide consists of the radionuclide lutetium bound to a peptide <sup>177</sup>Lu emits high-energy electrons and gamma rays (therapy and imaging)
- The peptide is designed to bind to the somatostatin receptor with high affinity



High affinity for SSTRs allows radiation to be delivered to the tumor with high specificity<sup>2</sup>

1. Theranostic Peptide Lutetium-177 Oxodotretotide. *Molecular* 2019;2022:201916. <https://doi.org/10.1021/acs.molpharmaceut.9b00161>



## milestones in RLT in Poland

- 1990s **[<sup>111</sup>In]-DTPA<sup>0</sup>-octreotide** Auger electrons
- EARLY 21st century **[<sup>90</sup>Y]-DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotide** pure beta emitter
- [<sup>177</sup>Lutetium]-DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotide** beta and gamma emitter
- January 2018 **FDA approves new treatment for certain digestive tract cancers** Lutetium (<sup>177</sup>Lu) oxodotretotide
- March 1, 2023 **Polish Drug Program B.139 TREATMENT OF PATIENTS WITH NEUROENDOCRINE TUMORS OF THE DIGESTIVE SYSTEM USING RADIOPHARMACEUTICALS (ICD-10: C25.4, C17.0-C17.9, C18.0-C18.4)**



## Qualification criteria for [<sup>177</sup>Lu]Lu-DOTATATE therapy in the B.139 drug program

- well-differentiated neuroendocrine tumor of the pancreas or MIDGUT (G1 or G2, Ki-67≤20%);
- unresectable or metastatic tumor;
- increased expression of somatostatin receptors in all lesions - confirmed by PET/CT with [<sup>68</sup>Ga]Ga-DOTATATE or SPECT/CT with [<sup>99m</sup>Tc]-HYNIC-TOC (Krenning scale ≥ 2);
- disease progression determined according to clinical and/or hormonal criteria and/or RECIST;
- performance status 0-2 according to the ECOG or WHO classification;
- adequate organ function (kidney, liver and bone marrow);
- exclusion of previous radiotherapy involving external beam irradiation covering more than 25% of the bone marrow;
- age ≥ 18 years.



# Lutetium-177 (177Lu)-dotatate - Polish experience after 2 years of reimbursement under Drug Program B.139. Polish Patient Registry

Prof. dr hab. n. med. Grzegorz Kamiński

## Exclusion criteria

1. hypersensitivity to the 177Lu oxodotreotide;
2. severe circulatory failure (NYHA grade III - IV);
3. pregnancy and breastfeeding;
4. use of interferon, everolimus or other systemic anticancer therapies in the last 4 weeks before entering the drug program;
5. surgical treatment, direct transarterial intrahepatic therapy or chemotherapy during the 12 weeks preceding participation in the drug program.



15 centers in 11 (out of 16) Polish voivodeships provide services for Polish Drug Program B.139



15 centers in 11 (out of 16) Polish voivodeships provide services for Polish Drug Program B.139



- 126 patients treated under the Drug Program
- 25 under emergency access to therapy (individual consent of the Polish NHS)
- 59 patients are still undergoing treatment
- 92 patients completed therapy with good compliance (73% of patients received 4 doses of therapy)



Polskie Towarzystwo Endokrynologiczne



## Registry



### Construction of a register of RLT patients:

- obtaining opinions on the characteristics of patients included in RLT
- obtaining information about the types of progression on the basis of which patients are qualified for RLT
- determining the information necessary to develop a patient's path from diagnosis of the disease to its treatment and monitoring of therapeutic effects, allowing for the development of treatment patterns based on the centers' own experience



Polskie Towarzystwo Endokrynologiczne



## Polish Patient Registry

The platform consists of several main modules

- Repository - register
- Expert Meeting - a place for video-communication of centers
- Statistics - access to partial data
- Forum - exchange of experiences between centers



Polskie Towarzystwo Endokrynologiczne



## Polish Patient Registry

6 research centers participate in the Registry

Expert Meetings

December 2023 – Toruń  
April 2024 – Katowice

October 2024 – on-line



THANK YOU



# New insights in neuroendocrine tumors therapy

Prof. dr hab. n. med. Beata Kos-Kudła



New insights in neuroendocrine tumors therapy

Beata Kos-Kudła  
Department of Endocrinology and Neuroendocrine Tumors, ENETS Center of Excellence, Medical University of Silesia, Katowice, Poland  
[endoklin@sum.edu.pl](mailto:endoklin@sum.edu.pl)

European Neuroendocrine Tumor Society (ENETS) 2024 Guidance Paper for Small Intestinal Neuroendocrine Tumours

*J Neuroendocrinol.* 2024;e13423  
<https://doi.org/10.1111/jne.13423>



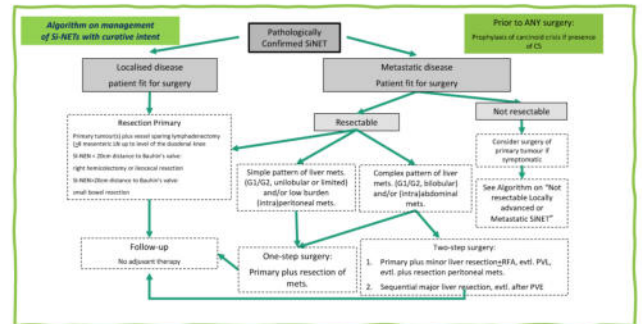
Angela Lamarca<sup>1,2</sup>, Detlef K. Bartsch<sup>3</sup>, Martyn Caplin<sup>4</sup>, Beata Kos-Kudła<sup>5</sup>, Andreas Kjaer<sup>6</sup>, Stefano Partelli<sup>7</sup>, Anja Rinke<sup>8</sup>, Eva Tiensuu Janson<sup>9</sup>, Christina Thirllwell<sup>10</sup>, Marie-Louise F. van Velthuisen<sup>11</sup>, Marie-Pierre Vullierme<sup>12</sup>, Marianne Pavel<sup>13</sup>



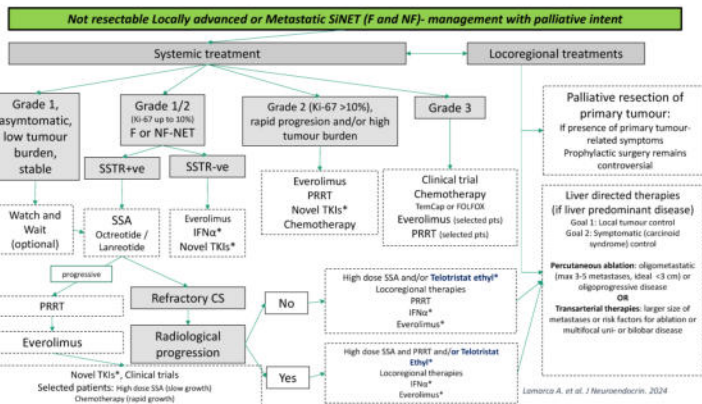
**Table 1. Ten major questions on diagnostic and therapeutic management of SI-NET**

- Q1** Which features need to be taken into consideration for the management of SI-NET?
- Q2** Is there any role of circulating biomarker measurement in SI-NET?
- Q3** Which is the most suitable diagnostic and staging work-up for patients with small intestinal NET?
- Q4** What is the role of surgery in localized SI-NET?
- Q5** What is the recommended first-line systemic treatment for advanced disease?
- Q6** What is the recommended treatment beyond first-line SSA therapy?
- Q7** Which is the role of locoregional and ablative therapies in advanced SI-NET?
- Q8** Which is the best therapeutic strategy in patients with Carcinoid Syndrome for syndrome and tumour control?
- Q9** What are the most recent developments for SI-NET?
- Q10** What is the recommended follow-up SI-NET?

Lamarca A. et al. ENETS 2024 Guidance Paper for SI-NET. *J Neuroendocrinol.* 2024; in press



Lamarca A. et al. ENETS 2024 Guidance Paper for SI-NET. *J Neuroendocrinol.* 2024;e13423



Lamarca A. et al. *J Neuroendocrinol.* 2024

*J Neuroendocrinol.* 2023;e13343  
<https://doi.org/10.1111/jne.13343>



DOI: 10.1111/jne.13343

CLINICAL GUIDELINE

Journal of Neuroendocrinology WILEY

## European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours

Beata Kos-Kudła<sup>1</sup> | Justo P. Castaño<sup>2</sup> | Timm Denecke<sup>3</sup> | Enrique Grande<sup>4</sup> | Andreas Kjaer<sup>5</sup> | Anna Koumarianou<sup>6</sup> | Louis de Mestier<sup>7</sup> | Stefano Partelli<sup>8</sup> | Aurel Perren<sup>9</sup> | Stefan Stättner<sup>10</sup> | Juan W. Valle<sup>11,12</sup> | Nicola Fazio<sup>13</sup>

# New insights in neuroendocrine tumors therapy

Prof. dr hab. n. med. Beata Kos-Kudła

**Table 1. Ten major questions on management of non-functioning pancreatic neuroendocrine tumours**

- Q1** How should we define and characterise a NF-Pan-NET patient at clinical presentation?
- Q2** Which biochemical tests should be performed in a patient with NF-Pan-NET?
- Q3** Which is the most suitable imaging work-up for NF-Pan-NET patients?
- Q4** What is the appropriate surgical management of NF-Pan-NET?
- Q5** What is the role of PRRT in patients with NF-Pan-NET?
- Q6** What is the role of biotherapy and molecular targeted therapies in patients with advanced NF-Pan-NET?
- Q7** What is the role of chemotherapy in patients with advanced NF-Pan-NET?
- Q8** In the setting of advanced disease, which is the most suitable first-line systemic therapy? Which sequence of treatments should be used?
- Q9** Is there a specific work-up in MEN1-associated NF-Pan-NET patients?
- Q10** What is the recommended follow-up in NF-Pan-NET patients?

Kos-Kudła B et al. ENETS 2023 guidance paper for non functioning Pancreatic NETs. J Neuroendocrinol. 2023

## Q4. What is the appropriate surgical management of NF-Pancreatic NET?

Surgery is strongly recommended for all NF-Pan-NET associated with main pancreatic duct dilation and/or larger >2cm.

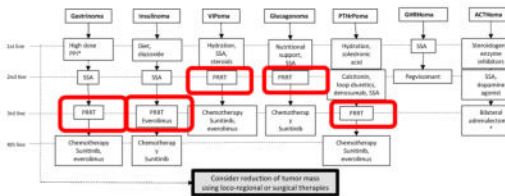
**NEW**

A minimally invasive approach for lesions of the body-tail, and for all those that can be enucleated, should be preferred whenever possible after a careful assessment of possible associated risks



Kos-Kudła B et al. ENETS 2023 guidance paper for nonfunctioning pancreatic NETs. J Neuroendocrinol. 2023

## Treatment algorithm for hormonal symptoms in advanced disease



Management of patients with functioning syndromes includes a multimodal approach of supportive, surgical, interventional, hormonal and anti-proliferative therapies. First-line treatment should be initiated in all patients with symptomatic and advanced disease as monotherapy or combination treatment. In case of refractory symptoms further lines of treatment should be explored and clinical benefit, also taking into account the need for antiproliferative control or cytoreduction based on tumor growth rate and bulk. \*Absence of cases of gastrinoma can be directly correlated with high-dose PPI. \*\*Agreement cases bilateral adrenalectomy should be considered the first-line option of choice. PPI: proton-pump inhibitor; SSA: somatostatin analogue; PRRT: peptide receptor radionuclide therapy.

Hoffland J et al. ENETS 2023 Guidance Paper for functioning PNET. J Neuroendocrinol. 2023;35(8)

## CHOICE OF CHEMOTHERAPY REGIMEN

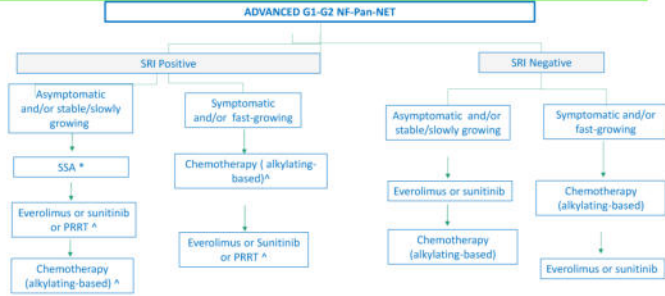
Treatment	Ki-67 < 20%		Ki-67 > 20%	
	PanNET G1	PanNET G2	PanNET G3	PanNEC
Targeted therapy				
Neoadjuvant or induction (preoperative)	-	-	-	-
Adjuvant (postoperative)	-	-	-	-
Neoadjuvant or induction (preoperative)	-	-	± individually; no studies available	+ PE/KE FOLFOLX
Adjuvant (postoperative)	-	-	± individually; no studies available	+ PE/KE FOLFOLX (I)
Paliative	-	-	± in second and subsequent lines (CAPTEM, STZ5-FU) Exceptionally in the first line depending on progression and dynamics	+ PE/KE CAPTEM FOLFOLX FOLFIRI FOLFIRINOX

Sorbye H et al. ENETS 2023 guidance paper for digestive NEC. J Neuroendocrinol. 2023;35(3):e13249.



Kos-Kudła B et al. Pancreatic NET –update of diagnostic and therapeutic guidelines ... Endokrynol Pol, 2022

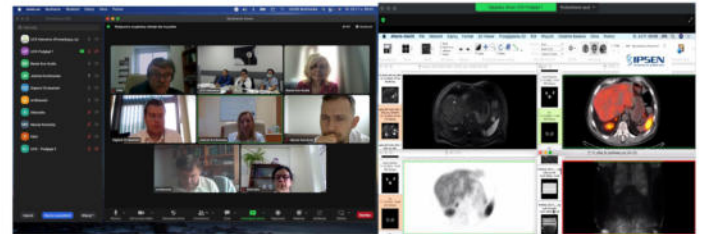
## Q 8. In the setting of advanced disease, which is the most suitable first-line systemic therapy? Which sequence of treatments should be used?



\*Preferably for Ki-67 < 10%

^ PRRT or Chemotherapy or TAE/other Liver-Directed Therapy if cytoreductive intent

Kos-Kudła B et al. ENETS 2023 guidance paper for nonfunctioning pancreatic NETs. J Neuroendocrinol. 2023

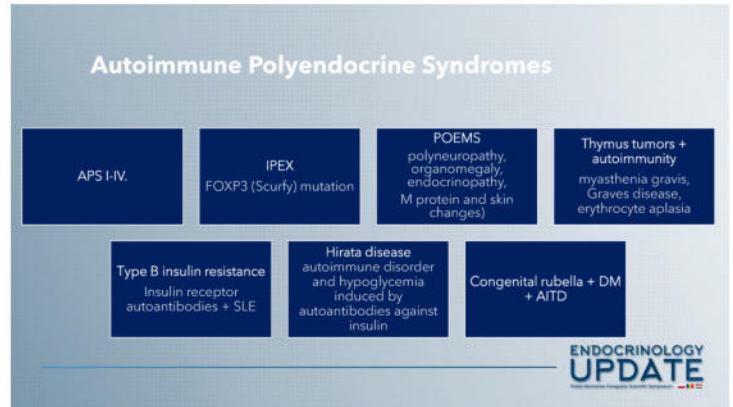


Nationwide Multi-specialty Council of Neuroendocrine Neoplasms

- x 2 times a month

# Association of other autoimmune conditions to endocrine autoimmune disorders

Professor Emese Mezösi



### APS (Autoimmune Polyendocrine Syndrome)

- Heterogeneous multifactorial disease group
- Involves multiple endocrine and non-endocrine organs
- APS I: Mutation of the autoimmune regulator gene (AIRE), early onset
- APS II: Addison's disease + autoimmune thyroid disease/type 1 diabetes mellitus
- APS III: Type 1 diabetes and/or autoimmune thyroid disease with other autoimmune diseases, excluding Addison's disease/hypoparathyroidism
- APS IV: Not fitting into the above categories

Copyright M. Autoimmun Rev. 2014; 13(2): 83-89

### Patients

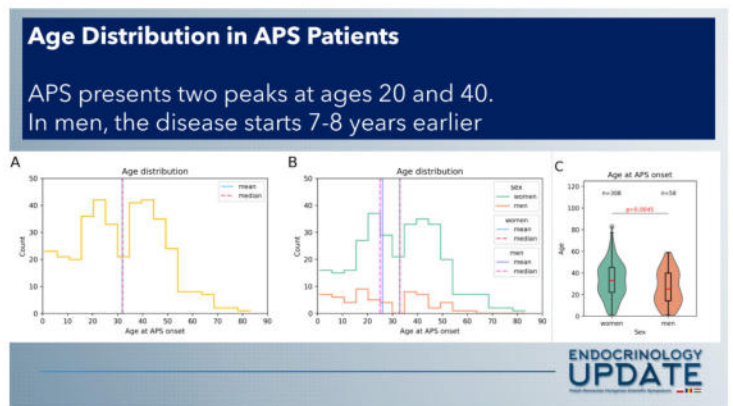
- Data collection: Between April 2007 and September 2018,
- 7,559 patient records were reviewed, 3,180 had confirmed autoimmunity.
- 380 patients (11.9%) had multiple autoimmune diseases

#### Examination Criteria

- Gender
- Age at disease onset
- First manifestation
- Second autoimmune disease
- Time elapsed between the two manifestations
- APS category

### Disorders n=28

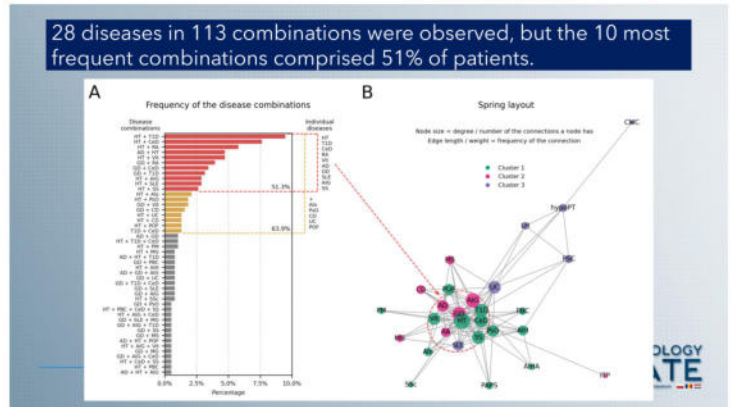
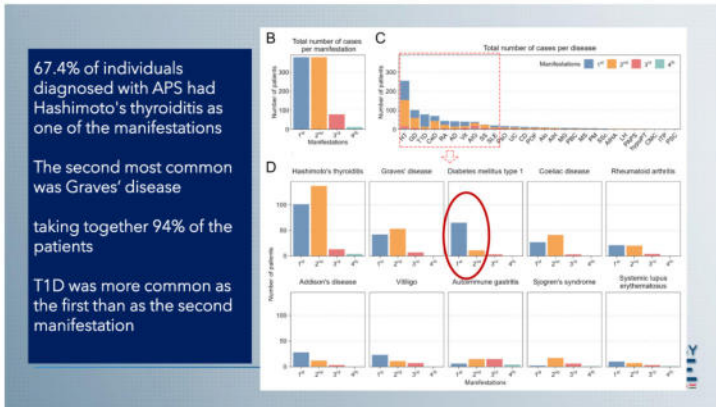
Endocrine organ-specific disorders	Non-endocrine organ-specific disorders	Systemic autoimmune disorders
Hashimoto's thyroiditis - HT (n=256)	Celiac disease - CED (n=72)	Rheumatoid arthritis - RA (n=45)
Graves' disease - GD (n=102)	Autoimmune gastritis - AIG (n=40)	Sjögren's syndrome - SS (n=26)
Diabetes mellitus - T1D (n=79)	Vitiligo - Vit (n=40)	SLE (n=21)
Addison's disease - AD (n=43)	Ulcerative colitis - UC (n=17)	Pсориаз - Pso (n=19)
Premature ovarian insufficiency - POF (n=14)	Crohn's disease - CD (n=14)	Polymyositis - PM (n=6)
Hypoparathyroidism - hypoPT (n=3)	Alopecia - Alo (n=11)	Systemic sclerosis - SSC (n=4)
Lymphocytic hypophysitis - LH (n=2)	Autoimmune hepatitis - AIH (n=9)	Primary antiphospholipid syndrome (n=2)
	Primary biliary cholangitis - PBC (n=8)	
	Sclerosis multiplex - SM (n=6)	
	Autoimmune hemolytic anemia - AIHA (n=3)	
	Sclerotic cholangitis - PSC (n=2)	
	Immune thrombocytopenia - ITP (n=1)	
	Chronic mucocutan candidiasis - CMC (n=1)	



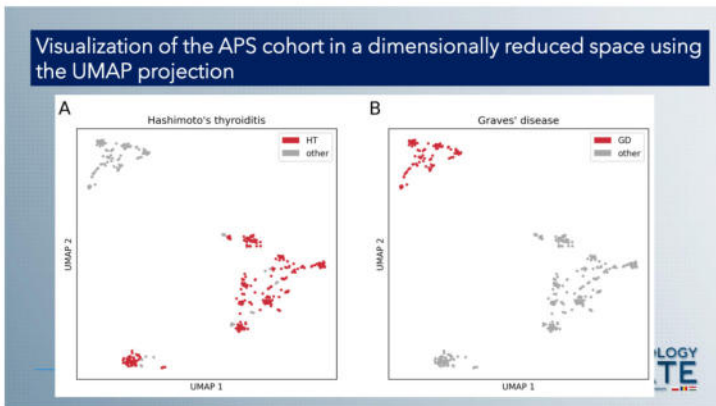
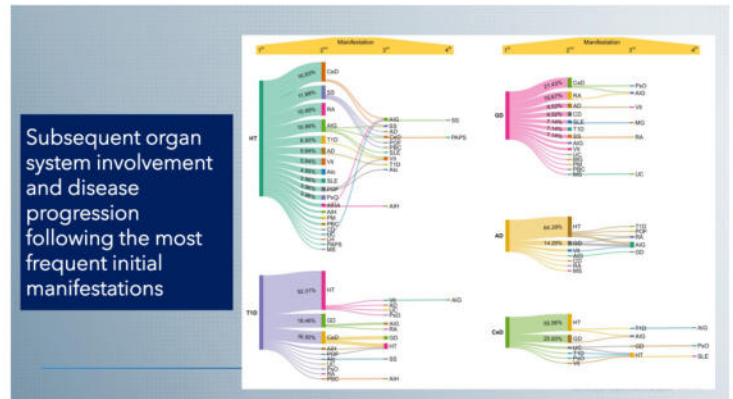
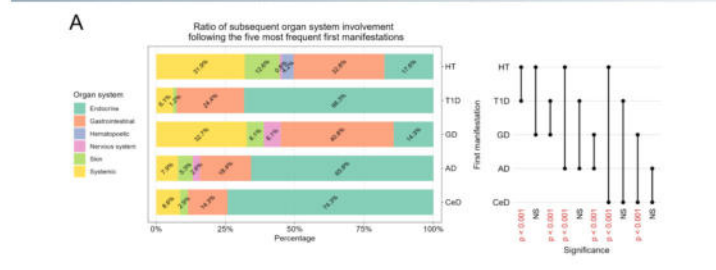


# Association of other autoimmune conditions to endocrine autoimmune disorders

Professor Emese Mezösi



Patients diagnosed with HT or GD had high prevalence of gastrointestinal (32.8% and 40.8% respectively), as well as systemic (31.9% and 32.7% respectively) diseases in the latter phases. In contrast, following T1D, AD, and CeD the endocrine system was predominantly involved in the later manifestations (68.3%, 65.8%, and 74.3%)



**Summary**

- APS is more common than previously thought
- The second autoimmune disease can develop over an extensive time interval
- In men, the disease starts 7-8 years earlier
- Type 1 diabetes and celiac disease manifest earlier than other conditions
- Endocrine autoimmune diseases can be associated with non-endocrine organ-specific and systemic autoimmune diseases, highlighting the heterogeneous clinical presentations
- The first manifestation is likely to impact the development of subsequent disorders in APS
- Hashimoto's thyroiditis and Graves' disease are key cornerstones in APS

ENDOCRINOLOGY UPDATE

# Osteosarcopenia - approaching the musculoskeletal frailty

Professor Ionela Pascanu

**ENDOCRINOLOGY UPDATE**  
 Polish-Romanian-Hungarian Scientific Symposium  
 Scientific and Organizational Committee: prof. dr hab. n. med. Beata Kobylińska, prof. dr hab. n. med. Renata Szczygielowska-Struska  
 Honorary Committee: prof. em. dr hab. n. med. Marek Bolanowski  
 10<sup>th</sup>-11<sup>th</sup> October 2024 GDAŃSK  
**Osteosarcopenia - Approaching the Musculoskeletal Frailty**  
 PROF. DR. PASCANU IONELA  
 UNIVERSITY OF MEDICINE, PHARMACY, SCIENCES AND TECHNOLOGY "GEORGE EMIL PALADE" OF TÂRGU MUREŞ, ROMANIA

## Aspects to discuss

- Sarcopenia-Definitions, diagnosis, epidemiology & Quality of Life
- Osteoporosis Guidelines & Fracture Risk, Economic burden of OP
- Osteosarcopenia definition & Sarcopenia assessment in women with postmenopausal osteoporosis
- Management of osteosarcopenia - current status

**ENDOCRINOLOGY UPDATE**

### Where to draw the line between "normal" sarcopenia and a disease state?

Group	Reference	Low muscle mass				Low muscle strength		Low physical performance
		Men	Women	Men	Women	Men	Women	
EWGOP	(Chen et al., 2010)	AKM/HR <sup>2</sup> < 7.23 kg/m <sup>2</sup>	AKM/HR <sup>2</sup> < 5.5 kg/m <sup>2</sup>	SM/HR <sup>2</sup> < 8.07 kg/m <sup>2</sup>	SM/HR <sup>2</sup> < 6.42 kg/m <sup>2</sup>	<18 kg	<10 kg	<0.8 m/s
EWGOP	(Chen et al., 2010)	Percentage of muscle mass > 2 SD below mean in young adults of the same sex and ethnic background (individuals aged 18-39 years in the NHANES III study)						<0.8 m/s
ICVD	(Mackrill et al., 2011)	AKM/HR <sup>2</sup> of 2 SD below the mean of healthy persons aged 30-39 years of the same ethnic group						<0.8 m/s or a walking distance <100 meters in 4-6 min walk
EWGOP	(Palting et al., 2011)	AKM/HR <sup>2</sup> < 7.23 kg/m <sup>2</sup>	AKM/HR <sup>2</sup> < 5.5 kg/m <sup>2</sup>					<1.0 m/s
AWGS	(Chen et al., 2014)	AKM/HR <sup>2</sup> < 7.23 kg/m <sup>2</sup>	AKM/HR <sup>2</sup> < 5.5 kg/m <sup>2</sup>	SM/HR <sup>2</sup> < 7.0 kg/m <sup>2</sup>	SM/HR <sup>2</sup> < 5.4 kg/m <sup>2</sup>			
EWGOP	(Chen et al., 2014)	AKM/HR <sup>2</sup> < 7.23 kg/m <sup>2</sup>	AKM/HR <sup>2</sup> < 5.5 kg/m <sup>2</sup>	AKM/HR <sup>2</sup> < 6.512				
EWGOP	(Chen et al., 2019)	Men: AKM < 18 kg, AKM/HR <sup>2</sup> < 7.2 kg/m <sup>2</sup>		Women: AKM < 15 kg, AKM/HR <sup>2</sup> < 5.5 kg/m <sup>2</sup>				

International Working Group on Sarcopenia (IWGS), European Working Group on Sarcopenia in Older People (EWGOP), Special Interest Group on sarcopenia assessment in chronic wasting diseases of the European Society for Clinical Nutrition and Metabolism (EWGOP), Society of Sarcopenia, Cachexia and Wasting Disorders (SCWD), Asian Working Group for Sarcopenia (AWGS), The Protocol for the National Institutes of Health Sarcopenia Project (NIH)-Appendix A: Lean Mass (LMS), Body mass index (BMI), Appendicular skeletal mass (ASM), Skeletal mass (SM)

## SARC-F

SARC-F = 5-point sarcopenia self-questionnaire, has high specificity but low sensitivity, making it the most accurate in detecting those with sarcopenia

Component	Question	Scoring
Strength	Difficulty in lifting and carrying 10 pounds?	None = 0
		Some = 1
Walking	Difficulty walking across a room?	A lot or unable = 2
		None = 0
Chair rise	Difficulty transferring from a chair or bed?	A lot or unable = 2
		None = 0
Stairs	Difficulty climbing a flight of 10 stairs?	A lot or unable = 2
		None = 0
Falls	Times have you fallen in the past year?	A lot or unable = 2
		None = 0

SARC-F score ≥4 best predicts the need for further, more comprehensive evaluation to confirm evidence of sarcopenia.

**ENDOCRINOLOGY UPDATE**

## Is sarcopenia a health concern?

### Mortality

- 12 prospective studies, OR 3.596 (95% CI 2.96-4.37)
- Sarcopenia patients face 4x higher risk of mortality vs. patients without sarcopenia
- The effect was higher in people aged ≥ 79 years vs. younger (p = 0.02)

17 studies for meta-analysis, subjects > 60 years, EWGOP definition

### Hospitalization

- 6 studies, higher risk of functional disability for sarcopenic subjects compared with non-sarcopenic ones (pooled OR 3.03 (95%CI: 1.80-5.12))

### Falls

- Significant association between sarcopenia and the incidence of falls

### Quality of life

- Meta-analysis of 43 observational studies, 30 322 sarcopenic and 26 214 non-sarcopenic
- EWGOPS (80%) EWGOPS1 & EWGOPS: AWGS
- SarQoL questionnaire
- Significantly lower HRQoL was observed for sarcopenic individuals compared with non-sarcopenic ones (SMD -0.76; 95% CI 0.95-0.57)

**ENDOCRINOLOGY UPDATE**

## Psychometric performance of the Romanian version of the SarQoL, a health-related quality of life questionnaire for sarcopenia

translation and cross-cultural adaptation of the original SarQoL questionnaire in Ro + the validation process.

SarQoL questionnaire in Romanian = equivalent to the English SarQoL questionnaire.

Discriminative power

Correlations between the Romanian SarQoL and similar or dissimilar domains of SF-36 and EQ-5D (convergent and divergent validity)

**ENDOCRINOLOGY UPDATE**

# Osteosarcopenia - approaching the musculoskeletal frailty

Professor Ionela Pascanu

## Since 2020 OP Guidelines Provide Common Understanding of Fracture Risk...

**VERY HIGH RISK\***

If one or more of the below is true<sup>1</sup>:

- ❑ Fx within past 12 months<sup>1,4</sup>
- ❑ Multiple Fx<sup>3,4</sup>
- ❑ Fx while on OP Tx<sup>1</sup>
- ❑ Fx while on medication harmful to bone<sup>1</sup>
- ❑ Very low T-score <-3.0<sup>1-3,4</sup>
- ❑ FRAX probability >30% MOF, >4.5% hip<sup>1,4</sup>

**HIGH RISK\***

If any of the below is true<sup>1</sup>:

- ❑ Age: postmenopausal<sup>1,4</sup> +
- ❑ Prior Fx or<sup>1,4</sup>
- ❑ T-score ≤ -2.5 or<sup>1-3</sup>
- ❑ T-score -1.0 to -2.5 and FRAX probability ≥20% MOF or ≥3% hip<sup>1,3</sup>

**LOW RISK\***

If all of the below are true<sup>1</sup>:

- ❑ Age: postmenopausal<sup>1-3</sup>
- ❑ No prior Fx<sup>2,3</sup>
- ❑ T-score > -1.0 and FRAX probability <20% MOF and <3% hip<sup>1-3</sup>

BMD = bone mineral density, FRAX = Fracture Risk Assessment Tool, Fx = fracture, MOF = major osteoporotic fracture, OP = osteoporosis, Tx = treatment.

\*Regional and local guidelines may override certain of these criteria based on differences in FRAX data and cost-effectiveness thresholds.

<sup>1</sup>If FRAX not available, major determinants of risk should include age, BMD, fracture, and medication harmful to bone.

<sup>2</sup>SENDQ requires both risk factors to be met for very high risk categorization.

**ENDOCRINOLOGY UPDATE**

## Epidemiology and economic burden of osteoporosis in Romania

D Grigorie · AI Gasparic · I Pascanu · D Grigorie · C Willem · N Norm · NC Harvey · T Jacobson · H Johansson · M Lorentzon · EV McCloskey · F Borgstrom · JA Kanis

**1,071,000**  
INDIVIDUALS WITH OSTEOPOROSIS IN 2019

**80.7%**  
WOMEN

**19.3%**  
MEN

**4.8% OF THE TOTAL POPULATION**

Category	Measure	Estimate	Rank
Burden of disease	Direct cost of incident fracture (€m)	91.02	
	Long-term disability cost (€m)	150.13	
	Intervention cost (€m)	16.17	
	Total cost (€m)	257.32	
	QALYs lost (€m)	1055	
	Cost per capita (€)	13.21	29
	Proportion of healthcare spending	2.5%	22
Prevalence of osteoporosis	4.8%	25	

**ENDOCRINOLOGY UPDATE**

## Osteosarcopenia

Osteosarcopenia is a new syndrome (2017) describing the co-existence of low bone density and sarcopenia

"Hazardous dust"

"Geriatric giant of the XXI century"

Individuals with osteosarcopenia are at higher risk of falls & fractures than those with sarcopenia or osteoporosis alone

→ resulting in significant impaired QoL and socioeconomic costs

**ENDOCRINOLOGY UPDATE**

## Table 5. Predictors for probable sarcopenia

Predictors	B	SE	Exp (CI)
Age (years)	-0.005	0.211	0.935
Menopausal age (years)	-0.106	0.137	0.960
Menopausal age (years)	-0.033	0.354	0.960
BMI (kg/m <sup>2</sup> )	-0.084	0.474	0.920
Sarcopenic index	-0.538	0.450	0.589
Speed	-3.755	0.007	0.023
Fractures (1)	3.299	0.044	3.444
Model (r <sup>2</sup> )	0.330	0.017	

Table 3. Main characteristics of the study group

	Probable sarcopenia	No sarcopenia	P-value
Age (years, SD)	68 (10.7)	64 (9.2)	0.00
Menopausal age (years, SD)	47 (6.0)	48 (6.4)	0.30
Osteoporosis diagnosis (years, SD)	31 (23.0)	48 (9.2)	0.00
Height/Weight area (m <sup>2</sup> )	1.7 (0.06) / 71 (10.0)	1.7 (0.06) / 71 (10.0)	0.99
Frailty frequency (%)	12 (14.6)	31 (21.6)	0.09
BMD, spine (T4-L4) (g/cm <sup>3</sup> )	1.0 (0.10)	1.1 (0.10)	0.00
FRAX hip (%) (SD)	1.0 (0.4)	1.1 (0.4)	0.00
FRAX hip (g/cm <sup>3</sup> ) (SD)	20 (5.0)	28 (5.0)	0.00
Sarcopenic index (kg/m <sup>2</sup> , SD)	4.3 (0.4)	7.0 (0.5)	0.00
Muscle strength (kg, SD)	13 (3.3)	23 (3.4)	<.001
Speed (m/s, SD)	0.8 (0.1)	0.9 (0.1)	0.00
BMI (kg/m <sup>2</sup> , g/cm <sup>3</sup> )	20.9 (2.0)	24.0 (2.1)	0.00
Calcium (mg, SD)	1.0 (0.1)	0.9 (0.0)	0.74
Phosphorus (mg, SD)	1.0 (0.0)	1.0 (0.0)	0.61
ESRD, total score (SD)	0.7 (0.3)	0.7 (0.3)	0.99

**ENDOCRINOLOGY UPDATE**

## The effect of pharmacological agents on osteoporosis and sarcopenia related outcomes

Pharmacological agent	Osteoporosis	Sarcopenia
Denosumab	Meta-analysis of 4 RCTs, investigating the effect of denosumab on BMD reported significant improvement in BMD at lumbar spine, hip, and radius. <sup>71</sup>	Reduction in falls in the Denosumab treatment group of the FREEDOM Study. No evidence of effect on muscle function. <sup>75</sup> Improves muscle strength and insulin sensitivity in osteoporotic humans. <sup>76</sup>
Testosterone	Intramuscular testosterone increased lumbar spine bone density in men. <sup>73</sup>	Testosterone in older men with decreased testosterone levels and muscle weakness can improve muscle mass, strength and physical performance. <sup>75</sup>
Growth hormone	Meta-analysis of 7 RCTs and one extension trial concluded that growth hormone may not improve bone density but decrease fracture risk in women with age related bone loss. <sup>77</sup>	Low growth hormone levels with age contribute to decrease in lean body mass and increase adipose tissue. <sup>78</sup>
Antimyoastatin antibodies	Antimyoastatin antibody in combination with resistance exercise improved bone health in rats. <sup>79</sup>	(1) Antimyoastatin antibodies increased muscle mass and strength in mice. <sup>80</sup> (2) Antimyoastatin antibodies increased lean mass and may improve functional measures of muscle power. <sup>81</sup>

BMD, bone mineral density, RCT, randomized controlled trial.

**ENDOCRINOLOGY UPDATE**

## Conclusions

- Osteoporosis and sarcopenia are age-related conditions and are associated with significant morbidity and mortality.
- Their prevalence is expected to increase over the years with important consequences for individuals and health-care systems.
- It has become evident that global agreement is needed on the conceptual definition of sarcopenia.
- Combined resistance and balance exercises with nutritional supplementation and treatment of osteoporosis are the current strategies to manage osteosarcopenia.
- Myostatin, Irisin, RANKL and SOST show great potential to serve as molecular targets for osteosarcopenia-related fracture treatment.

**ENDOCRINOLOGY UPDATE**

# Coexistence of papillary thyroid carcinoma with hyperparathyroidism. Experience of a tertiary endocrinology center

Professor Cristina Preda



## The link between papillary thyroid carcinoma and hyperparathyroidism

- The association of hyperparathyroidism with thyroid carcinoma in particular has been frequently stated.
- While a significant association between these conditions has been established, several aspects remain indistinct and require special exploration.
- The precise mechanistic interplay between hyperparathyroidism and thyroid cancer, whether causative or coincidental, merits deeper investigation.
- Understanding the molecular pathways or shared genetic factors contributing to their co-occurrence remains an open area for exploration.

Scerriano et al. J. Clin. Med. 2024, 13, 147.

## The link between papillary thyroid carcinoma and hyperparathyroidism

- The incidence of differentiated thyroid cancer has increased globally in the last 10-20 years, faster than that of any other cancer type. The rising incidence has been observed in females, young adults, and children. The possible explanation might be the new achievements in diagnostic procedures but also lifestyle changes and environmental influences may contribute to a real increase.
- The incidence of papillary thyroid carcinoma (PTC) in patients with hyperparathyroidism (HPT) varies from 2.8% to 47.1%.
- Possible predisposing factors for PTC in HPT: the tumor promoting effect of PTH, the goitrogenic effect and increased mitotic activity induced by hypercalcemia and neck irradiation.

Scerriano et al. J. Clin. Med. 2024, 13, 147; Preda C. Arch Clin Cases 2021; 8(4):62-63; Preda et al. BMC Surgery (2019) 19:94

## Coexistent PTC diagnosed in surgically treated patients for PHPT versus SHPT: same incidence, different characteristics

- The aim of the study was to evaluate the rate of thyroid cancer in patients operated for either primary (PHPT) or secondary hyperparathyroidism (SHPT).
- Methods: Our retrospective study included PHPT and SHPT patients submitted to parathyroidectomy and, when indicated, concomitant thyroid surgery, for a period of 8 years.
- Results: Parathyroidectomy was performed in 217 patients: 140 (64.5%) for PHPT and 77 (35.5%) for SHPT. Concomitant thyroid surgery was performed in 75 patients with PHPT (53.6%), and 19 papillary thyroid carcinomas (PTC) were found, accounting for 13.6% from all cases with PHPT and 25.3% from PHPT cases with concomitant thyroid surgery. Thirty one of operated SHPT patients (40.3%) also underwent thyroid surgery and 9 PTC cases were diagnosed (11.7% of all SHPT patients and 29% of patients with concomitant thyroid surgery).

Preda C, Branisteanu D, Armasu A, Danila R, Velicescu C, Ciobanu D, Covic A, Grigorovici A. BMC Surgery (2019) 19:94

## The frequency of thyroid cancer among patients with PHPT or SHPT, who underwent both parathyroidectomy and thyroid surgery

Preda C, Branisteanu D, Armasu A, Danila R, Velicescu C, Ciobanu D, Covic A, Grigorovici A. BMC Surgery (2019) 19:94

## Comparison of parathyroid and concomitant thyroid disease in patients with PHPT versus SHPT

General data	PHPT		SHPT		p-value
	No.	(%)	No.	(%)	
Number of patients	140	64.5	77	35.5	0.000
Mean age	59.6 (13)		68.4 (12)		<0.001
Sex					
Male	71	50	33	42.7	
Female	69	49.3	44	57.3	
Menstruation status	87	62.1	11	14.3	
Preoperative PTH level (pg/ml)	277.0 (86.7)		102.8 (16.8)		<0.001
Concomitant thyroid disease (n=217)					
Postoperative carcinoma	1	0.7%	0	0%	
Postoperative adenoma	30	21.4%	4	5.2%	
Adenomatous hyperplasia	47	33.6%	16	20.8%	
Nodule	27	19.3%	16	20.8%	
Cystic	7	5.0%	2	2.6%	
Hot nodule and diffuse	8	5.7%	8	10.4%	
Unspecified	1	0.7%	1	1.3%	
Multiple thyroid carcinoma (PTC)	19	13.6%	9	11.7%	0.802
Single lesion	9	6.4%	0	0%	0.000
Postoperative thyroid disease	0	0%	0	0%	
Adenomatous hyperplasia	16	11.4%	14	18.1%	
Adenomatous hyperplasia with nodules	40	28.6%	16	20.8%	
Adenomatous hyperplasia with microadenoma	12	8.6%	8	10.4%	
Simple nodular disease	0	0%	1	1.3%	

Preda C, Branisteanu D, Armasu A, Danila R, Velicescu C, Ciobanu D, Covic A, Grigorovici A. BMC Surgery (2019) 19:94

# Coexistence of papillary thyroid carcinoma with hyperparathyroidism. Experience of a tertiary endocrinology center

Professor Cristina Preda

## Particularities of PTC associated with PHPT or SHPT

	PHPT		SHPT		P
	No. cases	SD	No. cases	SD	
Papillary thyroid carcinoma (PTC)	19	27(1.5)	9	38(9.6)	0.017
Classic variant of PTC	4	27(1.5)	1	27(7.5)	
Follicular variant of PTC	3	25(1.5)	—	—	
Oncocytic variant of PTC	—	—	—	—	
T分期 classification					
T1 (≤ 10mm)	13	44(1.6)	9	70(9)	
T2 (10-20mm)	—	—	—	—	
T3 (20-40mm)	6	37(1.6)	—	—	
T4 (≥ 40mm)	—	—	—	—	
N分期 classification					
N0	19	64(1.6)	9	37(9.6)	0.049
N1	0	0(0)	0	0(0)	
N2	0	0(0)	0	0(0)	
Maximum tumor diameter					
< 10mm (microcarcinoma)	13	44(1.6)	9	70(9)	0.009
8-10 and < 10mm	0	0(0)	—	—	
20-30 and 10-20mm	1	3(1.1)	—	—	
3-40cm	0	0(0)	—	—	
Mean tumor size (mm)	13.6 ± 10.4	—	17.7 ± 27	—	0.005
Multifocality	4	21(1.1)	1	11(11)	0.007

Preda C, Branisteanu D, Armasu A, Danila R, Velicescu C, Ciobanu D, Covic A, Grigorovici A. BMC Surgery (2019) 19:94



## Coexistent PTC diagnosed in surgically treated patients for PHPT versus SHPT: results

- We found differences between PHPT and SHPT patients ( $p < 0.001$ ) with respect to age ( $54.6 \pm 13y$  versus  $48.8 \pm 12y$ ), female-to-male ratio (8.1 versus ~ 1:1), surgical technique (single gland parathyroidectomy in 82.8% PHPT cases; versus subtotal parathyroidectomy in 85.7% SHPT cases) and presurgical PTH ( $357.51 \pm 38.11$  pg/ml versus  $1020 \pm 161.38$  pg/ml).
- Morphopathological particularities, TNM classification and multifocality incidence of PTC were similar in the two groups.
- All PTC from patients with SHPT were thyroid microcarcinomas (TMC, i.e. tumors with a diameter smaller than 1 cm), whereas seven out of the 19 cases with PTC and PHPT were larger than 1 cm.

Preda C, Branisteanu D, Armasu A, Danila R, Velicescu C, Ciobanu D, Covic A, Grigorovici A. BMC Surgery (2019) 19:94



## Occurrence of malignant tumours in patients with PHPT

- Retrospective cohort study: PHPT was associated with various tumour types.
- The frequency of malignant tumours was 21.2%.
- Breast and thyroid cancers were the most common 2 cancers coexisting with PHPT.

Locations	47 malignant tumours in 42 patients, n (%)
Breast	17 (36.1)
Thyroid	8 (17.0)
Prostate	4 (8.5)
Colon	3 (6.4)
Stomach	3 (6.4)
Lung	2 (4.3)
Lymphoma	2 (4.3)
Ovarian	2 (4.3)
Kidney	2 (4.3)
Cervix	1 (2.1)
Multiple myeloma	1 (2.1)
Skin (malign melanoma)	1 (2.1)
Endometrial	1 (2.1)

Sezer H et al, Endokrynologia Polska, 74, 4/2023



## Coexistent PTC with HPT: coincidence or not?

- Autopsy controlled studies showed that thyroid cancer occurs more frequently in patients with PHPT; fact not observed for autoimmune or thyroid nodular disease (Lever E et al. Surgery 1983;94:893-900, Kaplan L et al. Cancer 1971;26:401-7).
- PHPT patients seem to have an increased overall cancer risk and parathyroidectomy is not a risk-reducing, but rather a delaying factor in the occurrence of cancer (Nilsson I-L et al. Endocr Relat Cancer 2007;14:135-40).
- Several authors described a more frequent association of chronic renal disease (CKD), chronic dialysis, SHPT or kidney transplant with thyroid cancer than in the general population. Although all these studies suggested that CKD is accompanied by an increased risk of malignancy, including PTC, they did not, however, systematically evaluate the patients with SHPT submitted to both parathyroidectomy and thyroidectomy (Ito Y et al. Thyroid 2014;24:27-34, Dideban S et al. Iran J Pathol 2016;11:1-19).
- No obvious genetic link between PTC and PHPT has been yet demonstrated (Thakker R. J Intern Med 2016;280:574-83).

Preda C, Branisteanu D, Armasu A, Danila R, Velicescu C, Ciobanu D, Covic A, Grigorovici A. BMC Surgery (2019) 19:94



## Coexistent PTC with HPT: coincidence or not?

- The high concurrence of these two disorders in the same patients might not be coincidental; some specific factors, such as: environmental factors, genetic factors, or some other unknown factors, might connect non-medullary thyroid carcinoma (NMTC) with PHPT.
- Possible risk factors for the coexistence of NMTC and PHPT: history of head and neck irradiation, mostly during adolescence and childhood.
- High PTH levels have been reported to affect phagocytosis, T-cell sensitivity, and B-cell function, thus accounting for the immune dysfunction of patients and increased incidence of cancers.
- It was remarkable that PHPT patients with NMTC demonstrated significantly lower preoperative albumin-corrected serum calcium levels compared with PHPT patients with benign thyroid nodules.

Xue Y. et al. Med Sci Monit, 2016; 22: 4482-4489



## Conclusions

- Among the patients with SHPT, 31 (40.3%) had both thyroid and parathyroid surgery, revealing 9 cases of papillary thyroid carcinoma (PTC), accounting for 11.7% of SHPT cases and 25.7% of those who had both surgeries.
- Both PHPT and SHPT cases revealed a significant occurrence of papillary thyroid cancer (PTC), accounting for 13.6% and 11.7%, respectively. Variations in tumor size and features were observed; larger PTCs were prevalent in PHPT, while SHPT exhibited micropapillary tumors predominantly.
- PHPT leaned towards minimally invasive parathyroidectomy, while SHPT required subtotal parathyroidectomy due to gland hyperplasia.
- PHPT favored females in their fifth to sixth decades, while SHPT occurred across genders, albeit at a slightly younger age.
- SHPT patients displayed notably higher preoperative PTH levels compared to PHPT cases.

Preda C, Branisteanu D, Armasu A, Danila R, Velicescu C, Ciobanu D, Covic A, Grigorovici A. BMC Surgery (2019) 19:94



# Thyroid medullary carcinoma – etiopathogenesis, clinical picture, diagnosis, treatment and prognosis

Profesor Anhelii Syrenicz

**ENDOCRINOLOGY UPDATE**  
Polish-Romanian-Hungarian Scientific Symposium  
Scientific and Organizational Committee: prof. dr hab. n. med. Anhelii Syrenicz  
Honorary Committee: prof. em. em. prof. dr hab. n. med. Marek Rutkowski  
10<sup>th</sup>-11<sup>th</sup> October 2024 GDAŃSK  
Thyroid medullary carcinoma - etiopathogenesis, clinical picture, diagnosis, treatment and prognosis  
PROF. DR HAB. N. MED. ANHELLI SYRENICZ  
DEPARTMENT OF ENDOCRINOLOGY, METABOLIC DISEASES AND INTERNAL DISEASES  
POMERANIAN MEDICAL UNIVERSITY, SZCZECIN

## Definition of medullary thyroid carcinoma

- Medullary thyroid carcinoma (MTC) is a rare type of thyroid malignancy and a member of the neuroendocrine type of tumor. MTC arises from parafollicular cells (C cells), derived from the neural crest, which produce a specific MTC tumor marker – calcitonin and some other peptides, including: carcinoembryonic antigen (CEA), ACTH, CRH, chromogranin A, histaminase, neurotensin, serotonin, prostaglandins, kinins, VIP and GRP

**ENDOCRINOLOGY UPDATE**

Dabala N et al. Acta Clin Croat (suppl) 11, 2020, 59: 50 - 59  
Walczyk A, Kowalska A. Thyroid cancer diseases Medical Tribune Poland 2021

## Epidemiology of MTC

- MTC accounts for less than 5% (2 – 4%) of thyroid cancers. According to current SEER (Surveillance, Epidemiology, and End Results) data, medullary thyroid carcinoma accounts for 1 – 2% of thyroid cancers in the United States, which is much lower than previously cited, primarily due to the significant increase in the relative incidence of papillary thyroid carcinoma (PTC) over the last several decades

**ENDOCRINOLOGY UPDATE**

Kishikawa CM, Sosa JA. Nat Rev Endocrinol. 2014; 12(11):646 - 653  
Dabala N et al. Acta Clin Croat (suppl) 11, 2020, 59: 50 - 59

## Etiology of MTC

- Up to 25% of MTCs occur as part of a hereditary syndrome and 75% are sporadic. Hereditary MTC occurs in MEN syndromes type 2 (formerly 2A) and 3 (formerly 2B), and familial MTC, which is now considered a subset of MEN2. These are all autosomal dominant syndromes caused by pathogenic germline variants in the RET proto-oncogene. Similar somatic RET alterations are also found in around 60% of sporadic MTCs. Many of the remainder of sporadic MTC are driven by somatic mutations in RAS.

**ENDOCRINOLOGY UPDATE**

Mattioli D et al. Endocrinol Rev. 2023; 44(2): 934 - 946  
Fussey JM et al. Clin Endocrinol (Oxf) 2019; 91(8): 677 - 707

## Etiology of MTC

- In MEN 2A and FMTC, mutations are typically located within the cysteine-rich region in the extracellular domain
  - almost 90% of MEN 2A mutation are present in a single codon, codon 634
  - in contrast in FMTC, they are more evenly distributed along the cysteine-rich region
- In MEN 2B, the vast majority of germline mutations occur in the intracellular tyrosine kinase domain of RET, in codon 918
- In sporadic MTCs, somatic mutations of the RET gene in tumor tissue can be detected in approximately 50% of patients. Almost all of those affect codon 918, although they have also been identified in a few other gene regions

**ENDOCRINOLOGY UPDATE**

Elisei R et al. J Clin Endocrinol Metab. 2008; 93(3): 682 - 687  
Agrawal N, et al. J Clin Endocrinol Metab. 2013; 98(2): E344 - 369  
Dabala N et al. Acta Clin Croat (suppl) 11, 2020, 59: 50 - 59

## Clinical characteristics patients with MTC

- MTCs either sporadic or hereditary may present as:
  - most commonly as a thyroid lump
  - as a mass from metastatic disease (cervical lymph nodes or distant metastases)
  - symptoms secondary to elevated calcitonin (diarrhea, flushing)
  - as ectopic Cushing syndrome
  - detected after familial screening
- Patients with MEN 2A syndrome can have
  - medullary thyroid cancers
  - pheochromocytomas (~50%)
  - parathyroid hyperplasia or adenomas (~20 - 30%)

**ENDOCRINOLOGY UPDATE**

# Thyroid medullary carcinoma – etiopathogenesis, clinical picture, diagnosis, treatment and prognosis

Profesor Anhelii Syrenicz

## Clinical characteristics patients with MTC

Patients with MEN 2B syndrome can have

- medullary thyroid carcinoma
- mucosal neuromas
- pheochromocytomas (bilateral and often malignant)
- mucocutaneous pigmented nevi and small intestinal polypus
- intestinal autonomic ganglion dysfunction (often leading to multiple diverticula and megacolon)
- marfanoid habitus

Kabibov S, et al. *Cancer* 2000, 88(5): 1139-1148  
 Matsi LG et al. *Endocrine Rev* 2023, 44(3): 934-946

**ENDOCRINOLOGY UPDATE**

RET variant	AJK risk level	MEN2D	PCH/PTN risk	Other
C622C	MOD	3	PC+	
C609R/G501Y	MOD	2	PC+++/PTN+	Mechanoregulation
C618R/G501Y	MOD	2	PC+++/PTN+	Mechanoregulation
C630R/G501Y	MOD	2	PC+++/PTN+	Mechanoregulation
C634R/G501Y	MOD	2	PC+++/PTN+	
C675Y	MOD	2	PC+++	
C675S/G501Y	HIGH	3	PC+++/PTN++	21.8% freq. in MEN2D, 10.7% frequency in sporadic MTC
K661E	MOD	2	PC+	
E740D	MOD	2	PC+	
L760F	MOD	2	PC+	
N904L	MOD	2	PC+/PTN+	
K905E	MOD	2	PC+/PTN+	19.0% freq. in MEN2D, 28.6% freq. in sporadic MTC
A985F	HIGH	3	PC+++	
S974A	MOD	2	PC+/PTN+	
R927P	MOD			MTC risk
M918T	HIGHEST	3	PC+++	12.8% freq. in MEN2D, 87% freq. in sporadic MTC

Genotype-phenotype correlations, allelic frequency and risk levels for medullary thyroid carcinoma behavior. Adapted from Wells et al., 2015 Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Rare mutations based on very few families with genetic variants of unknown significance are not included. These variants by amino acid change are displayed according to abbreviation. Please note HGVS nomenclature now suggests variants be described as in text (ie, M918T as p.MET918Thr). Frequency of variants in MEN 2/3 and sporadic MTC sourced.

**ENDOCRINOLOGY UPDATE**

## Diagnostics procedures

- Genetic testing
  - laboratory testing
  - tumor markers (Calcitonin, CEA)
  - PTH
  - catecholamines and their metabolites in serum and urine
- Structural imaging
  - MRI (is often employed in structural evaluation for recurrent or metastatic MTC for staging and then for evaluation of treatment response; liver metastasis is best assessed with dedicated MRI)
  - CT is preferred for imaging lymph nodes and lung metastases
- Functional imaging
  - <sup>18</sup>F-DOPA-PET, <sup>18</sup>FDG-PET, <sup>67</sup>Ga-DOTATATE, DOTATOC and DOTANOC
- Histopathology

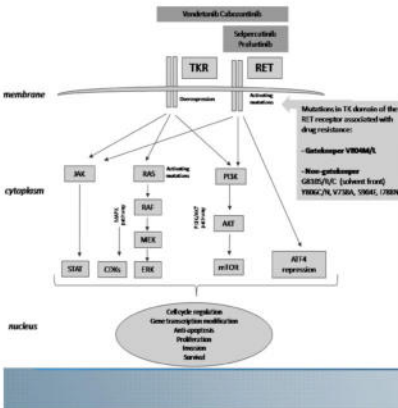
Wells SA et al. *Thyroid* 2015, 25(6): 567-610  
 Conry BG et al. *Eur J Nucl Med Mol Imaging* 210, 37(1): 49-57

Conry BG et al. *Eur J Nucl Med Mol Imaging* 210, 37(1): 49-57

**ENDOCRINOLOGY UPDATE**

Management algorithm for MTC. Dashed line, alternative option; solid line, recommended; USS, ultrasound; Ct, calcitonin; CEA, carcinoembryonic antigen; MKI, multikinase inhibitor; TKI, tyrosine kinase inhibitor; PRRT, peptide receptor radionuclide therapy; CT, computed tomography; MRI, magnetic resonance imaging

**ENDOCRINOLOGY UPDATE**



A comprehensive view of the major signaling pathways involved in MTC tumorigenesis with gatekeeper and non-gatekeeper mutations conferring resistance to MKIs (multikinase inhibitors) and selective RET inhibitors. RET, rearranged during transfection; TKR, tyrosine kinase receptor.

**ENDOCRINOLOGY UPDATE**

## Prognostic factors

- The stage of the disease at diagnosis and the possibility of radical surgical resection are the most important factors in achieving cure in MTC.
- The classical main prognostic factors in MTC are:
  - age,
  - tumor size,
  - local and distant metastases,
  - somatic M918T mutations,
  - calcitonin, and CEA doubling times.

Dabalic N et al. *Acta Clin Croat* (suppl. 1), 2020, 59, 50-59

**ENDOCRINOLOGY UPDATE**

# Management of adrenal incidentaloma – update

Profesor Renata Świątkowska-Stodulska

## Recommendations - radiological imaging

R.1.2.

It is recommended to establish whether the adrenal mass is **benign** or **malignant** at the time of initial assessment.

**Non contrast CT** should be performed as the first radiological imaging and it should answer if the tumor is:

- Homogeneous
- Lipid-rich

As these features are typical for benign lesions.

## Recommendations - multidisciplinary expert team (MDT)

## R.2.3-R.2.6. Imaging work-up in patients with adrenal incidentaloma

Any size, Homogeneous and HU ≤10	Homogeneous and HU 11-20 and Tumor <4cm	Homogeneous, HU 11-20 and tumor ≥4cm or Homogeneous, HU >20 and tumor <4cm or Heterogeneous and tumor <4 cm	Homogeneous, HU >20 and tumor ≥4 cm or Heterogeneous and tumor ≥4 cm
No further imaging required	<ul style="list-style-type: none"> <li>• Immediate additional imaging<sup>1</sup> alternatively</li> <li>• Interval imaging in 12 months (CT, MRI)</li> </ul>	Discuss in MDT meeting. <b>Urgent additional imaging<sup>2</sup></b> (or immediate surgery)	Discuss in MDT meeting, consider <b>proceeding swiftly to surgery<sup>3</sup></b> for further imaging (FDG-PET/CT)

<sup>1</sup> - To avoid any further work-up  
<sup>2</sup> - According to the center expertise and availability: CT, MRI or FDG-PET/CT  
<sup>3</sup> - Before surgical treatment - requires FDG scan of chest, abdomen and pelvis

## Recommendations - hormonal work-up

R.3.1. It is recommended that all patients with adrenal incidentaloma should undergo a **careful assessment**, including a **clinical examination** for symptoms and signs of adrenal hormone excess.

R.3.2. All patients with adrenal incidentaloma are recommended to undergo an overnight 1 mg dexamethasone **suppression test** to exclude autonomous cortisol secretion. (⊕⊕⊕○).

In patients in a poor clinical condition with limited life expectancy, this test may not be warranted.

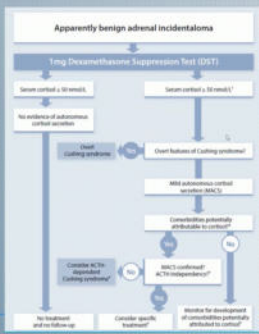
R.3.3. It is recommended to use serum cortisol concentration of **50 nmol/l (1,8 ug/dl)** as a diagnostic criterion for the exclusion of autonomous cortisol secretion (⊕⊕○○).



# Management of adrenal incidentaloma – update

Profesor Renata Świątkowska-Stodulska

## Recommendations - How to diagnose MACS?



- Detailed **physical examination** to exclude specific clinical signs of Cushing's syndrome.
- **Repeat the 1 mg dexamethasone test** to confirm MACS.
- Conditions that alter the result of the 1 mg dexamethasone test should be excluded.
- **ACTH-independence** should be confirmed.
- **Additional biochemical tests** to assess the degree of cortisol secretion could be useful in some cases.
- Look for **comorbidities** potentially attributable to excess cortisol.

ENDOCRINOLOGY UPDATE

## Recommendations - MACS

R.3.8. It is recommended to discuss the option of surgery in patients with MACS and relevant comorbidities in the presence of a unilateral adrenal mass (Ⓟ000).

Factors such as:

- Age
- Sex
- General health
- Severity of the comorbidities (HA, DM, osteoporosis)
- Patients' preference
- Persistence of nonsuppressible cortisol in overnight test
- Degree of cortisol excess

Should be taken into account for clinical decision.

➤ In all cases, the decision to perform surgery should be established within the MDT.

ENDOCRINOLOGY UPDATE

## Recommendations - MACS

- R.4.7. The panel of experts recommended perioperative glucocorticoid treatment in all patients undergoing surgery who cannot achieve complete suppression of cortisol secretion after 1 mg of dexamethasone.
- R.4.4. The panel of experts suggested that patients with MACS (similarly to patients with adrenal Cushing's syndrome) should be followed by an endocrinologist after surgery until the hypothalamic-pituitary-adrenal axis recovers proper function after surgery.

ENDOCRINOLOGY UPDATE

## Recommendations - hormonal work-up

R.3.9. The panel of experts recommended the exclusion of pheochromocytoma by measurement of free metanephrines in plasma or fractionated metanephrines in urine in all patients with an adrenal tumor with features not typical for a benign adenoma (e.g., density greater than 10 HU).

R.3.10. It is recommended that in patients with adrenal lesions and concomitant hypertension and/or unexplained hypokaliemia, the exclusion of primary aldosteronism should be performed using the aldosterone/renin ratio.

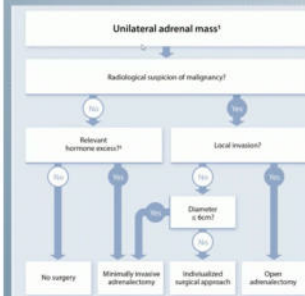
ENDOCRINOLOGY UPDATE

## Recommendations - surgical treatment

R.4.2. The panel of experts recommended against performing surgery in patients with an asymptomatic, nonfunctioning unilateral adrenal mass with radiological features typical of benign tumors (ⓅⓅ00).

ENDOCRINOLOGY UPDATE

## Recommendations - surgical treatment



- R.4.3. If surgery is indicated for a benign adrenal mass causing hormone excess (including MACS), minimally invasive approach is indicated (Ⓟ000).
- R.4.4. The panel of experts suggested that minimally invasive adrenalectomy could be performed in patients with unilateral adrenal masses  $\leq 6$  cm and with radiological findings suspicious of malignancy, but without evidence of local invasion (Ⓟ000).
- R.4.5. Classic adrenalectomy is recommended for adrenal masses with radiological findings suspicious of malignancy and signs of local invasion (Ⓟ000).
- **ALL adrenal surgeries should be performed by an expert high-volume adrenal surgeon!**

ENDOCRINOLOGY UPDATE

# Aggressive pituitary tumours and carcinomas

Professor Miklós Tóth



**ENDOCRINOLOGY UPDATE**  
 Polish-Romanian-Hungarian Scientific Symposium  
 Scientific and Organizational Committee: prof. dr hab. n. med. Beata Kós-Kułyta, prof. dr hab. n. med. Ferenc Erdélyi-Székely  
 Honorary Committee: prof. dr hab. n. med. Andrzej Zieliński, prof. dr hab. n. med. Marek Bolekiewicz  
 10<sup>th</sup>-11<sup>th</sup> October 2024 GDAŃSK  
**Aggressive pituitary tumours and carcinomas**  
 PROF. MIKLÓS TÓTH, MD, PHD

## Aggressive pituitary tumours and carcinomas

Prof. Miklós Tóth, MD, PhD  
 Department of Internal Medicine and Oncology  
 Faculty of Medicine, Semmelweis University

### Prevalence of pituitary tumours

	Expected cases/million
Subclinical cases (autopsy)	100.000
Clinically significant cases	830
Patients requiring surgical intervention	380
Invasive	53
Carcinoma	1

Melmed S et al., Endocrine Reviews, 43, 1003-1037, 2022

### High risk histological subtypes

WHO 2022

- Silent corticotroph tumours
- Lactotroph tumours (especially in males and densely granulated ones)
- Sparsely granulated somatotroph tumours
- Crooke's cell tumours
- Immature PIT-1 plurihormonal tumours
- Acidophil stem cell tumours
- Null cell tumours

### Ki-67 index of aggressive pituitary adenomas and carcinomas

2nd ESE survey

1st ESE survey: 76 + 23 patients first surgery  
 2nd ESE survey: 107 + 43 patients last surgery

McCormack, Eur J Endocrinol, 178, 265-276, 2018  
 Burman P, JCEM, 108, 2019

### Aggressive pituitary tumours

European guideline

We recommend the diagnosis of an aggressive tumour be considered in patients with

1. radiologically invasive tumour and
2. unusually rapid tumour growth rate or clinically relevant tumour growth despite optimal standard therapies

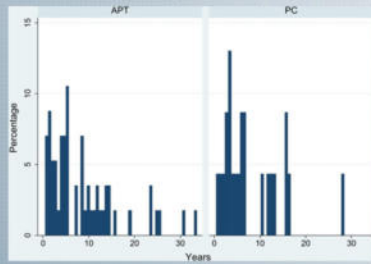
Raverot G és mtsai, Eur J Endocrinol., 178, G1-G24, 2018

# Aggressive pituitary tumours and carcinomas

Professor Miklós Tóth

## Time between first diagnosis and recognition of aggressive behaviour

2nd ESE survey, 97 APT/PC patients

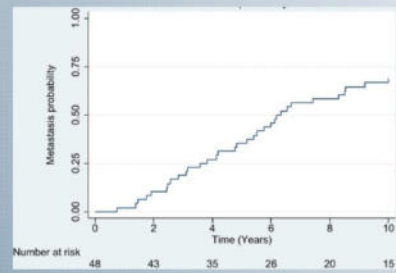


Burman P, EJE, 187: 593-605, 2022  
Burman P, JCEM, 108:1585-1601, 2023

ENDOCRINOLOGY  
UPDATE

## Time from diagnosis of the pituitary tumour to detection of metastasis

2nd ESE survey, 48 pituitary carcinomas



Burman P, EJE, 187: 593-605, 2022

ENDOCRINOLOGY  
UPDATE

## Medical treatment of aggressive pituitary tumours and carcinomas European guideline

Standard medical treatment with maximally tolerated doses

First-line treatment: temozolomide monotherapy (strong recommendation)

First evaluation of treatment after three cycles of TMZ

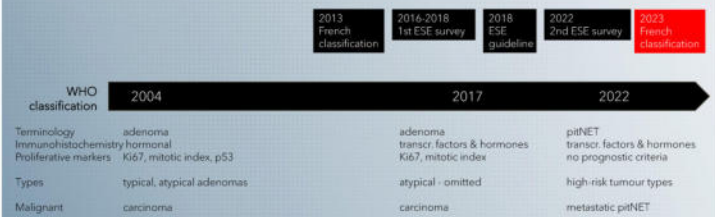
Evaluate MGMT status

In case of rapid progression on TMZ, a trial with other chemotherapy is suggested

Ravenot G és mtsai, Eur J Endocrinol., 178, G1-G24, 2018

ENDOCRINOLOGY  
UPDATE

## Evolution of classification of pituitary tumours



ENDOCRINOLOGY  
UPDATE

European Journal of Endocrinology, 2023, 188, C1-C5  
https://doi.org/10.1093/ejend/ckad002  
Advance access publication 23 March 2023  
Germany

EJE

## Initial pathology in aggressive pituitary tumours and carcinomas: 2b or not 2b? – that is the question

Jacqueline Trouillas, Pia Burman, Marco Lusa, Ann McCormack, Stephan Petersenn, Vera Popovic, Marly Theodoropoulou, Olaf M. Dohkers, and Gerald Raverot

**Table 2.** Comparison of the grades, at the initial surgery, in two surgical cohorts: 365 unselected tumours (cohort 1) and 43 selected APT/PC (cohort 2).

Grades	Cohort 1 of unselected tumours	Cohort 2 of selected tumours**	
		APT + PC	APT / PC
Patients (n)	365	43	23
Grades n (%)			
1a	197 (51.2)	0	0
1b	28 (7.7)	0	0
1b*	3 (0.8)	1 (2.3)	0
2a	118 (32.3)	13 (30.2)	7 (30.4)
2b	12 (3.3)	29 (67.4)	16 (69.5)
2b*	6 (1.6)	16 (37.2)	7 (30)

We recommend that the pathological assessment of pituitary tumours includes the three markers (Ki-67, p53, and mitotic count).

This study highlights the clinical utility of the 5-tiered classification and supports the proposal that grade 2b tumours may be

- "tumours with malignant potential" or
- "malignant tumour without metastases"

Trouillas J et al, Eur J Endocrinol, 188: C1-C5, 2023

ENDOCRINOLOGY  
UPDATE

## When to suspect an aggressive pituitary tumour?

Take home message

- Corticotroph invasive macroadenomas, especially in men
- Macro/giant prolactinomas initially not responding to high doses of cabergoline, or losing sensitivity to dopamine agonists
- Somatotroph invasive macroadenomas progressing on treatment with somatostatin analogues
- Nonfunctioning invasive macroadenomas switching to functioning tumors, especially silent corticotroph tumors (SCTs) becoming adrenocorticotropin (ACTH) secreting
- Rapid relapse/progression after surgical removal
- Tumors progressing after radiotherapy (RT)
- Tumors with high proliferative markers (eg, Ki67 > 10% and/or high mitotic count) and extensive p53 expression
- Tumors harboring TP53 or ATRX mutations

Burman P, JCEM, 108:1585-1601, 2023

ENDOCRINOLOGY  
UPDATE

# Hypogonadism and male health

Professor Zsuzsanna Valkusz

**ENDOCRINOLOGY UPDATE**  
 Polish-Romanian-Hungarian Scientific Symposium  
 Scientific and Organizational Committee: prof. dr hab. n. med. Beata Kobylińska, prof. dr hab. n. med. Bernarda Szepietowska-Stojak  
 Honorary Committee: prof. dr hab. n. med. Marek Szymanski, prof. dr hab. n. med. Marek Dolanowski  
 10<sup>th</sup>-11<sup>th</sup> October 2024 GDAŃSK  
**Hypogonadism and male health**  
 ZSUZSANNA VALKUSZ MD, PHD UNIVERSITY OF SZEGED HUNGARY

## Clinical features of hypogonadism

- Reproductive**
  - sexual dysfunction, infertility, gynaecomastia
- Non-reproductive**
  - Physical:** fatigue, reduced strength & endurance, anaemia, osteoporosis or fracture, vasomotor symptoms.
  - Psychol:** loss of motivation or concentration, irritability, low or labile mood, body shame.

**ENDOCRINOLOGY UPDATE**

## Testosterone and hematopoiesis

**ENDOCRINOLOGY UPDATE**

## Testosterone substitution form and results

HEAT (Hypogonadism in the Aging Male: Efficacy of Testosterone)

**HEAT study concluded that testosterone replacement therapy in older men with hypogonadism is effective in improving sexual function, mood, muscle mass, and metabolic health, with relatively manageable side effects. However, ongoing monitoring for cardiovascular and prostate health is recommended for men undergoing testosterone therapy.**

Study of 1,493 hypogonadal men (average age, 49.2±13.9 years). Patients received up to five testosterone undecanoate injections over 9 to 12 months. Erectile function, libido, vitality, mood, and ability to concentrate were assessed by physician interview. Physical and circulatory parameters as well as hematocrit, glucose control, and lipid profiles were recorded. No cases of prostate Ca observed. Overall mean PSA levels increased from 1.1±0.9 ng/mL to 1.3±1.2 ng/mL and remained stable.

**ENDOCRINOLOGY UPDATE**

## Testosterone and diabetes mellitus

### T4DM study: results – co-primary outcome measures

- TTh + lifestyle intervention significantly reduced the prevalence of T2D vs lifestyle intervention alone in men with low testosterone levels

Men with T2D* after 2 years	TTh + lifestyle program (n=443)	Placebo + lifestyle program (n=413)
	12.4% (n=28)	21.1% (n=87)

**41%** Reduction in T2D prevalence with TTh vs placebo  
 Relative risk (95% CI): 0.59 (0.43 to 0.80); p=0.0007

**ENDOCRINOLOGY UPDATE**

## Optimized Testosterone level

**HIMS-Study**  
 3,690 Men, Age 70-89 Years, Australia (2001-2010)

Mortality vs Testosterone (nmol/l). The graph shows a U-shaped curve where mortality is lowest at approximately 15-20 nmol/l testosterone. The red line represents expected mortality (any cause), and the grey shaded area represents the 95% confidence interval.

**ENDOCRINOLOGY UPDATE**

# Hypogonadism and male health

Professor Zsuzsanna Valkusz

## Testosterone therapy

**Hypogonadism in young men**, due to hypothalamic, pituitary and/or testes damage, is regularly treated with testosterone replacement therapy (TRT) and for long time no reports of increased cardiovascular risk or cardiovascular events has been reported. On the other hand, in the last decades, the prescription of TRT in middle-aged or older men with age-related or obesity-related hypogonadism has highly increased

2010, the *New England Journal of Medicine* published the results of a study conducted on **209 hypogonadal men**, with a **middle age of 74 years**, which were treated with a formulation of testosterone gel for a period of 6 months. The study group, at baseline, presented a high prevalence of mobility limitations, hypertension, diabetes, hyperlipidemia and obesity. The authors concluded that in this population of older men with limitations in mobility and a **high prevalence of chronic disease, the treatment with testosterone was associated with an increased risk of cardiovascular adverse events.**

790 symptomatic hypogonadal older men, treated for 1 year with testosterone gel therapy, shown moderate benefit on sexual function and depression while shown no benefit on mobility.<sup>7</sup> **In this study group the testosterone treatment, given to rise testosterone concentrations from moderately low to the mid-normal range of young men, was not associated with increased cardiovascular risk, however the authors concluded that trial was too small to exclude other than a large increase**

Reuter S, Caviezzo AD, Trivison TG, Heuser TW, Poppo W, Joffe AM, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2014;361:1019-22.  
Snyder PJ, Shores L, Cunningham GR, Matsumoto AM, Slaughter-Stubb AL, Cully JA, et al. Testosterone Treatments Investigator. Effects of Testosterone Treatment in Older Men. *N Engl J Med* 2010;363:1091-102.



## EDITORIAL

# Testosterone replacement therapy in older hypogonadal men: a focus on cardiovascular safety from the TRAVERSE study

Emanuela A. GRECO \*

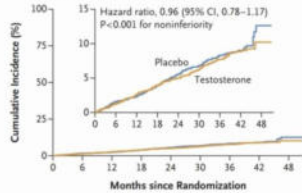
Niccolò Cusano University, Rome, Italy

\*Corresponding author: Emanuela A. Greco, Niccolò Cusano University, Via Don Carlo Gnocchi 3, 00100 Rome, Italy  
E-mail: emanuela.greco@unicusano.it



## Cardiovascular safety endpoint

### CV Death, non-fatal MI, non-fatal Stroke Safety Set Population



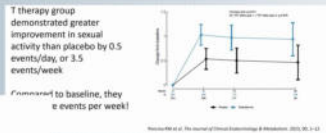
## Tesosteron and Pca

- No difference in incidence of high-grade prostate cancer:
  - 5 of 2596 [0.19%] in the TTh group
  - 3 of 2602 [0.12%] in the placebo group
- No difference in (TTh vs placebo):
  - Incidences of any prostate cancer (12 vs 11)
  - Acute urinary retention (20 vs 16)
  - Invasive surgical procedures (23 vs 12)
  - Prostate biopsy (16 vs 14)
  - New pharmacologic treatment (101 vs 87)

Bhavin et al. *JAMA Netw Open*. 2023 Dec 1;6(12):e2348692



## Traverse on erectile function and sexual activity



- Largest testosterone RCT ever
- Designed to specifically address CV risk and prostate cancer
- No increased CV risk
- No increased PCa risk
- Demonstrated clear sexual and other benefits



## Take home message

Trial	Risks	Benefits
CV	MACE - No	
Prostate	Cancer - No BPH/LUTS - No	
Sexual Function		Libido – Yes ED - No
Depression		Yes
Bone Fracture		No
Anemia		Yes
Diabetes		No



# X-linked hypophosphatemia - a rare cause of short stature

Professor Mihaela Vlad

**ENDOCRINOLOGY UPDATE**  
Polish-Romanian-Hungarian Scientific Symposium

Scientific and Organizational Committee  
prof. dr hab. n. med. Beata Kobylińska  
prof. dr hab. n. med. Simona Endreanovici-Stodulescu

Honorary Committee  
prof. dr hab. n. med. Ioana Zeman  
prof. dr hab. n. med. Marek Bolanowski

10<sup>th</sup>-11<sup>th</sup> October 2024 **GDAŃSK**

**X-Linked Hypophosphatemic Rickets  
A Rare Cause of Short Stature**  
MIHAELA VLAD, CARMEN DOROGI

\*"Victor Babeș" University of Medicine and Pharmacy, Timisoara, Romania  
\*\*"Psih Severus" Emergency County Hospital, Timisoara, Romania

## Introduction

- X-linked hypophosphatemic rickets (XLH) is a very rare cause of growth deficiency, usually diagnosed in childhood.

The mutation of the PHEX gene in these patients causes higher levels of FGF-23 and hypophosphatemia.

**ENDOCRINOLOGY UPDATE**

## Patients information

	Case 1 S.G.	Case 2 A.R.	Case 3 A.D.
Admission date	21.09.2022	24.10.2022	13.12.2023
Gender	F	M	F
Age	43 yo	20 yo	55
Height	Ht=139 cm	Ht=156 cm	Ht=131 cm
Residence	Bucovat, Timis county	Timisoara, Timis county	Timisoara, Timis county
Occupation	Disability retirement	Worker in the food industry	Housekeeper

**ENDOCRINOLOGY UPDATE**

## Family tree

**ENDOCRINOLOGY UPDATE**

## Patient history – Case 1, S.G., fem.

Childhood: Undocumented growth deficit

2009 (30 yo): Pituitary Dwarfism

2019 (40 yo): Achondroplastic Dwarfism

Sept. 2022 (43 yo): Routine Check-up

Dec. 2022 (43 yo): XLH diagnosis, Conventional therapy started

Persistent hypophosphatemia

**ENDOCRINOLOGY UPDATE**

## Patient history – Case 2, A.R., male

2004 (2 yo): Dx: Familial hypophosphatemic vitamin D resistant rickets

From 5 yo (2008) To 7 yo (2010): Alpha D3 0.5 mcg/day + P rich diet

Sept. 2022 (20 yo): Presentation in adult Endocrinology department

Nov. 2022: XLH diagnosis

May 2023: Burosumab was started

Current treatment: Alpha D3 1 mcg/day + 1.5 g P/day, Divided in 3 doses

**ENDOCRINOLOGY UPDATE**


\*Case 2 is the nephew of case 1, he came to our clinic after the diagnosis of case 1.  
\*\*Case 3 had no medical records and was never investigated for growth deficit. She is the sister of case 1 and the mother of case 2.

# X-linked hypophosphatemia - a rare cause of short stature

Professor Mihaela Vlad


### History taking

XLH	Case 1	Case 2	Case 3
Muscle pain	✓	✓	✓
Joint pain	✓	✓	✓
Lower limbs more affected	✓	✓	✓
Headache	✓	✗	✗
Family history	✓	✗	✗

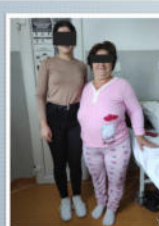


### Physical examination


XLH	Case 1	Case 2	Case 3
Short stature	Ht= 139 cm	Ht= 156 cm	Ht= 131 cm
Gait abnormalities	Waddling gait	Waddling gait	Waddling gait
Bone deformities (genu varum /valgum)	Intercondylar distance = 4 cm	Intercondylar distance = 10 cm	Intercondylar distance = 12 cm
Dental problems	✓	✓	✓
Hearing loss	✗	✗	✓
Signs of IH	✗	✗	✗




Case 1



Case 1 with her daughter (who doesn't have XLH)



Case 2





Case 1



Case 2




### Laboratory results

FEPO4 = [PO<sub>4</sub> (Urine) \* Creatinine (Serum)] / [PO<sub>4</sub> (Serum) \* Creatinine (Urine)] \* 100


XLH	Case 1	Case 2	Case 3	Normal range
Serum P	Low	<b>2.4</b>	<b>1.8</b>	2.5 - 4.9 mg/dl
Serum Ca	N	9	9.1	8.6-10 mg/dl
Serum Cr	N	0.6	0.6	0.6-1.3 mg/dl
iPTH	N	35.9	57.8	97.1
Bone ALP	High	<b>18.9</b>	<b>14.52</b>	4.5-16.9 mcg/L
25 (OH) VitD	N	29.75	<b>4.98</b>	30 - 100 ng/mL
1,25 (OH) <sub>2</sub> VitD	N/Low	<b>42.8</b>	<b>25.30</b>	25-86.6 pg/ml
Urinary Ca (24 h)	N/Low	123	86.4	257.40
Urinary P (24 h)	N/ high	0.62	1.065	1.06
FePO4	N/ high	<b>12.14%</b>	<b>24%</b>	13%
FGF-23		<b>146</b>	<b>73</b>	26-110 kRU/10

\*All other causes for short stature and growth deficiency were excluded.  
\*\* Case 3 had normal phosphate levels and severe vitamin D deficiency on the first evaluation.




### Radiology


Case 1




Case 2





Case 3





### Genetic test result Case 1







### Treatment follow-up

	Case 1 (conventional treatment)		Case 2 (burosumab)				Case 3 (conventional treatment)		Values range
	Before treatment	1 year	Before treatment	1 month	4 month	1 year	Before treatment	5 month	
Serum P	<b>2.4</b>	<b>2</b>	<b>1.8</b>	2.8	<b>2.2</b>	3.5	2.8	<b>2</b>	2.5 - 4.9 mg/dl
Serum Ca	9	<b>8.2</b>	9.3	9.3	10.4	9.1	8.6	8.7	8.6-10 mg/dl
iPTH	35.9	42.9	57.8	76.8	80.2	61.9	<b>97.1</b>	<b>109</b>	13.6- 85.8 pg/mL
Serum Cr	0.6	0.6	0.7	0.6	0.8	0.8	0.6	0.67	0.6- 1.2 mg/dl
Bone ALP	<b>18.9</b>	12.3	<b>14.52</b>			31.7	<b>4.98</b>	<b>13.27</b>	4.5-16.9 mcg/L
25 (OH) VitD	29.75	40.2	<b>42.8</b>			72.5	<b>4.98</b>	<b>13.27</b>	30 - 100 ng/mL
1,25 (OH) <sub>2</sub> VitD	42.8		<b>25.30</b>						25-86.6 pg/ml
Urinary Ca (24h)	123	291	86.4	<b>165</b>	<b>151</b>		257.40	238	42.353 mg/24h
Urinary P (24h)	0.62	0.63	1.065	<b>1.5</b>	<b>1.6</b>		1.06	<b>1.53</b>	0.4-1.3 g/24h


\*In case 1, the levels of bone-specific alkaline phosphatase normalized despite the continued low levels of serum phosphate.  
\*\*In case 2, both serum phosphorus and 1,25 OH vitamin D, normalized under treatment with burosumab.  
\*\*\*Case 3 presented with a severe vitamin D deficiency with initially normal phosphate levels. After conventional treatment, it was observed that as the level of 25 OH vitamin D increased, serum phosphate levels decreased and urinary phosphate excretion increased.



### Take home messages



- Being so rare, XLH as a cause of short stature can be easily overlooked.
- X linked - hypophosphatemia rickets can be **diagnosed** even in adulthood.
- Any patient with **undocumented** short stature **should be investigated**, regardless their age.
- There are newly approved medication for XLH that can also be prescribed for **adults** patients.
- In this cases, although the diagnosis was **late**, it can change the quality of patient's life and the life of **future generations**.



# Thyroid cancer and toxic adenoma

Professor Ioana Zosin

**ENDOCRINOLOGY UPDATE**  
Polish-Romanian-Hungarian Scientific Symposium  
Scientific and Organizational Committee: prof. dr hab. n. med. Beata Kozłowska, prof. dr hab. n. med. Renata Szepielowska-Stodulka  
Honorary Committee: prof. em. dr hab. n. med. Ioana Zosin, prof. dr hab. n. med. Marek Dolanowski  
10<sup>th</sup>-11<sup>th</sup> October 2024 GDAŃSK  
Title: **THYROID CANCER AND TOXIC ADENOMA**  
NAME: Prof. Dr. IOANA ZOSIN

**Title**  
**THYROID CANCER AND TOXIC ADENOMA**  
Prof. Dr. IOANA ZOSIN  
University of Medicine and Pharmacy  
„Victor Babeș” Timișoara/ROMANIA  
ENDOCRINOLOGY UPDATE

**Introduction**

- Thyroid carcinoma coexisting with hyperthyroidism represents an uncommon occurrence, as low TSH levels can suppress the development and growth of thyroid carcinoma cells.
- Thyroid nodules (TN) are common in clinical practice and approx. 95 % are benign. Thyroid cancer (TC) is usually diagnosed in a clinically euthyroid nodule with “cold” scintigraphic appearance.
- Autonomously hyperfunctioning nodules, representing approx. 5-10 % of all TN, are generally benign. However, an increasing number of thyroid hot nodules has been reported to own a malignancy risk. Different studies showed that hyperfunctioning thyroid carcinomas may present as autonomous functioning thyroid nodules (AFTN) or as functioning lesions in metastatic foci.

ENDOCRINOLOGY UPDATE

**Hot Nodule Harboring a Thyroid Carcinoma (I)**

- The first reported case, a 68-year-old male, presented thyrotoxicosis and a nodular goiter. He issued from a geographical area with former iodine deficiency.
- Thyroid function tests (TFT) revealed clinical thyrotoxicosis. Thyroid ultrasonography (USG) visualized a single nodule (hypoechoic, mainly solid) in the right thyroid lobe (RTL).
- Thyroid scintigraphy highlighted an abnormal high uptake of radioiodine in the nodule, with uptake suppression in the rest of gland, suggestive for a toxic adenoma.
- Therapeutical attitude was represented by right thyroid lobectomy after drug euthyroidization. The postoperative histological evaluation emphasized a papillary thyroid carcinoma, follicular variant (PTCFV). The patient underwent total thyroidectomy. No ablative radioiodine therapy was necessary. There were not diagnosed distant metastases by means of radioactive whole-body scan.

ENDOCRINOLOGY UPDATE

**Hot Nodule in the RTL, Harboring a Thyroid Carcinoma (II)**

RI, male, 68 years  
RTL nodule  
Scintigraphy Tc 99  
RTL nodule Doppler

ENDOCRINOLOGY UPDATE

**Prevalence of Toxic Adenoma Associated with Thyroid Carcinoma**

- The data regarding the prevalence of intranodular thyroid carcinoma in patients undergoing resection of a solitary hyperfunctioning nodule are scarce and heterogenous.
- A summarization of 14 studies (1967-2008) found a prevalence of malignancy in hot nodules of 3.1 %. More recent surveys, reported increased prevalences: 12 %, 19 % and even 22 %. The differences between studies are related to selection of patients: for the operation, type of operation, histological examination, geographical differences, etc.
- The main histological subtypes of thyroid cancers associated with autonomous adenomas are: papillary thyroid carcinomas (57%), follicular thyroid carcinomas (36.4 %) and Hürthle cell carcinomas (7.8 %). Medullary and anaplastic cancers were also reported.

ENDOCRINOLOGY UPDATE



# Thyroid cancer and toxic adenoma

Professor Ioana Zosin

## Presumed Distinctive Features of Malignant Hot Nodules and Opportunity of Cytological Examination (FNAB)

- Demographical data show a higher prevalence of this association in younger patients and in women. Important clinical data are represented by family history of different thyroid cancers, history of head and neck irradiation, some clinical peculiarities (rapid growth of the nodule, cervical adenopathy, different compressive signs).
- Thyroid USG has a controversial use. Thyroid scintigraphy with an incomplete suppression of isotope uptake in the extranodular parenchyma is more often observed in malignant cases. The degree of autonomous hyperfunction is variable and malignant nodules may not produce sufficient amounts of thyroid hormones (TH), to suppress TSH.
- FNAB is not traditionally recommended by different academic societies guidelines (ATA, AACE/AME/ETA), because of exceptionally low rate of malignancy in toxic adenomas.

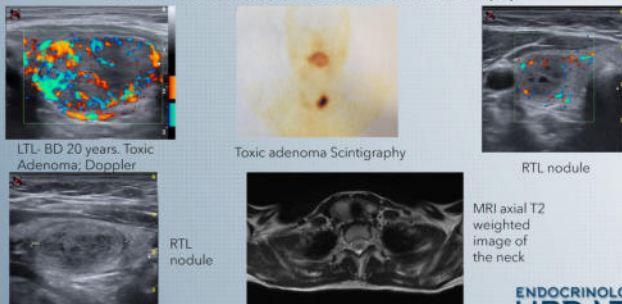
ENDOCRINOLOGY  
UPDATE

## Hot Nodule in the LTL, Thyroid Carcinoma in the Contralateral Lobe Second Case (I)

- The second case was represented by a young female patient with thyrotoxicosis and a left TN. USG revealed a hypoechoic solid nodule. Scintigraphically, the nodule was a „hot“ one. In the RTL, two small cysts were visualized. The patient was no more evaluated 2 years because of COVID pandemia.
- At the beginning of 2022, in the RTL USG found a large nodule (30/16/21mm), without clear malignant traits. A RMN examination did not show mass effects or local lymphadenopathies (laterocervical, submandibular, supraclavicular).
- The morphopathological examination established the diagnosis of a thyroid carcinoma poorly differentiated, of insular type (pT2, Nx, L-V0, Mx, R0). After total thyroidectomy, radioactive iodine was administered, followed by whole body scan (PET CT) and thyroxine.

ENDOCRINOLOGY  
UPDATE

## Hot Nodule in one Thyroid Lobe (LTL), Thyroid Carcinoma in the Contralateral Lobe (II)



LTL- BD 20 years. Toxic Adenoma; Doppler

Toxic adenoma Scintigraphy

RTL nodule

RTL nodule

MRI axial T2 weighted image of the neck

ENDOCRINOLOGY  
UPDATE

## Morphopathological Examination of Case 2

- Macroscopically, in the RTL it was seen a tumoral mass with a diameter of about 3.0 cm, with bosselated contour, well demarcated and encapsulated.
- Microscopically, the tumor showed a dense cellularity. Tumoral cells are small and monomorphic with reduced cytoplasm and round or oval nuclei. Atypical mitotic activity and tumoral necrosis were noticed.
- The tumoral growth has an insular pattern (solid cellular nests). At the tumoral periphery there were observed areas with well-differentiated thyroid carcinoma (papillary carcinoma, follicular variant); some nuclei are papillary carcinoma-like (convolute), expression of dedifferentiation process of an adjacent papillary carcinoma.
- Tumoral capsular invasion is limited and no tumoral emboli are noticed.

ENDOCRINOLOGY  
UPDATE

## Insular Carcinoma of the Thyroid

- Insular thyroid carcinoma (ITC) is a rare histiotype of thyroid malignancy, with intermediate characteristics between well-differentiated and anaplastic carcinomas, in respect to its morphologic, biologic, and clinical behaviour.
- ITC is considered an entity of PDTC (Poorly Differentiated Thyroid Carcinomas), a group which includes tumoral aggressive carcinoma subtypes: insular, trabecular, solid cancers. The aggressive course of ITC is represented by local recurrences or distant metastases.
- Total thyroidectomy with nodal resection (for lymph node disease) represents the cornerstone of the treatment approach, even in cases with distant metastases. Radioiodine exceeds 80 % in the initial stages even in metastatic cases and has benefic effects.

ENDOCRINOLOGY  
UPDATE

## Final Remarks

- The possibility of diagnosing a malignant tumor in a hot nodule must be considered in clinical practice. However, as the incidence of hyperfunctioning thyroid carcinoma is very low, the diagnosis may be delayed, and the subsequent choice of treatment may be unsuitable. The criteria of malignancy in a toxic adenoma are controversial and relative.
- A relation between a toxic nodule in a thyroid lobe and a cancer in the contralateral is very difficult to establish. The reported association may be a fortuitous one. The diagnosed thyroid cancer, ITC, is a rare one, presenting an aggressive course.
- These reported cases reveal that thyroid toxic adenoma is not always an innocent disease and that thyrotoxicosis is no insurance against thyroid cancer.

ENDOCRINOLOGY  
UPDATE