BOOK OF ABSTRACTS

ENDOCRINOLOGY UPDATE

Polish-Romanian-Hungarian Scientific Symposium

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prof. dr hab. n. med. Beata Kos-Kudła
prof. dr hab. n. med. Renata Świątkowska-Stodulska

Honorary Committee
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10TH – 11TH OCTOBER 2024

GDANSK

SympoMed
konferencje medyczne

WYDARZENIE INFARMA 8572 CERTYFIKOWANE

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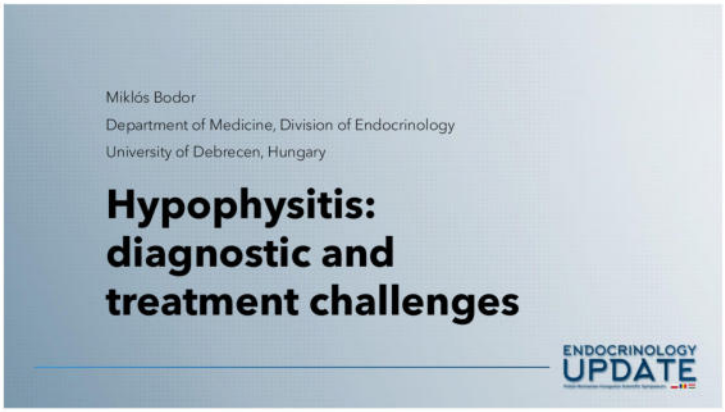
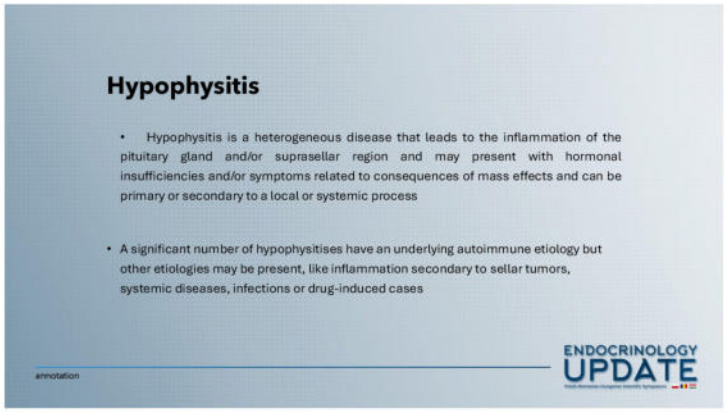
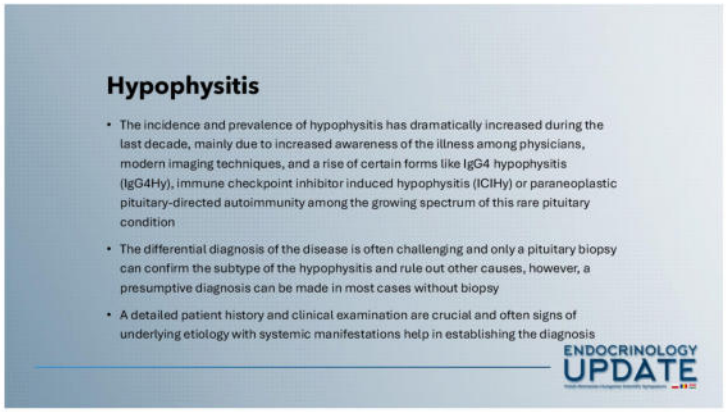
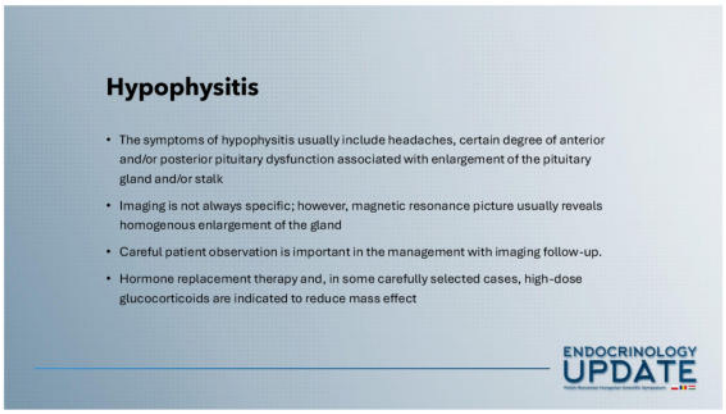
Hypophysitis: diagnostic and treatment challenges

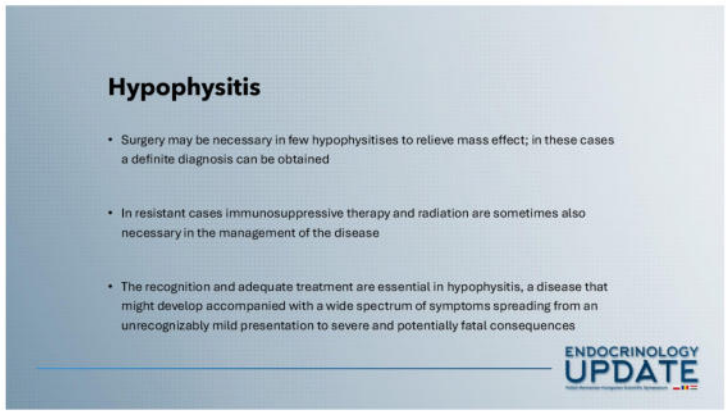
Professor Miklós Bodor





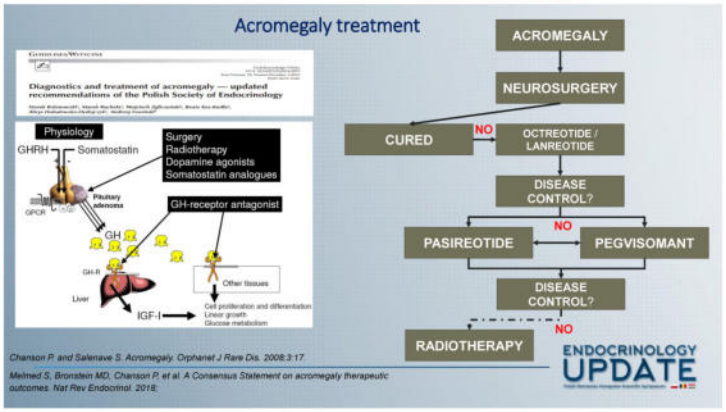


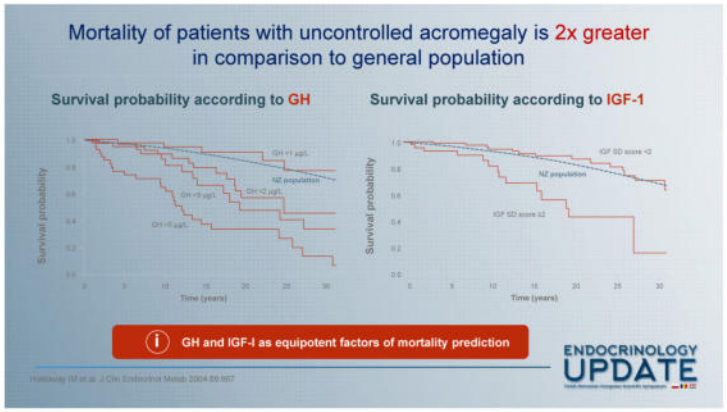


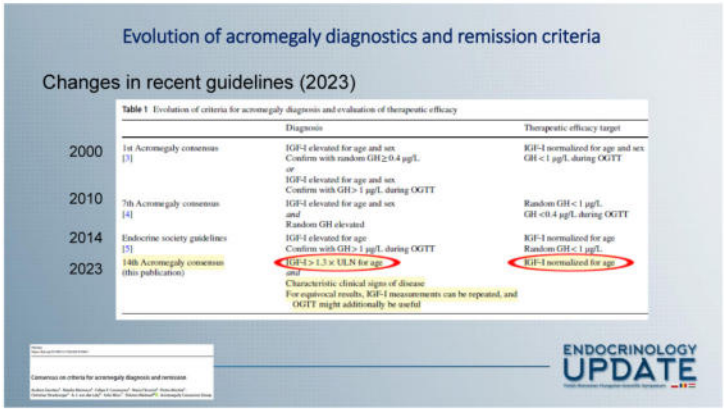


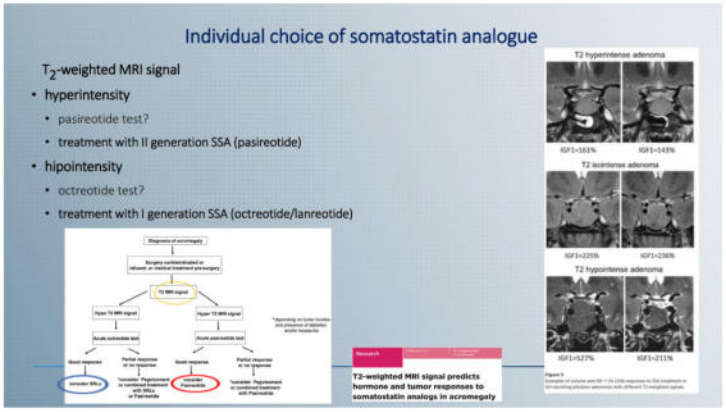
How can we improve the management of our patients with acromegaly and Cushing's disease?

Profesor Marek Bolanowski









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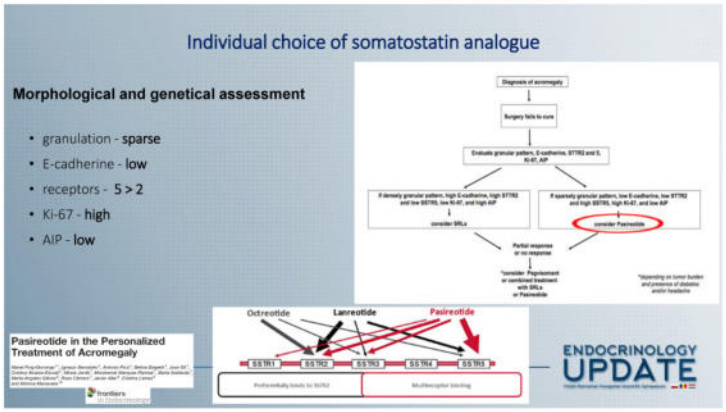
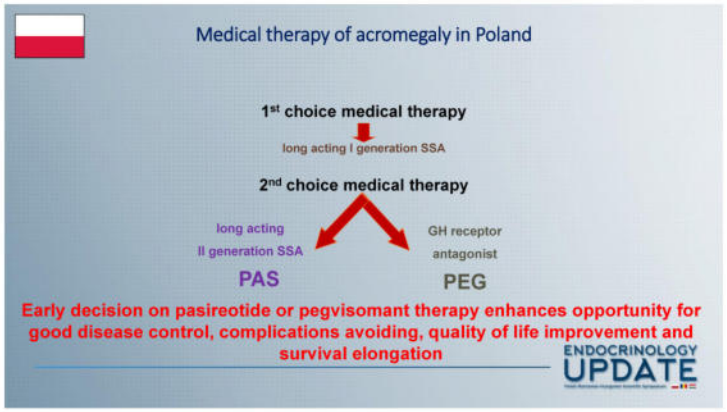
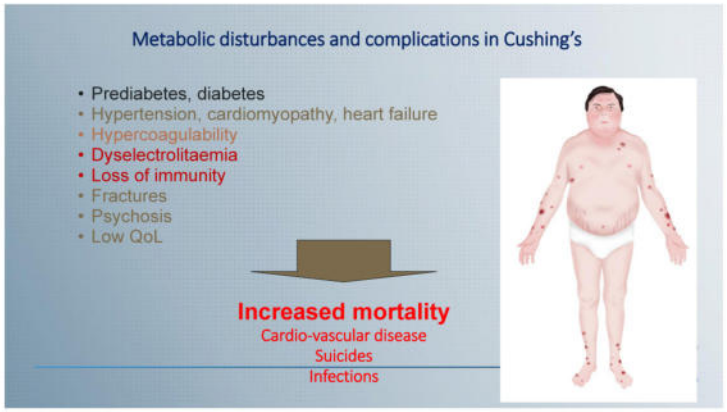
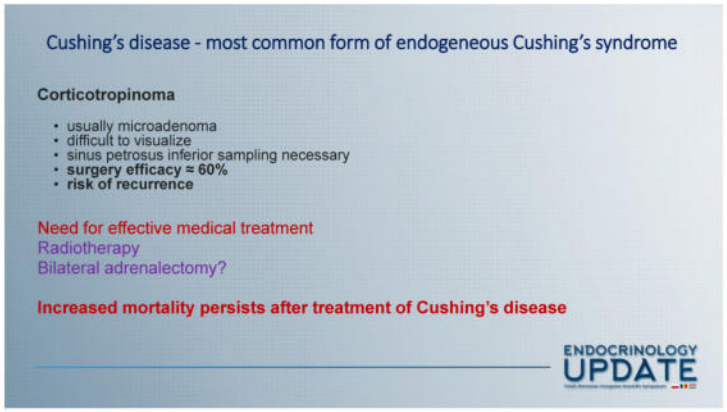
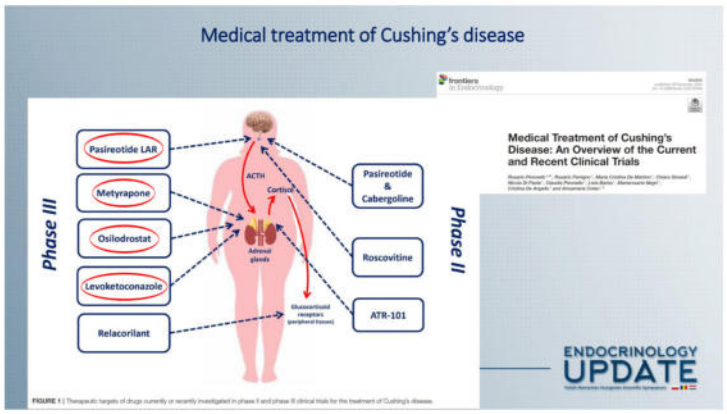
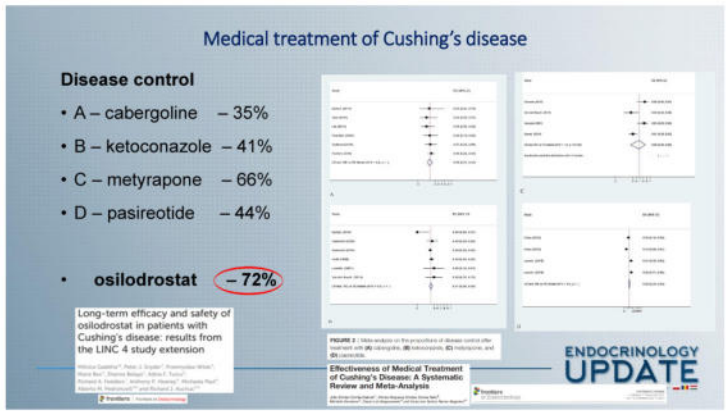






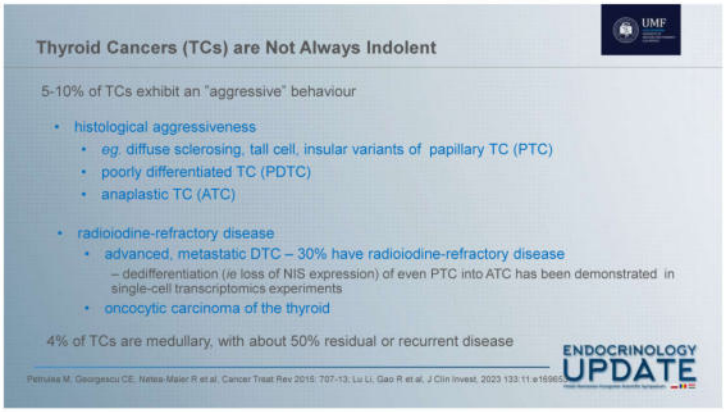


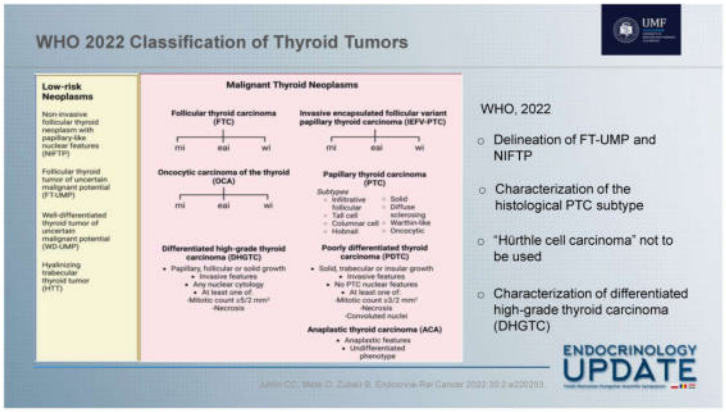


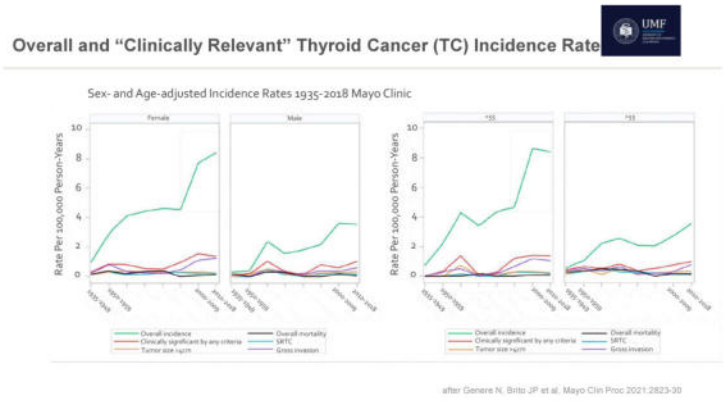


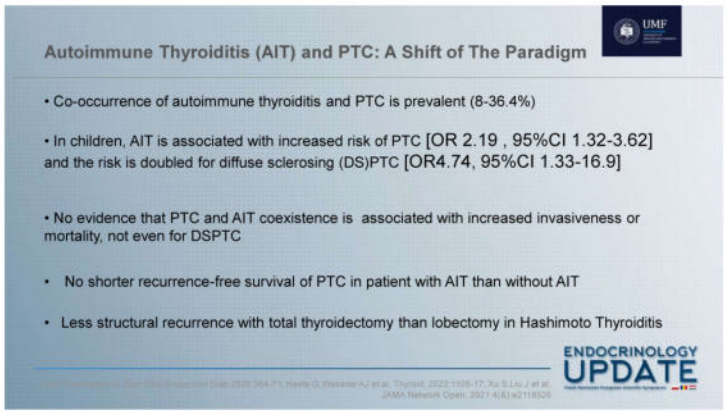
Thyroid (auto)immunity and thyroid cancers

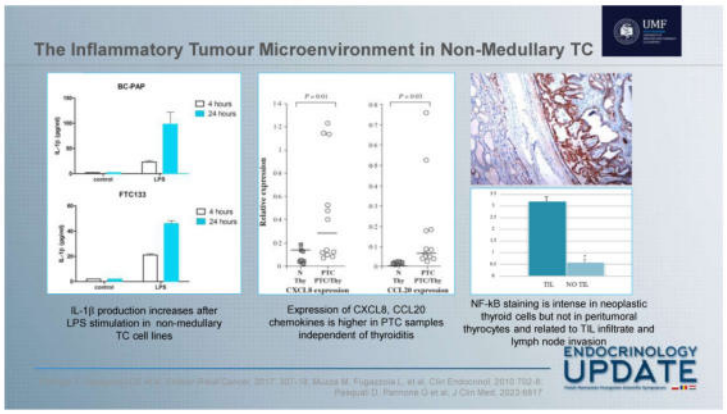
Professor Carmen Georgescu











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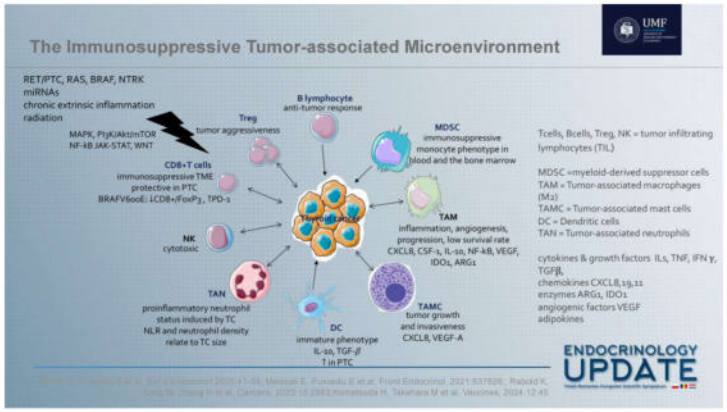
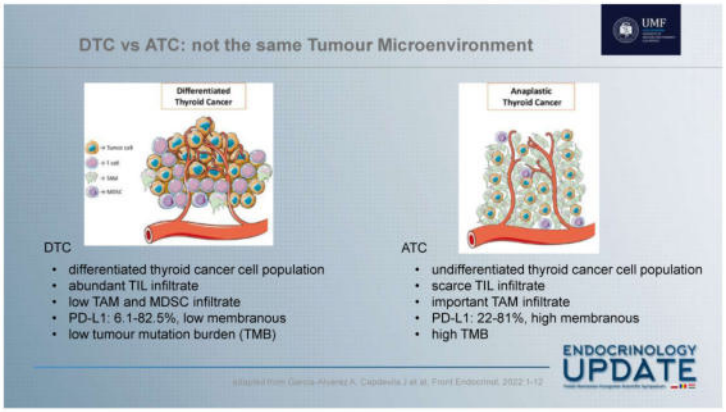
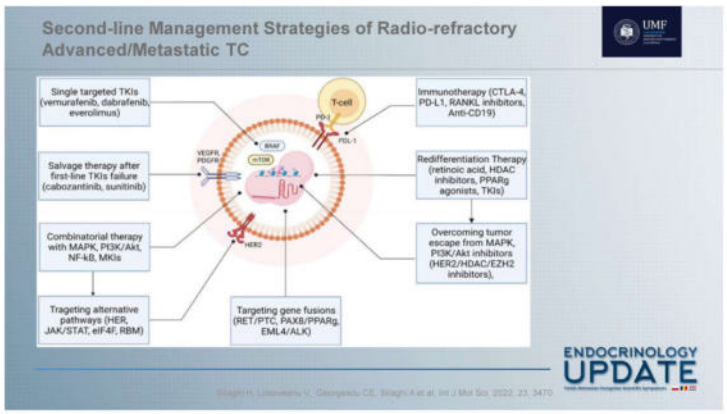
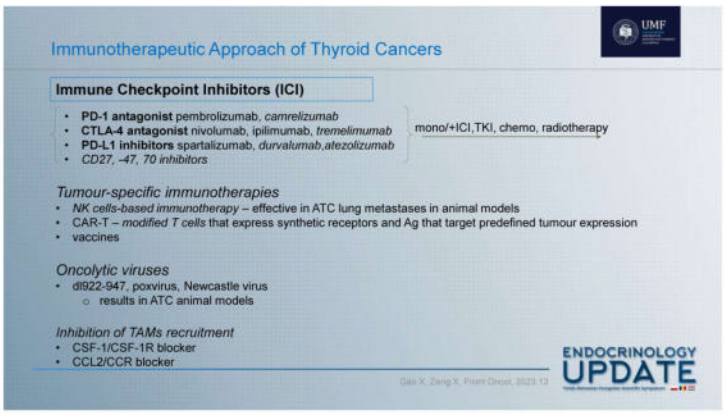


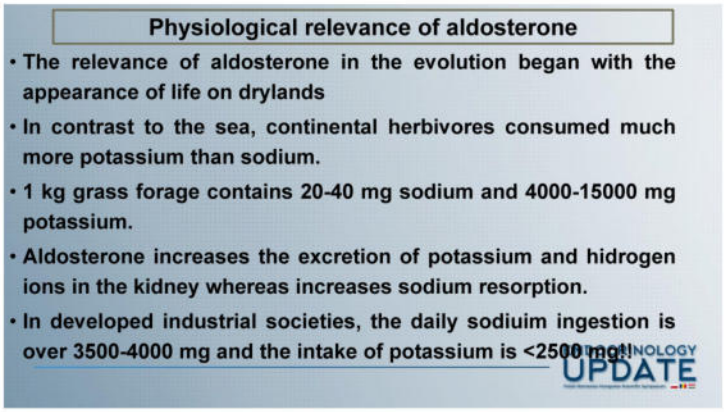


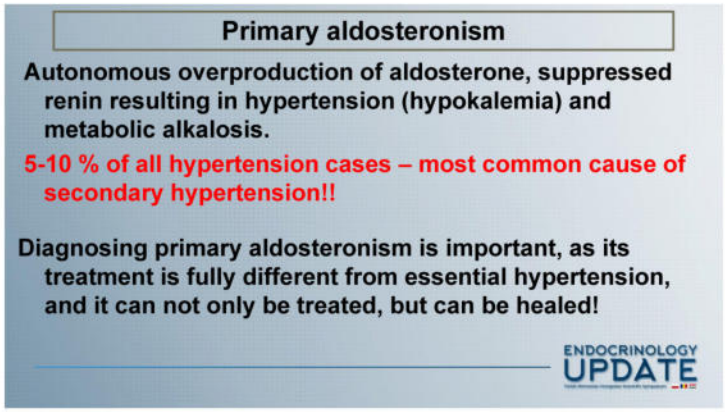


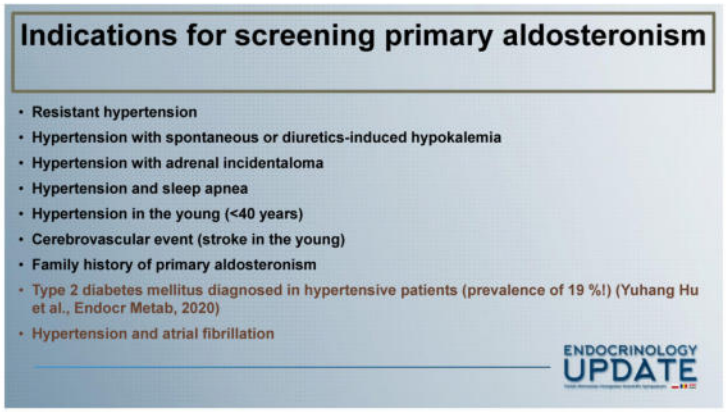


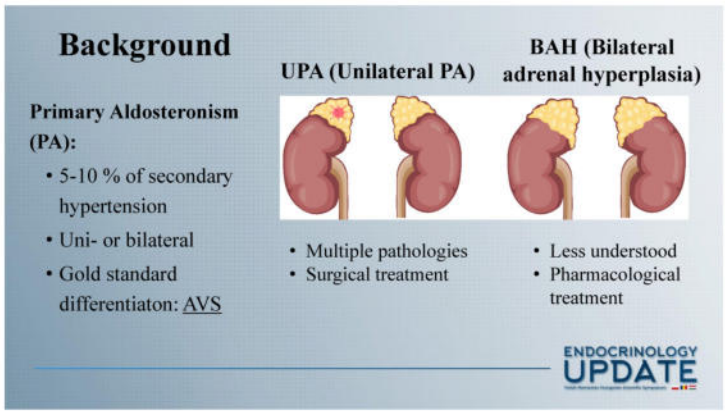
Recent Advances in Primary Aldosteronism

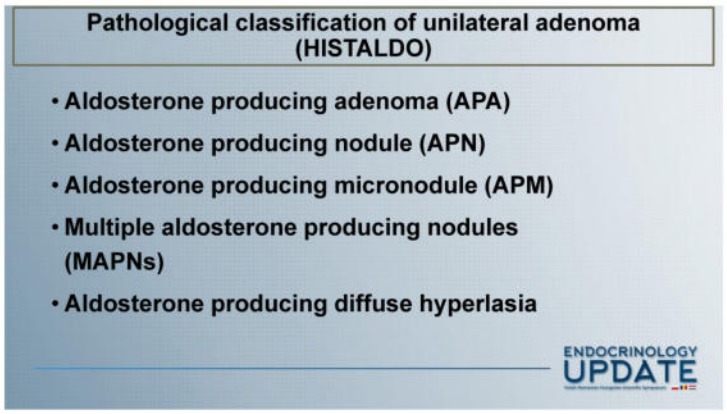
Professor Péter Igaz











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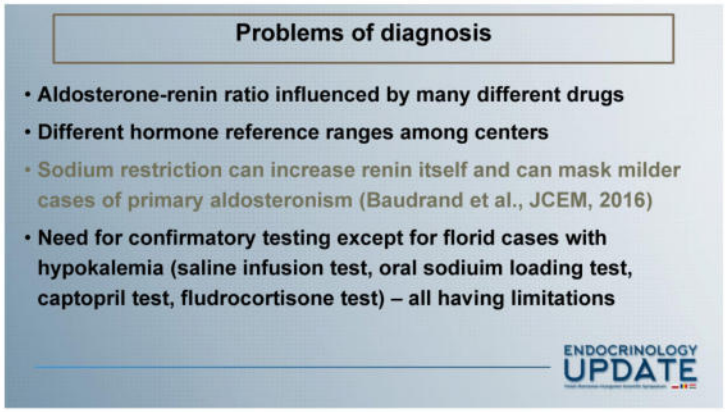
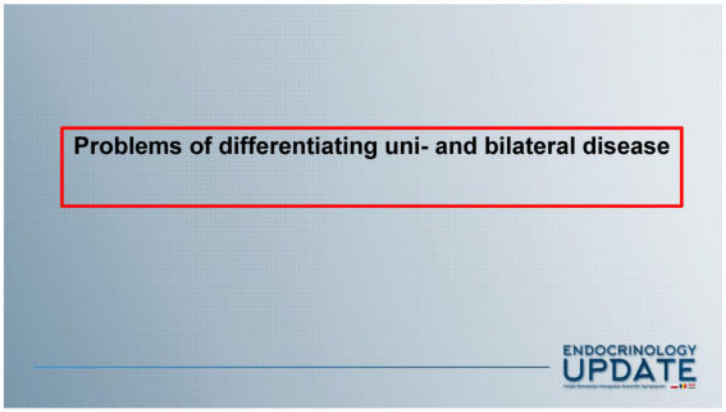
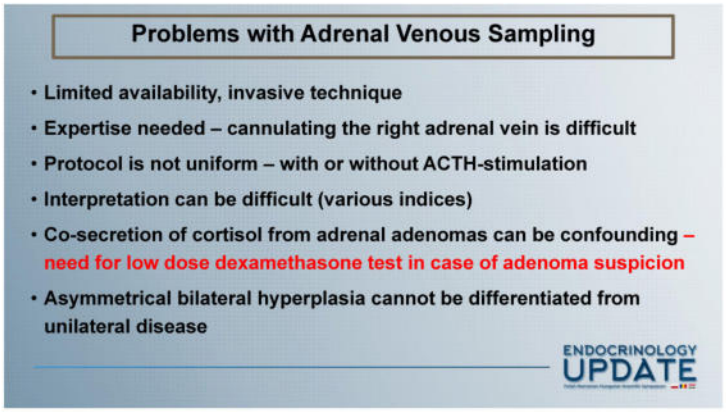
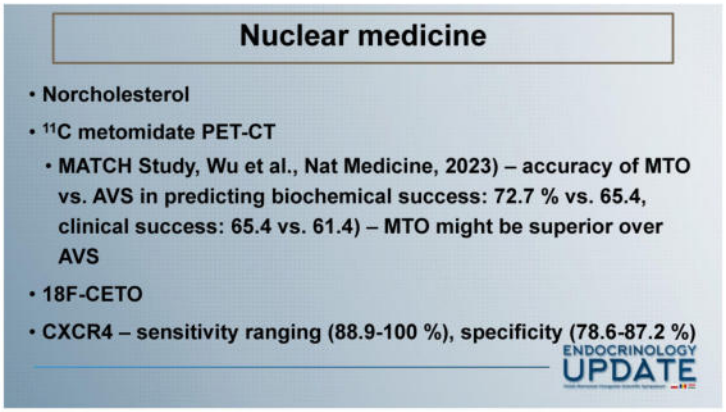
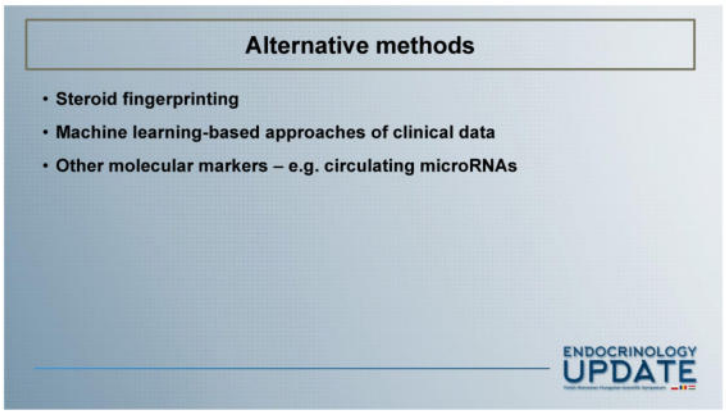
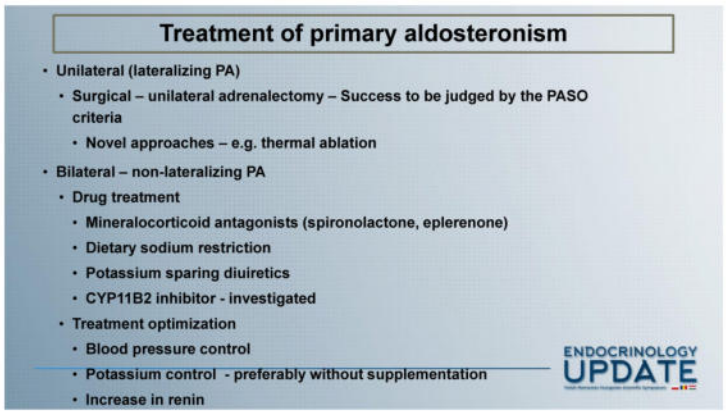






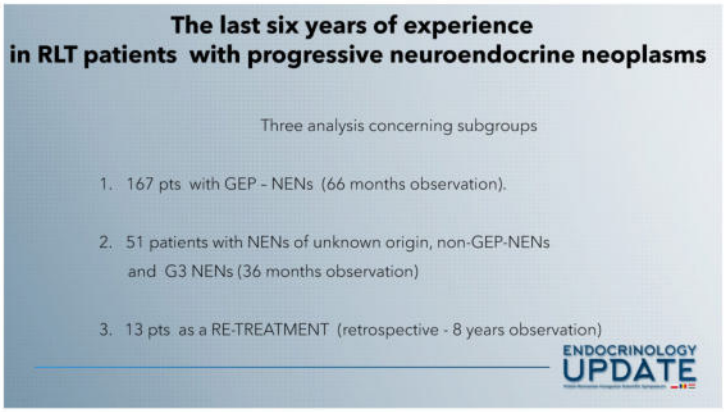


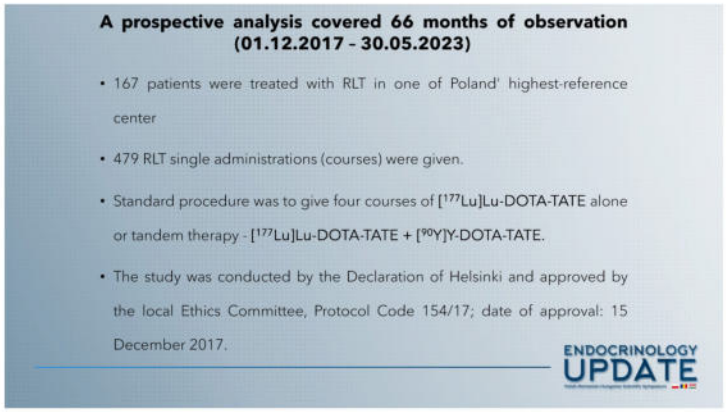


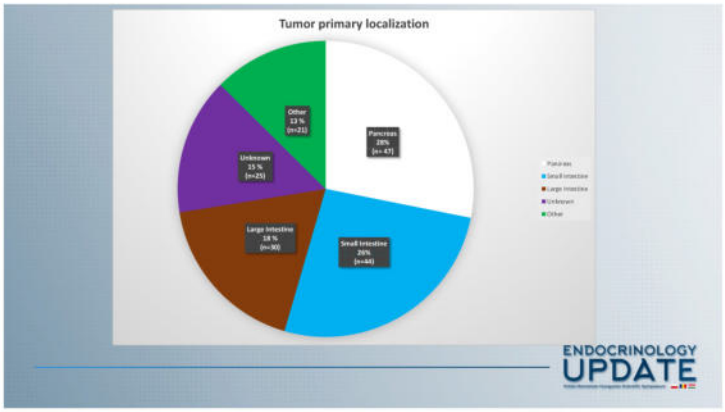


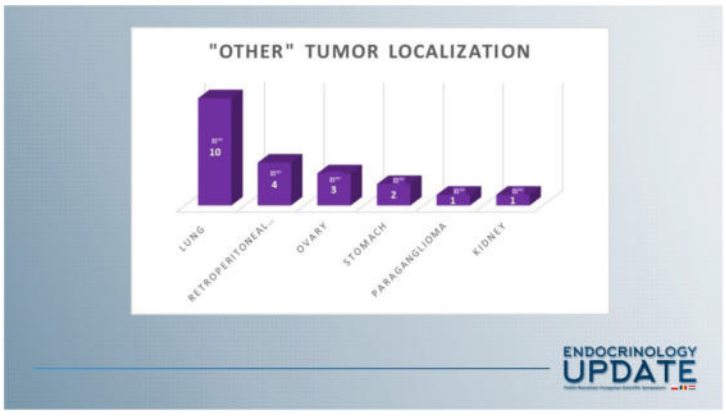
The last six years of experience in radioligand therapy of progressive neuroendocrine neoplasms

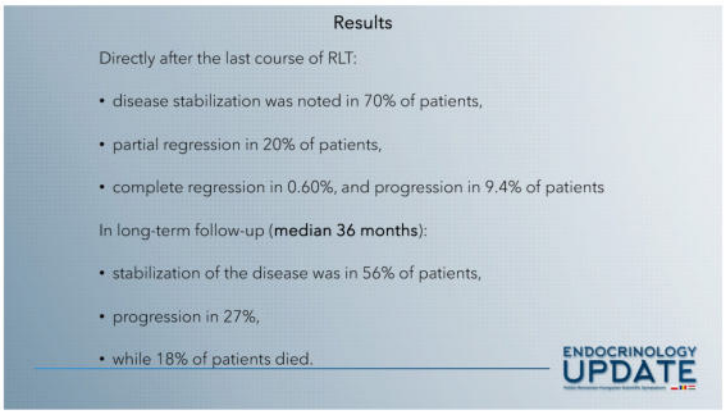
Prof. dr hab. n. med. Grzegorz Kamiński







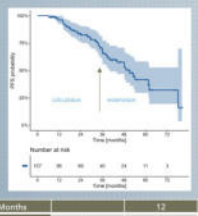


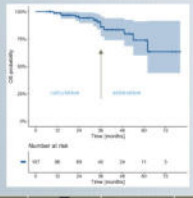


The last six years of experience in radioligand therapy of progressive neuroendocrine neoplasms

Prof. dr hab. n. med. Grzegorz Kamiński

PFS and OS probability – Kapplan-Meyer estimation
*(median OS was not reached)





Months		12	24	36	48	60
PFS	%	96.1	82.4	69.6	57.5	41.5
	CI 95%	(92.4, 99.9)	(75.2, 90.4)	(55.6, 77.3)	(46.7, 70.9)	(29.6, 58.3)
OS	%	99.0	94.3	86.0	83.5	74.0
	CI 95%	(97.1, 100.0)	(89.5, 99.3)	(77.5, 95.5)	(74.1, 94.1)	(60.0, 91.2)

ENDOCRINOLOGY UPDATE

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

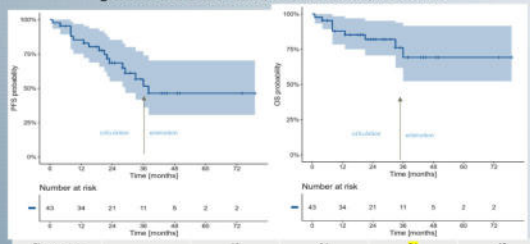
- In subgroups of patients with unknown tumor localization,

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 ^{177}Lu and 16 pts received ^{177}Lu + ^{90}Y

ENDOCRINOLOGY UPDATE

RLT of 51 patients with NENs
of unknown origin, non-GEP-NENs, and with G3
grade **LONG THERM (36 MONTHS)** RESULTS



Characteristic		12	24	36	48
PFS	%	85.3	68.5	51.5	46.4
	CI 95%	(75.1, 96.9)	(55.0, 85.2)	(36.0, 73.8)	(30.6, 70.2)
OS	%	87.8	82.0	69.2	69.2
	CI 95%	(78.4, 98.4)	(70.6, 95.2)	(52.3, 91.5)	(52.3, 91.5)

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

Prof. dr hab. n. med. Grzegorz Kamiński

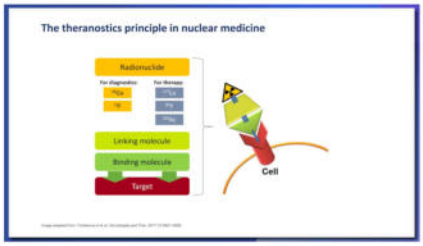
Lutetium-177 (177Lu)-dotatate - Polish experience after 2 years of reimbursement under Drug Program B.139. Polish Patient Registry

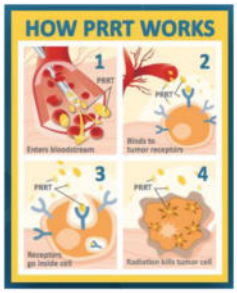
prof. Grzegorz Kamiński,
Department of Endocrinology and Radioisotope Therapy, Military Institute of Medicine – National Research Institute, Warsaw, Poland

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.

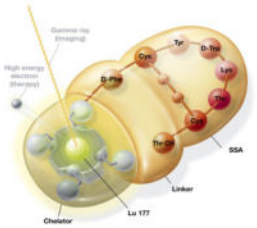




structure of the 177Lu oxodotreotide[1]

- 177Lu oxodotreotide is used in radioisotope therapy with somatostatin analogues (PRRT)
- 177Lu oxodotreotide consists of the radionuclide lutetium bound to a peptide 177Lu 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[2]



milestones in RLT in Poland

1990s [^{111}In]-DTPA^{0}-octreotide — Auger electrons

EARLY 21st century [^{90}Y]-DOTA^{0}-Tyr^{3}-octreotide — pure beta emitter

[^{177}Lutetium]-DOTA^{0}-Tyr^{3}-octreotate — beta and gamma emitter

January 2018 **FDA approves new treatment for certain digestive tract cancers** — Lutetium (^{177}Lu) oxodotreotide

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 [^{177}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 [^{68}Ga]Ga-DOTATATE or SPECT/CT with [^{99m}Tc]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.

WOJSKOWY INSTYTUT MEDYCZNY

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

WOJSKOWY INSTYTUT MEDYCZNY

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)

WOJSKOWY INSTYTUT MEDYCZNY

Polskie Towarzystwo Endokrynologiczne

Polska Sieć Guzów Neuroendokrynnych

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

Registry

WOJSKOWY INSTYTUT MEDYCZNY

Polskie Towarzystwo Endokrynologiczne

Polska Sieć Guzów Neuroendokrynnych

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

WOJSKOWY INSTYTUT MEDYCZNY

Polskie Towarzystwo Endokrynologiczne

Polska Sieć Guzów Neuroendokrynnych

Polish Patient Registry

6 research centers participate in the Registry

Expert Meetings

December 2023 – Toruń
April 2024 – Katowice

October 2024 – on-line

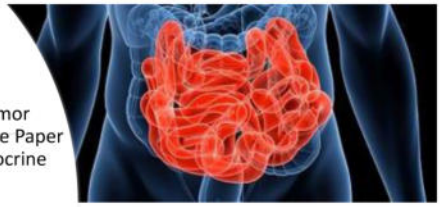
SKOWY INSTYTUT MEDYCZNY

THANK YOU

WOJSKOWY INSTYTUT MEDYCZNY

New insights in neuroendocrine tumors therapy

Prof. dr hab. n. med. Beata Kos-Kudła



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

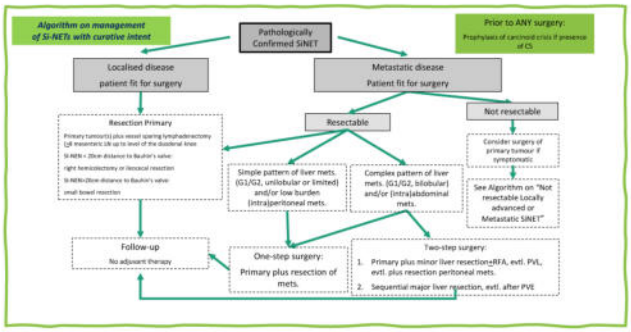
J Neuroendocrinol. 2024;e13423.
https://doi.org/10.1111/jne.13423

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

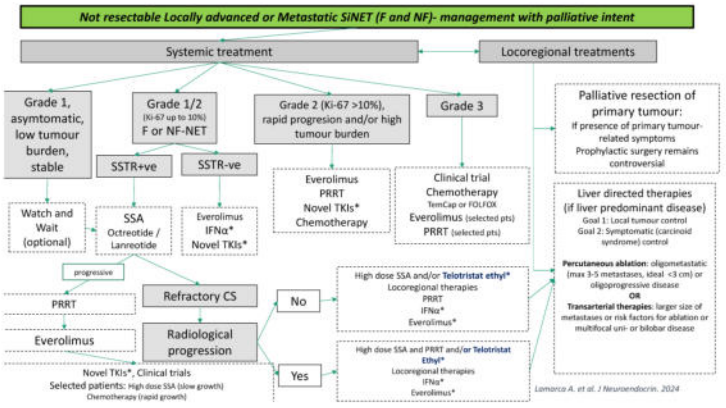
Table 1. Ten major questions on diagnostic and therapeutic management of Si-NET

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 Neuroendocrin. 2024 in press



Lamarca A, et al. ENETS 2024 Guidance Paper for Si-NET. J Neuroendocrin. 2024;e13423



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

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?

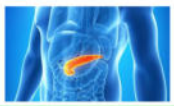
Kos-Kudla B et al. ENETS 2023 guidance paper for non functioning Pancreatic NETs. J Neuroendocrinol. 2023

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.

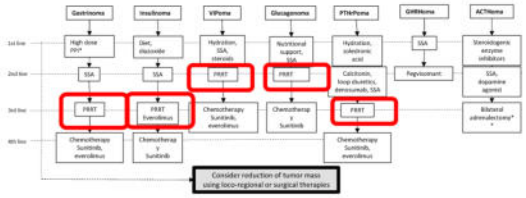
NEW

- **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-Kudla B et al. ENETS 2023 guidance paper for nonfunctioning pancreatic NETs. J Neuroendocrinol. 2023

Treatment algorithm for hormonal symptoms in advanced disease



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

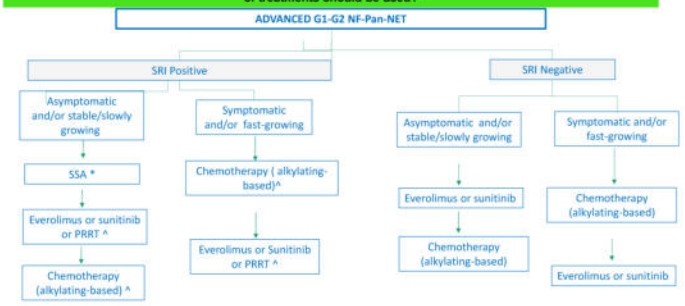
CHOICE OF CHEMOTHERAPY REGIMEN

Treatment	Ki-67 < 20%		Ki-67 > 20%	
	PanNET G1	PanNET G2	PanNET G3	PanNEC
Targeted therapy				
Neoadjuvant or induction (preoperative)	–	–	–	–
Adjuvant (postoperative)	–	–	–	–
	Everolimus	Everolimus		
Neoadjuvant or induction (preoperative)	–	–	± individually: no studies available	+ PE/KE FOLFOX
Adjuvant (postoperative)	–	–	± individually: no studies available	± PE/KE FOLFOX
Palliative	– In second and subsequent lines (CAPTEM, STZ/5-FU)	± in second and subsequent lines (CAPTEM, STZ/5-FU) Exceptionally in the first line depending on progression and dynamics	+ CAPTEM STZ/5-FU	+ PE/KE CAPTEM FOLFOX FOLFIRI FOLFIRINOX

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

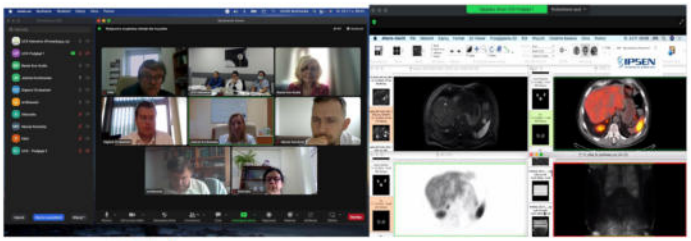
Kos-Kudla B et al. Pancretic NET –update of diagnostic and therapeutic guidelines ... Endokrynol Pol, 2022

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



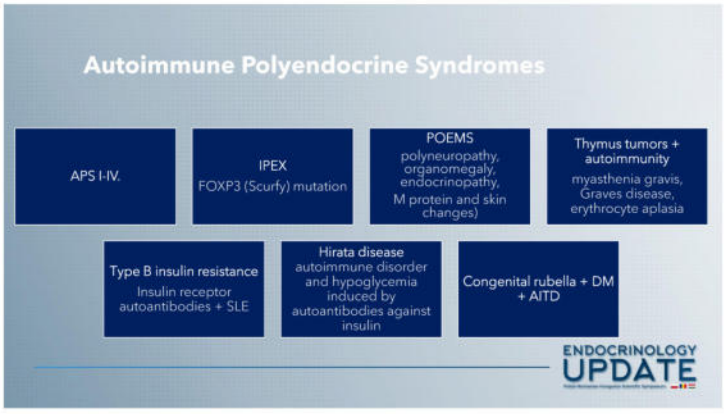
tele NEN

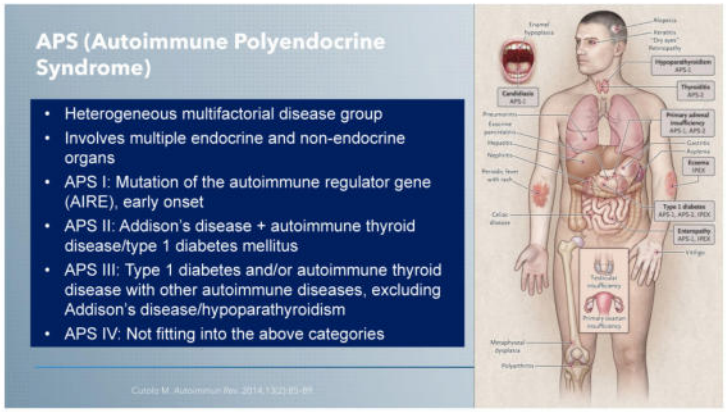
Nationwide Multi-specialty Council of Neuroendocrine Neoplasms

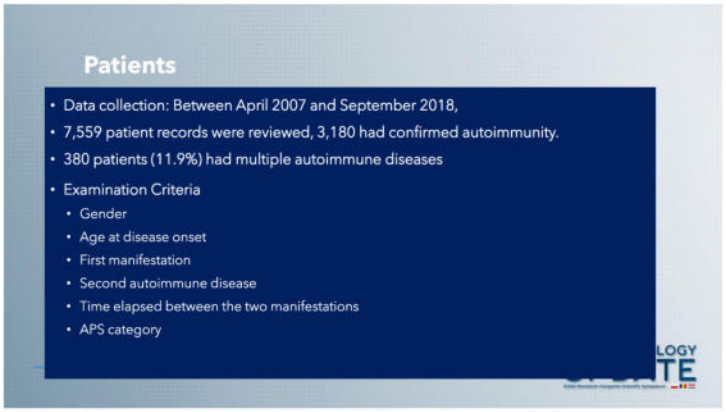
- x 2 times a month

Association of other autoimmune conditions to endocrine autoimmune disorders

Professor Emese Mezősi

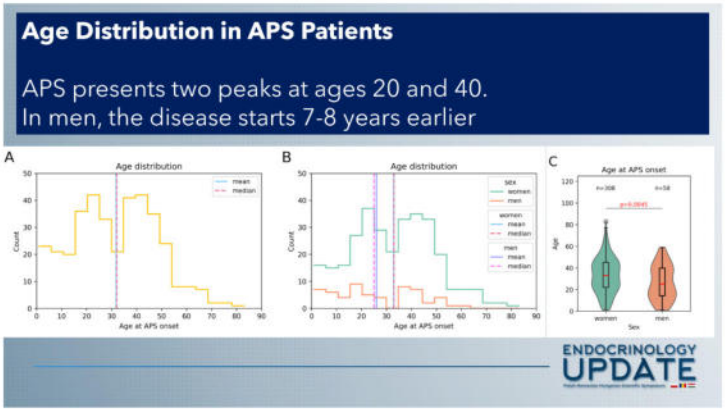






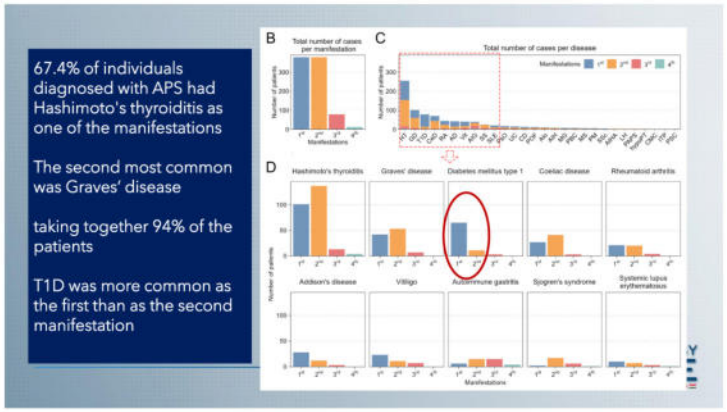
Disorders n=28

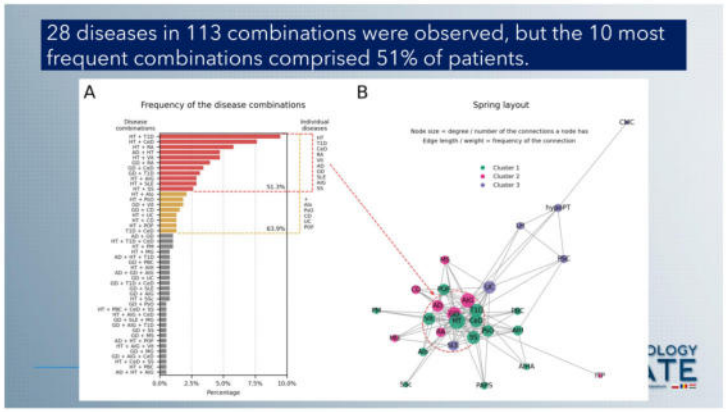
Endocrine organ-specific disorders	Non-endocrine organ-specific disorders	Systemic autoimmune disorders
Hashimoto's thyroiditis - HT (n= 256)	Celiac disease - CED (n=72)	Rheumatoid arthritis - RA (n=45)
Graves' disease - GD (n=102)	Autoimmune gastritis - AIG (n=40)	Sjögren's szindrome -SS (n=26)
Diabetes mellitus - T1D (n=79)	Vitiligo - Vit (n=40)	SLE (n=21)
Addison's disease - AD (n=43)	Ulcerative colitis - UC (n=17)	Psoriasis - 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)
	Myasthenia gravis - MG (n=8)	
	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)	
	Cronic mucocutan candidiasis - CMC (n=1)	

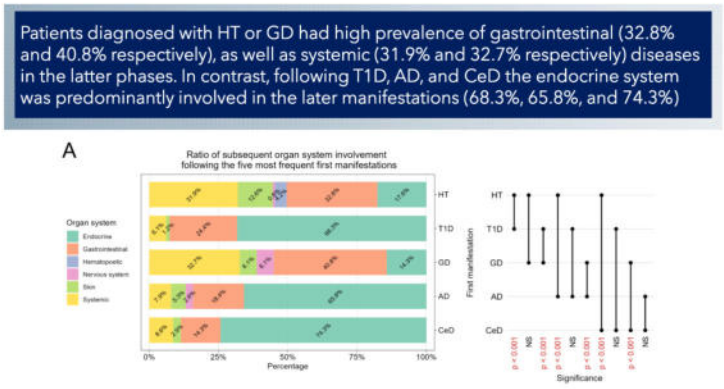


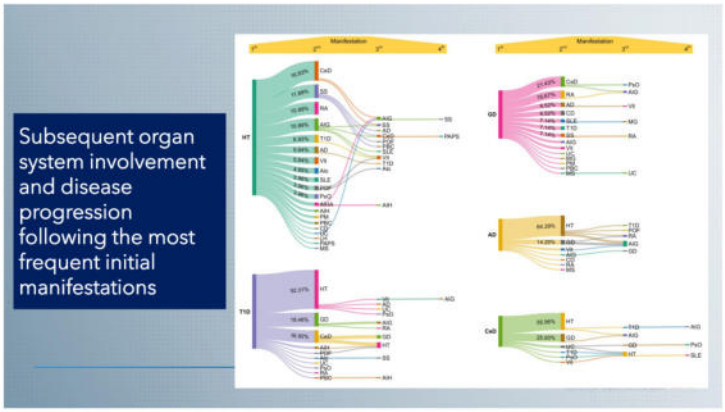
Association of other autoimmune conditions to endocrine autoimmune disorders

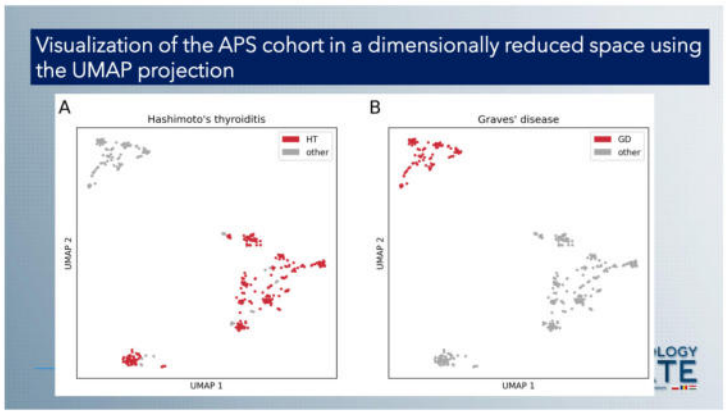
Professor Emese Mezősi

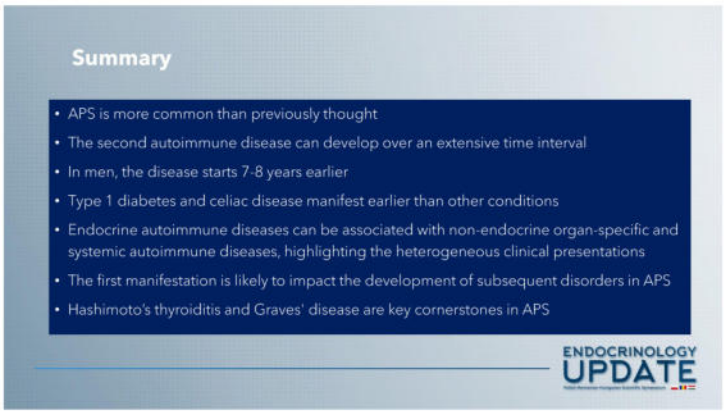






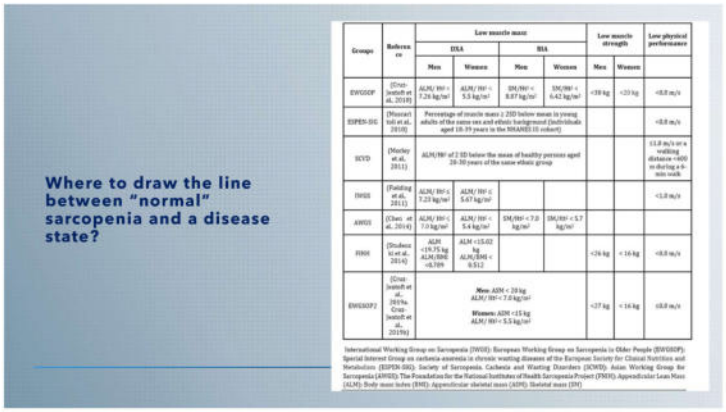


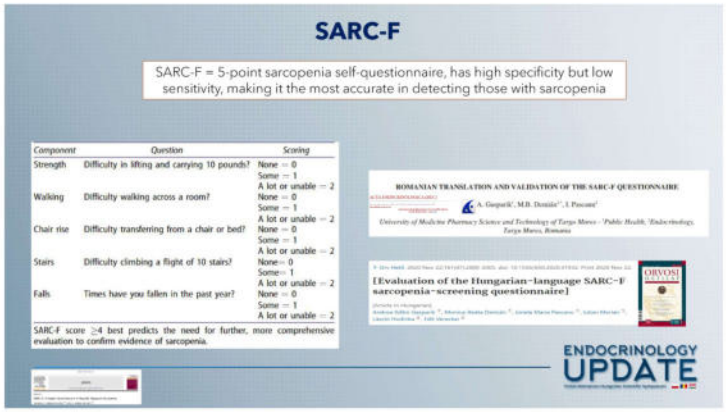


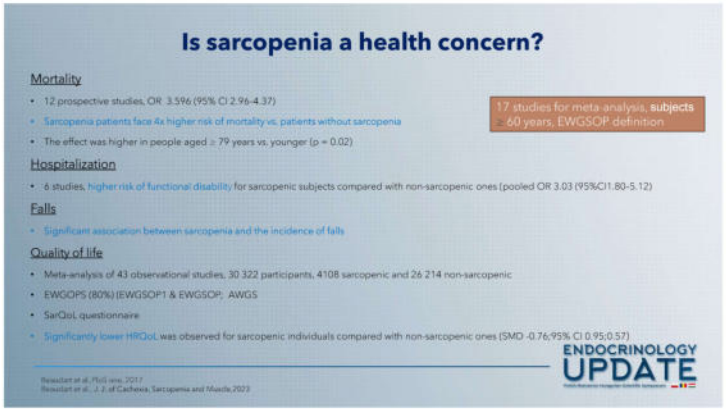


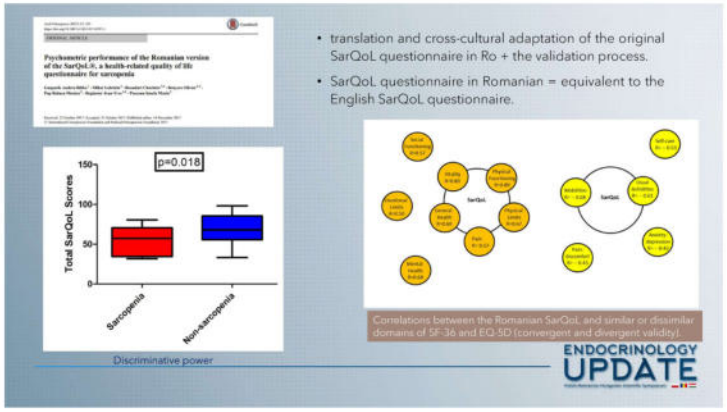
Osteosarcopenia - approaching the musculoskeletal frailty

Professor Ionela Pascanu









Osteosarcopenia - approaching the musculoskeletal frailty

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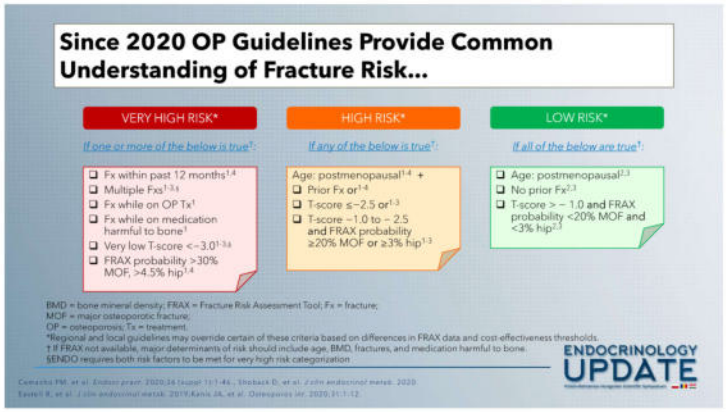
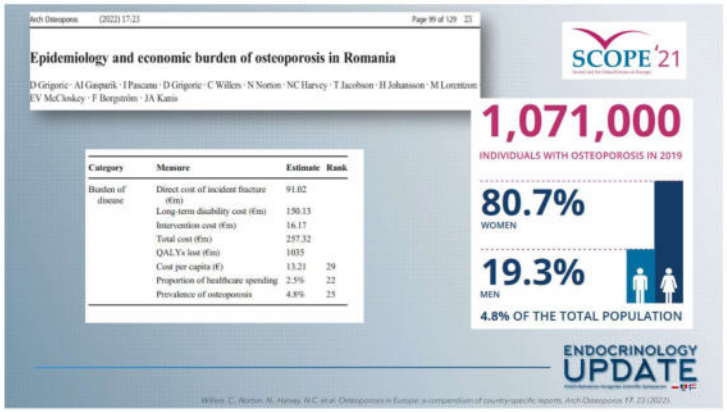
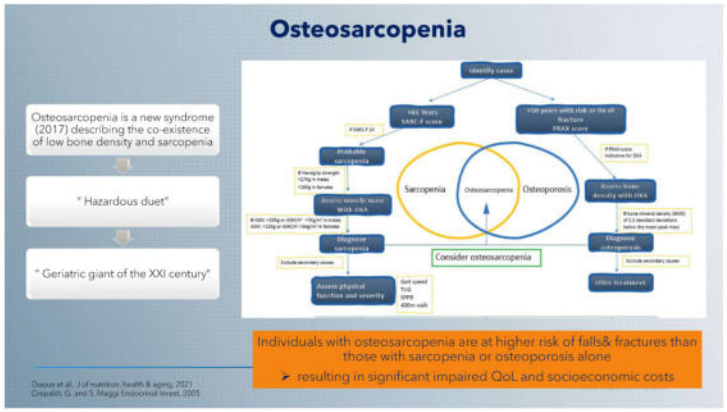
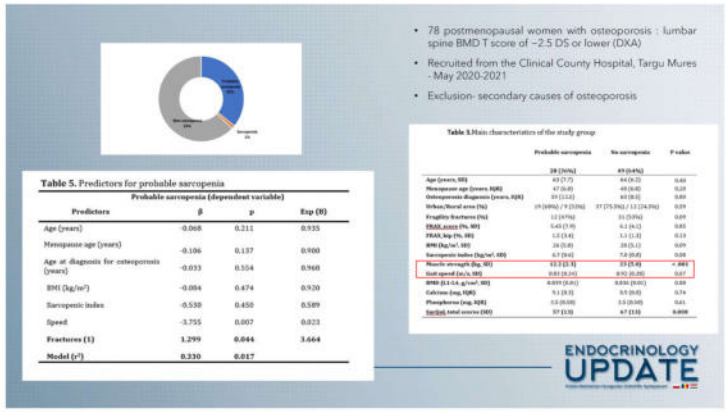
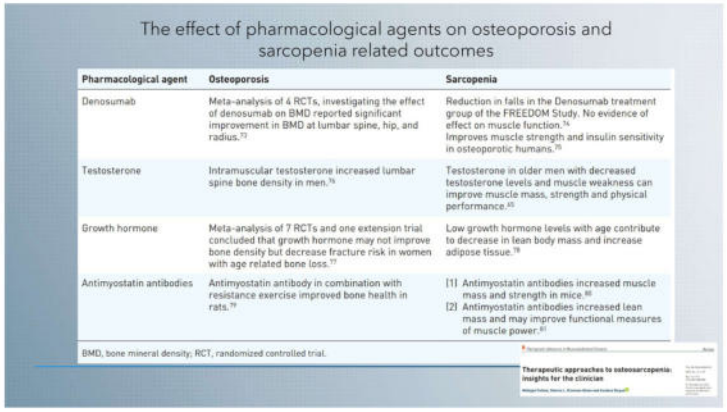
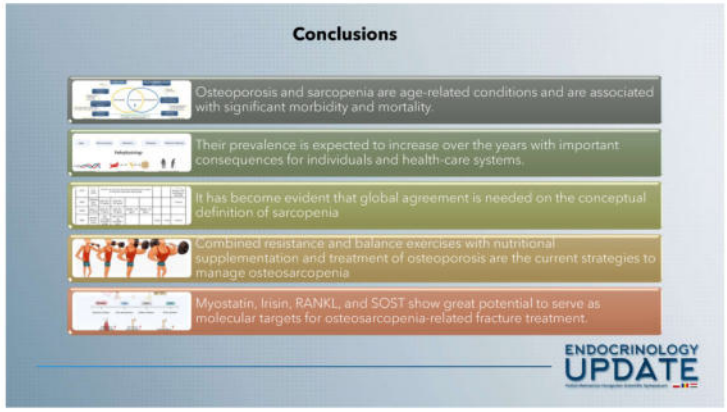






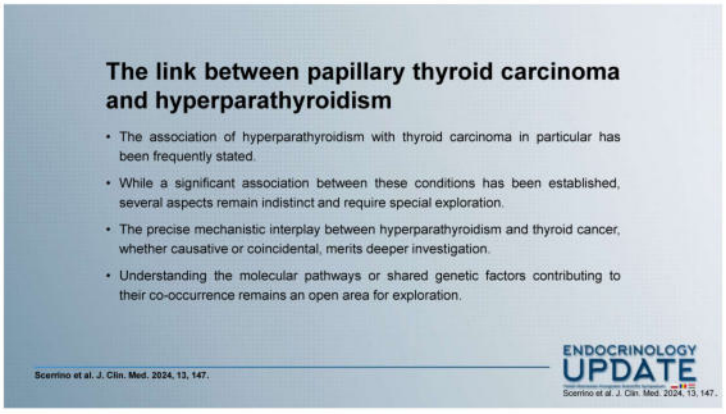


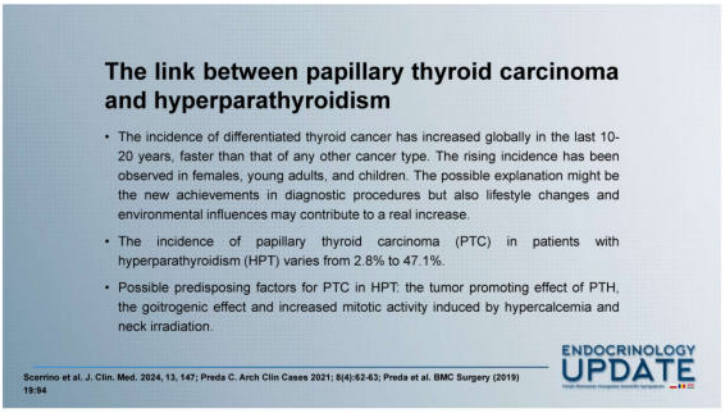


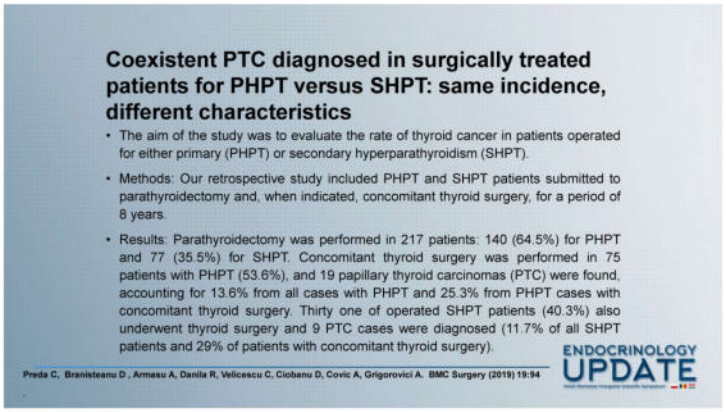


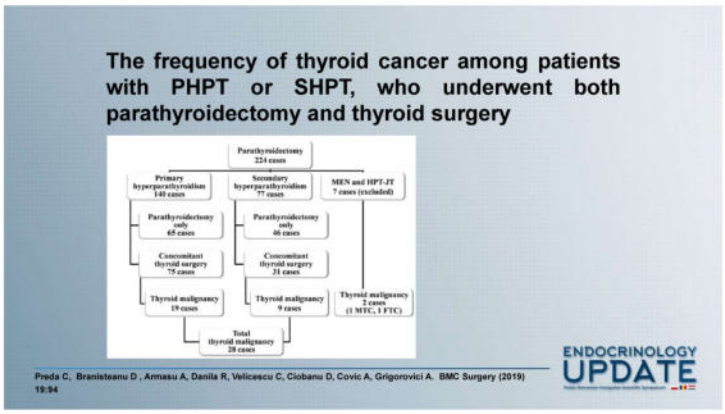
Coexistence of papillary thyroid carcinoma with hyperparathyroidism. Experience of a tertiary endocrinology center

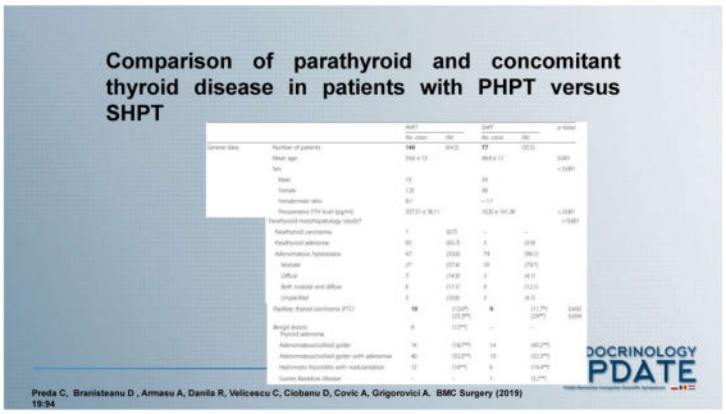
Professor Cristina Preda







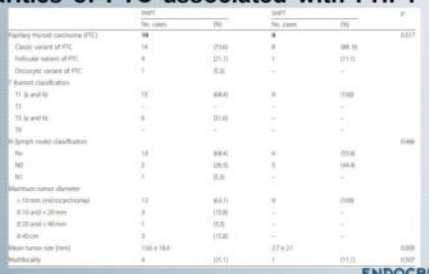




Coexistence of papillary thyroid carcinoma with hyperparathyroidism. Experience of a tertiary endocrinology center

Professor Cristina Preda

Particularities of PTC associated with PHPT or SHPT



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

ENDOCRINOLOGY UPDATE

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 ± 13y versus 48.8 ± 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 ± 38.11 pg/ml versus 1020 ± 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.content

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

ENDOCRINOLOGY UPDATE

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

ENDOCRINOLOGY UPDATE

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;28:401–7).*
- 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).*

ENDOCRINOLOGY UPDATE

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

ENDOCRINOLOGY UPDATE

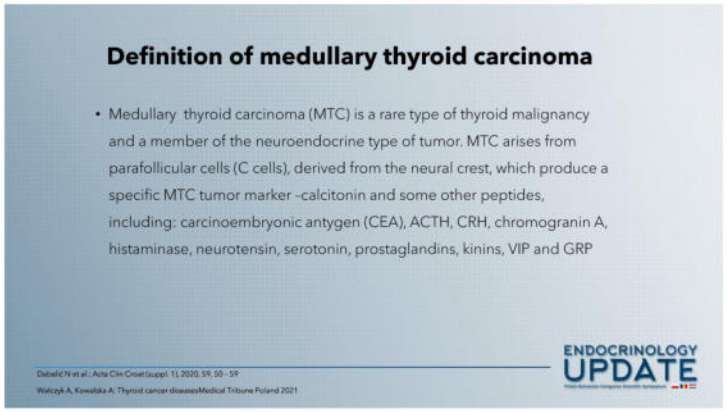
Conclusions

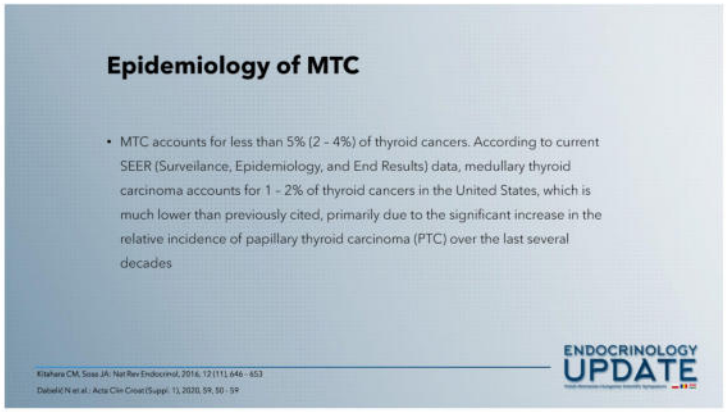
- Among the patients with SHPT, 31 (40.3%) had both thyroid and parathyroid surgery, revealing 9 cases of papillary thyroid carcinoma (PTC), accounting for 11.7% of SHPT cases and 25.7% of those who had both surgeries.
- Both PHPT and SHPT cases revealed a significant occurrence of papillary thyroid 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.

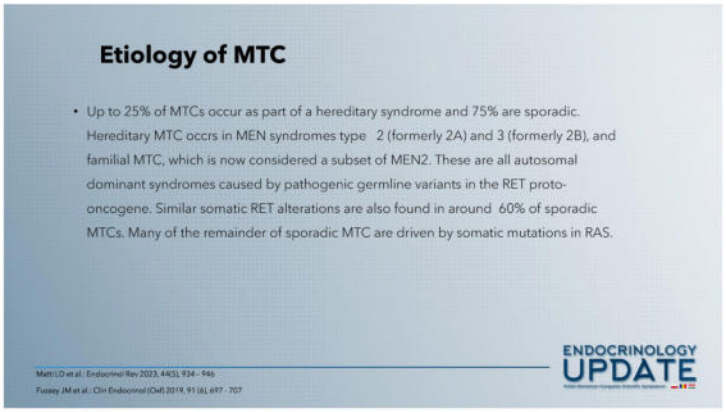
ENDOCRINOLOGY UPDATE

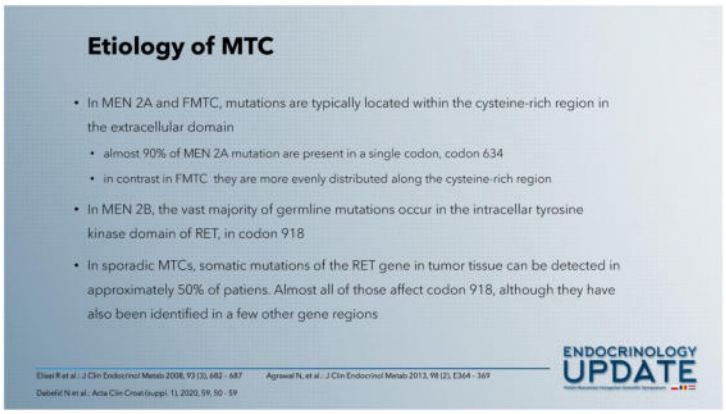
Thyroid medullary carcinoma – etiopathogenesis, clinical picture, diagnosis, treatment and prognosis

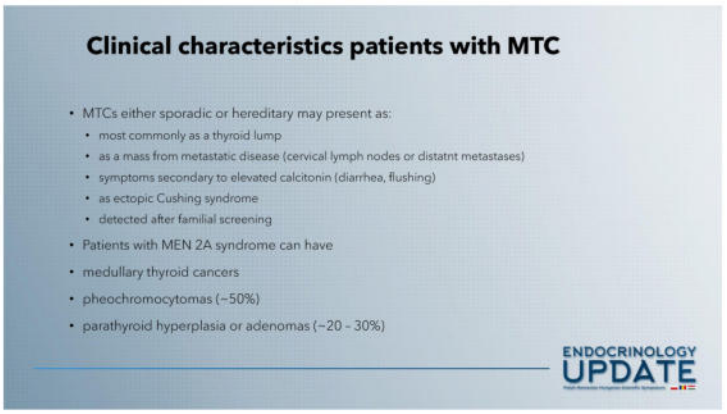
Profesor Anhelii Syrenicz











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

Profesor Anhelii Syrenicz

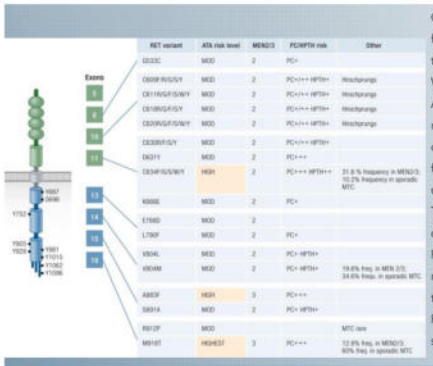
Clinical characteristics patients with MTC

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 diverticule and megacolon)
- marphanoid habitus

Kebebew SI, et al.: Cancer 2000, 88 (5), 1139 - 1148
Matti LG et al.: Endocrine Rev 2023, 44 (5), 934 - 946

ENDOCRINOLOGY UPDATE



Genotype-phenotype corralations, allelic frequency and risk levels for medullary thyroid carcinoma behavior. Adapted from Wells et al., 2015 Revised American Thyroid Association guidelines for the mamagement 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 nowsuggests variants be described as in text (ie, M918T as p.MET918Thr). Frequency of variants in MEN 2/3 and sporadic MTC sourced.

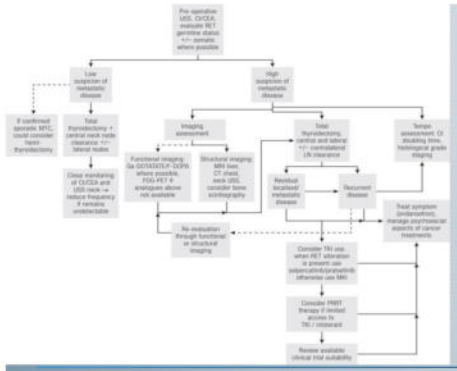
ENDOCRINOLOGY UPDATE

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
  - ^{18}F-DOPA-PET, ^{18}FDG-PET, ^{68}Ga-DOTATATE, DOTATOC and DOTANOC
- Histopathology

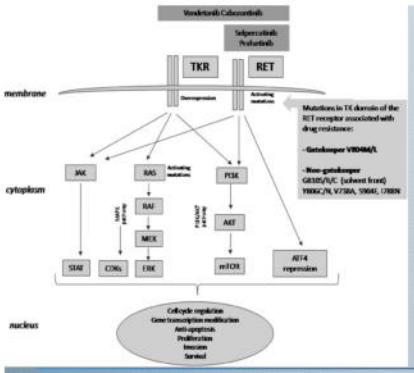
Wells SA et al.: Thyroid 2015, 25 (6), 567 - 610
Matti LG et al.: Endocr Rev 2023, 44 (5), 934 - 946
Conry BG et al.: Eur J Nucl Med. Mol Imaging 210, 37 (1), 49 - 57

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

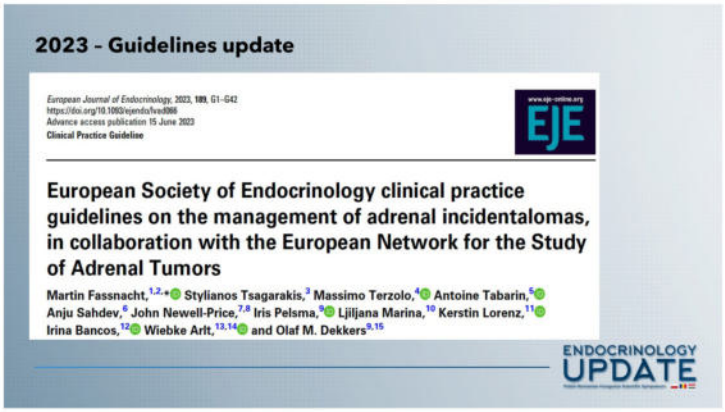
- The stage of the disease at diagnosis and the possibility of radical surgical resection are the most important factors in achieving cure in MTC.
- The classical main prognostic factors in MTC are:
  - age,
  - tumor size,
  - local and distant metasteses,
  - somatic M918T mutatons,
  - calcitonin,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

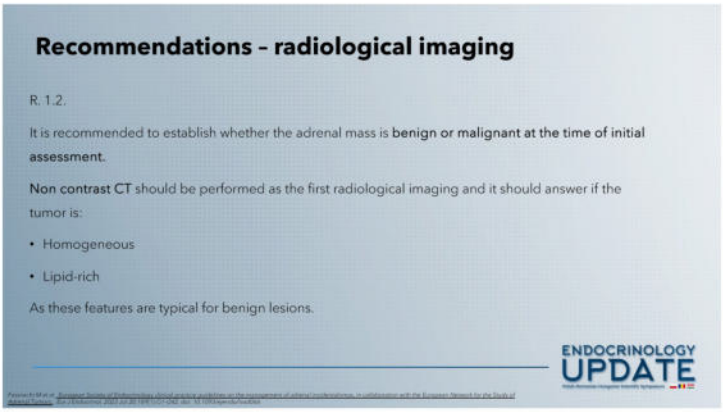
Dabelić N et al.: Acta Clin Croat (suppl. 1), 2020, 59, 50 - 59

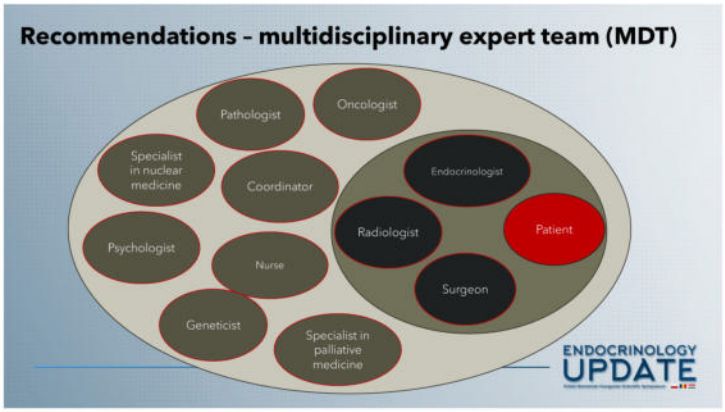
ENDOCRINOLOGY UPDATE

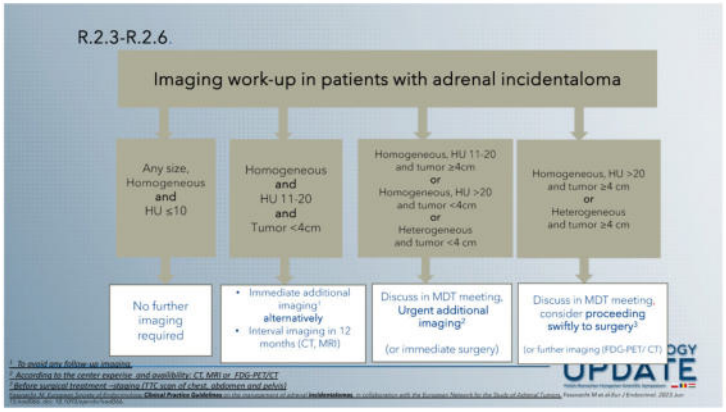
Management of adrenal incidentaloma – update

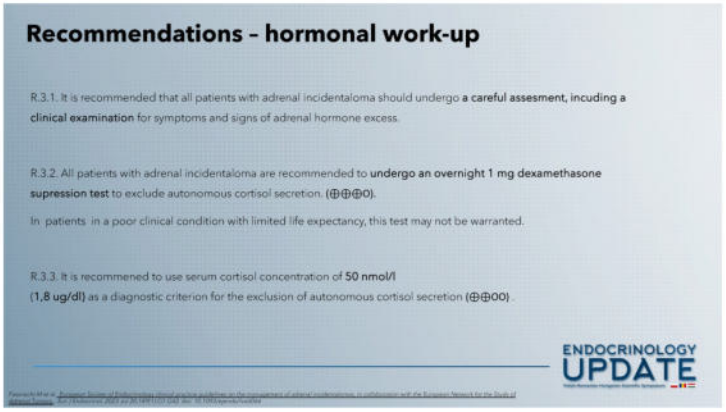
Profesor Renata Świątkowska-Stodulska







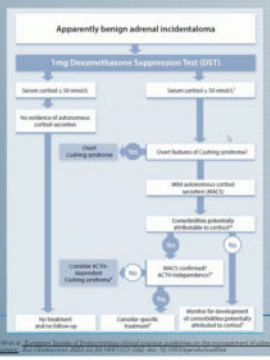




Management of adrenal incidentaloma – update

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 (⊕OOO) .

Factors such as:

- Age
- Sex
- General health
- Severity of the comorbidities (HA, DM, osteoporosis)
- Patients' preference
- Persistence of nonsupressible cortsol 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 fractioned 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.

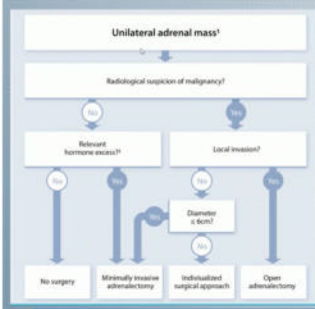
ENDOCRINOLOGY UPDATE

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 (⊕⊕OO).

ENDOCRINOLOGY UPDATE

Recommendations – surgical treatment

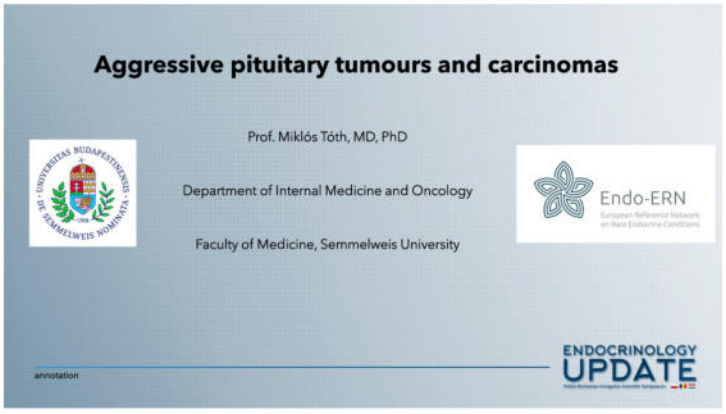


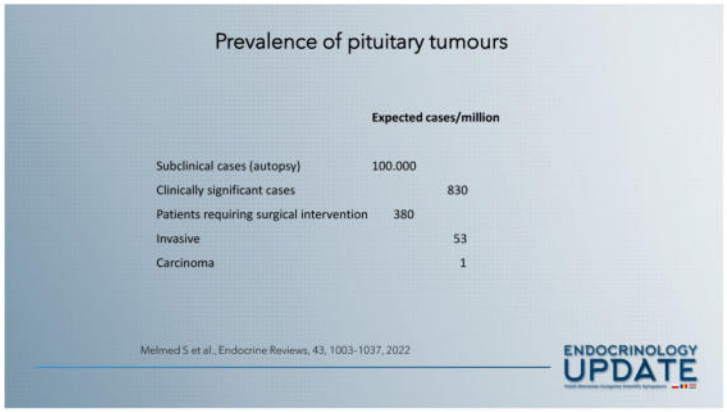
- R.4.3. If surgery is indicated for a benign adrenal mass causing hormone excess (including MACS), minimally invasive approach is indicated (⊕OOO).
- R.4.4. The panel of experts suggested that minimally invasive adrenalectomy could be performed in patients with unilateral adrenal masses ≤ 6 cm and with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

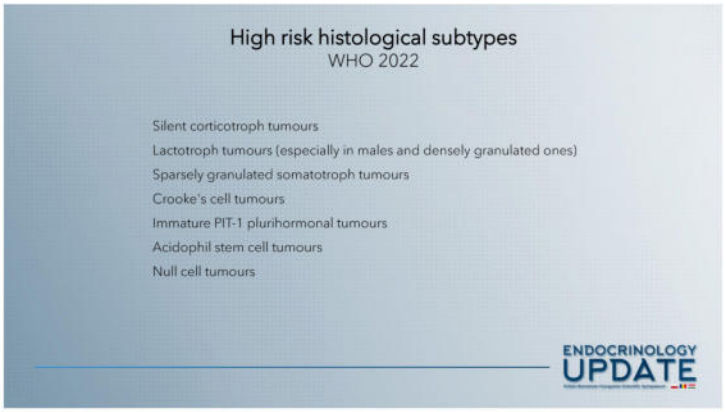
ENDOCRINOLOGY UPDATE

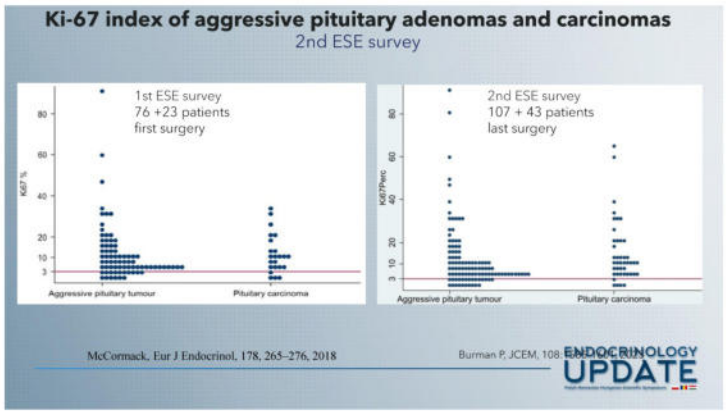
Aggressive pituitary tumours and carcinomas

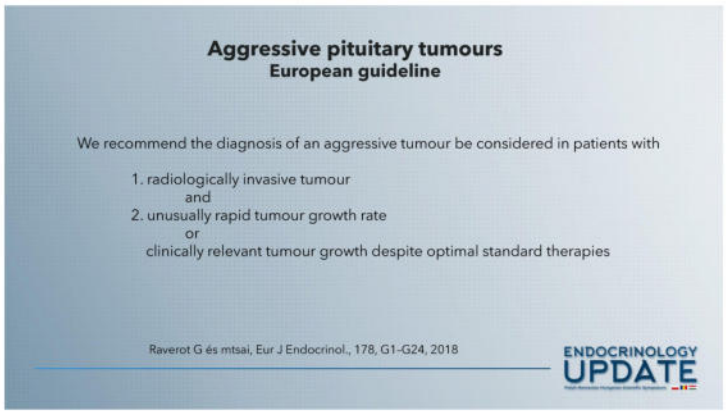
Professor Miklós Tóth









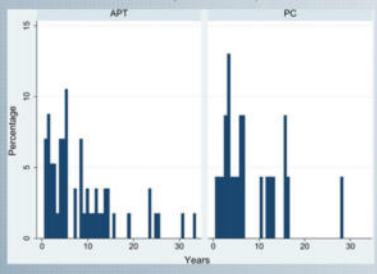


Aggressive pituitary tumours and carcinomas

Professor Miklós Tóth

Time between first diagnosis and recognition of aggressive behaviour

2nd ESE survey, 97 APT/PC patients

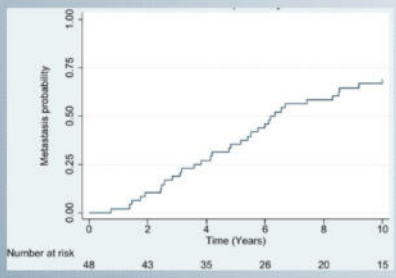


Burman P, EJE, 187: 593-605, 2022
Burman P, JCEM, 108:1585-1601, 2023

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

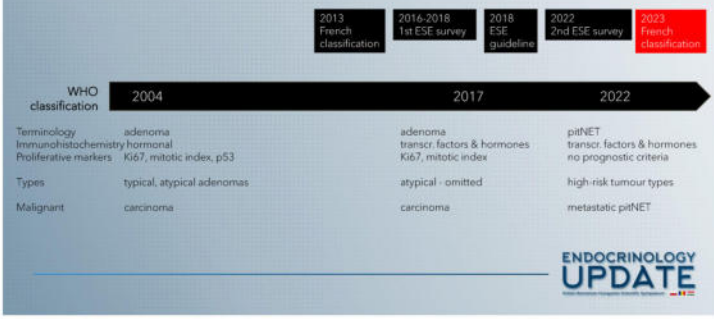
Standard medical treatment with maximally tolerated doses

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

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

ENDOCRINOLOGY UPDATE

Evolution of classification of pituitary tumours



ENDOCRINOLOGY UPDATE

EJE

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

Jacqueline Trouillas,[1] Pia Burman,[2] Marco Losa,[3] Ann McCormack,[4] Stephan Petersenn,[5] Vera Popovic,[6] Marily Theodoropoulou,[7] Olaf M. Dekkers,[8] and Gerald Raverot[1,9,*]

Table 2. Comparison of the grades, at the initial surgery, in two surgical cohorts: 305 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	20
Grades n (%)				
1a	187 (51.2)	0	0	0
1b	28 (7.7)	0	0	0
1b*	3 (0.8)	1 (2.3)	0	1 (5)
2a	118 (32.3)	13 (30.2)	7 (30.4)	6 (30)
2b	32 (8.8)	29 (67.4)	16 (69.5)	13 (65)
2b*	6 (1.6)	16 (37.2)	9 (39.1)	7 (36)

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

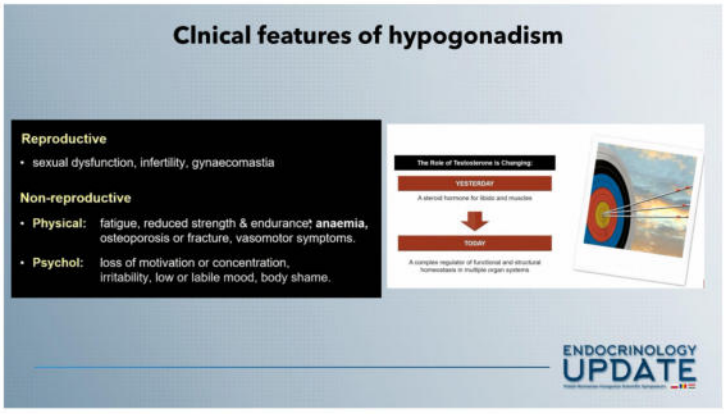
- Corticotroph invasive macroadenomas, especially in men
- Macro/giant prolactinomas initially not responding to high doses of cabergoline, or losing sensitivity to dopamine agonists
- Somatotroph invasive macroadenomas progressing on treatment with somatostatin analogues
- Nonfunctioning invasive macroadenomas 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

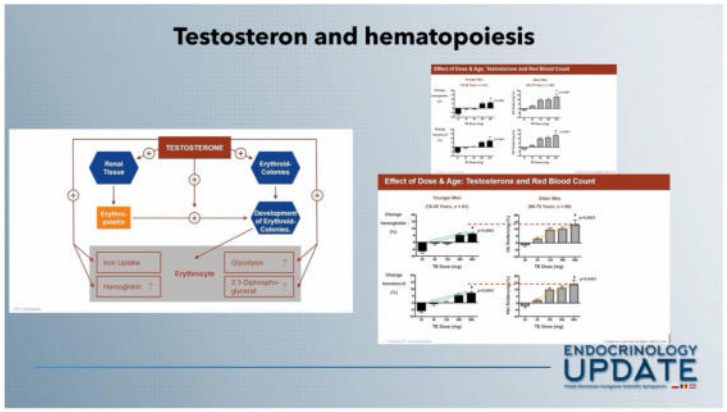
Burman P, JCEM, 108:1585-1601, 2023

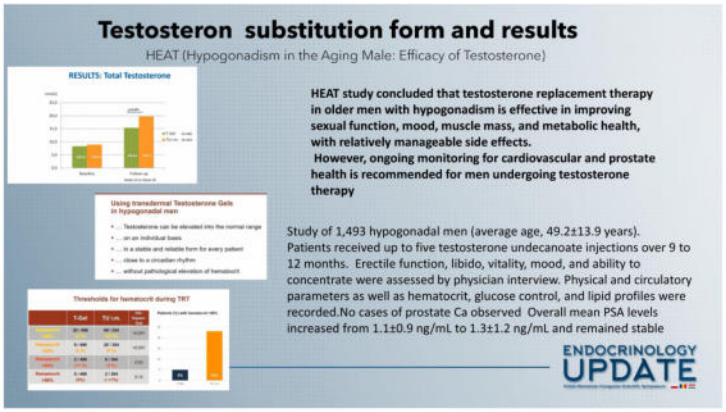
ENDOCRINOLOGY UPDATE

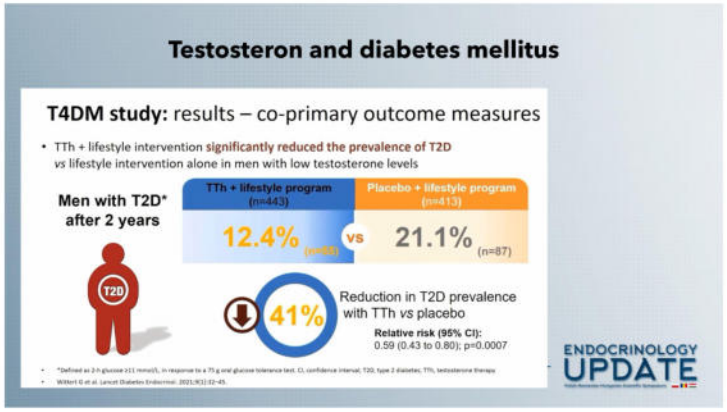
Hypogonadism and male health

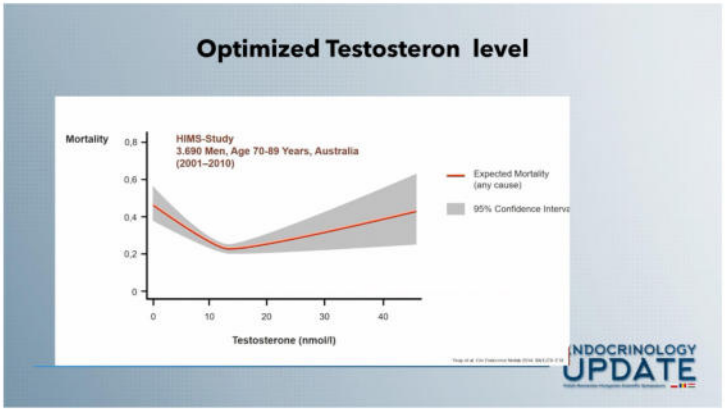
Professor Zsuzsanna Valkusz











Hypogonadism and male health

Professor Zsuzsanna Valkusz

Testosteron 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.1 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.7 **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

ENDOCRINOLOGY UPDATE

EDITORIAL

Testosterone replacement therapy in older hypogonadal men: a focus on cardiovascular safety from the TRAVERSEstudy

Emanuela A. GRECO *

Niccolò Cusano University, Rome, Italy

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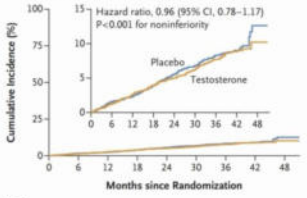
E-mail: emanuela.greco@unicusano.it

ENDOCRINOLOGY UPDATE

Cardiovascular safety endpoint

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



No. at Risk

Placebo	2602	2507	2323	2088	1792	1568	1337	598	33
Testosterone	2596	2504	2339	2120	1829	1605	1380	653	39

ENDOCRINOLOGY UPDATE

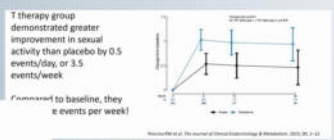
Tesosteron and Pca

- 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)

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

ENDOCRINOLOGY UPDATE

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

ENDOCRINOLOGY UPDATE

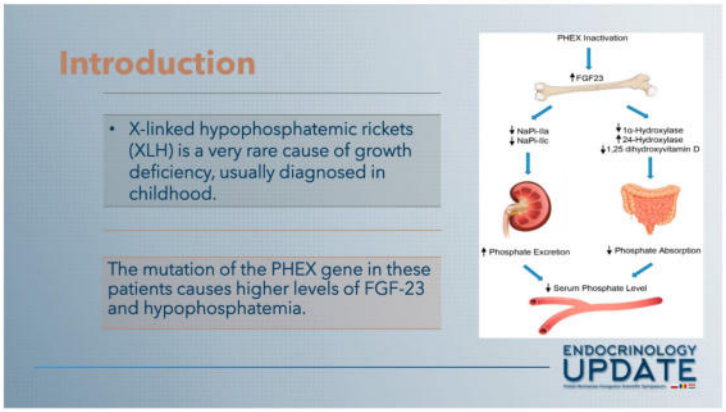
Take home message

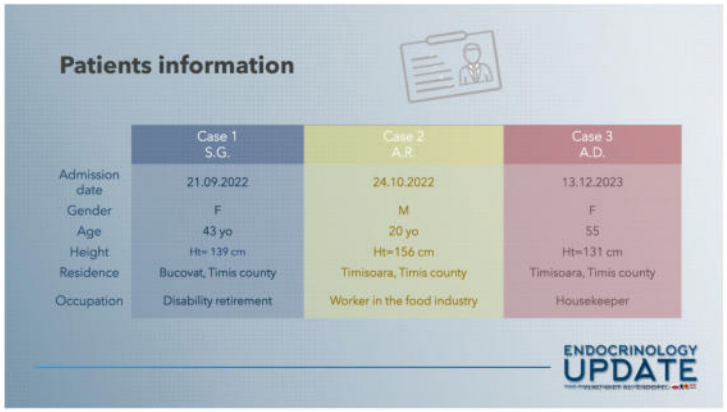
Trial	Risks	Benefits
CV	MACE - No	
Prostate	Cancer - No BPH/LUTS - No	
Sexual Function		Libido – Yes ED - No
Depression		Yes
Bone Fracture		No
Anemia		Yes
Diabetes		No

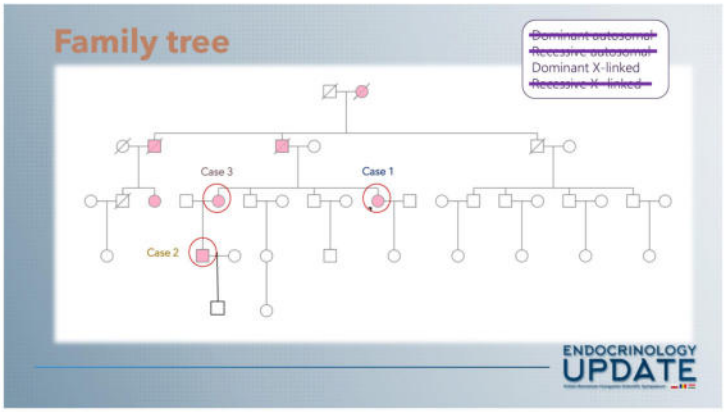
ENDOCRINOLOGY UPDATE

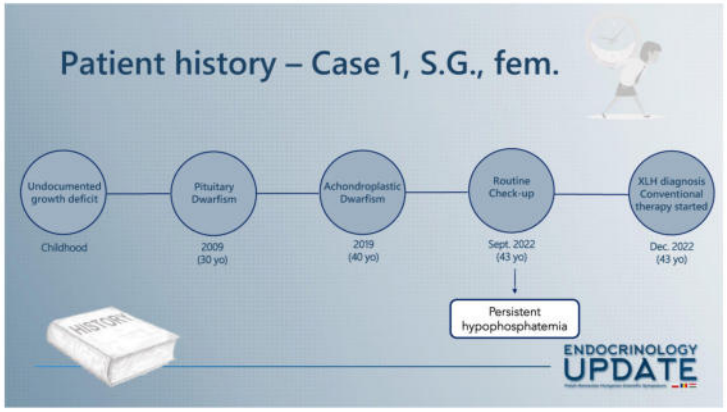
X-linked hypophosphatemia - a rare cause of short stature

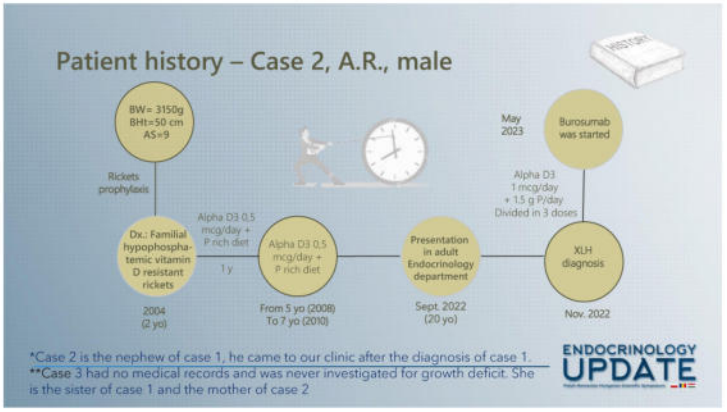
Professor Mihaela Vlad











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	✗	✗	✗

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Laboratory results

FEPO4 = [PO_4 (Urine) * Creatinine (Serum)] / [PO_4 (Serum) * Creatinine (Urine)] * 100

	XLH	Case 1	Case 2	Case 3	Normal range
Serum P	Low	**2.4**	**1.8**	2.8	2.5 - 4.9 mg/dl
Serum Ca	N	9	9.3	8.6	8,6-10 mg/dl
Serum Cr	N	0.6	0.6	0.6	13.6 - 85.8 pg/mL
iPTH	N	35.9	57.8	**97.1**	4.5-16,9 mcg/L
Bone ALP	High	**18.9**			30 - 100 ng/mL
25 (OH) VitD	N	29,75	**14.52**	**4.98**	25- 86.6 pg/ml
1,25 (OH) 2 VitD	Ni/Low	**42.8**	**25.30**		
Urinary Ca /24 h	N/Low	123	86.4	257.40	42-353 mg/24h
Urinary P/24 h	N/ high	0,62	1.065	1.06	0.4-1.3 g/24h
FePO4	N/ high	**12,14%**	**24%**	**13%**	<5%
FGF-23		**146**	**73**		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.

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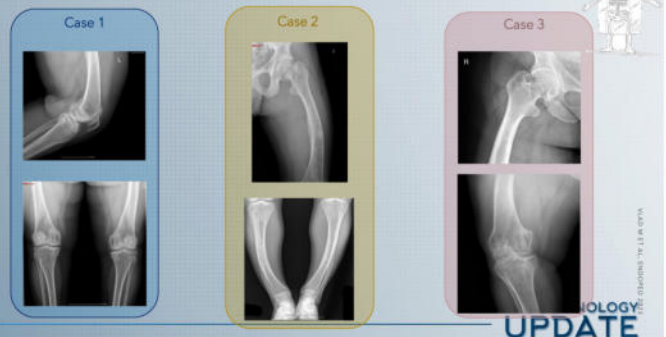
Radiology



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Genetic test result Case 1

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Treatment follow-up

	Case 1 (conventional treatment)		Case 2 (Burosumab)				Case 3 (conventional treatment)		Values range
	Before treatment	1 year	Before treatment	1 month	6 months	1 year	Before treatment	5 months	
Serum P	**2.4**	**2**	**1.8**	2.8	**2.2**	3.5	2.8	**2**	2.5 - 4.9 mg/dl
Serum Ca	9	**8.2**	9.3	9.3	10.4	9.1	8.6	8.7	8,6-10 mg/dl
iPTH	35.9	42.9	57.8	74.8	60.2	61.9	**97.1**	**109**	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	**18.9**	12.3							4.5-16,9 mcg/L
25 (OH) VitD	29,75	40.2	**14.52**			31.7	**4.98**	**13.27**	30 - 100 ng/mL
1,25 (OH) 2 VitD	42.8		**25.30**			72.5			25- 86.6 pg/ml
Urinary Ca /24h	123	291	86.4		**165**	**151**	257.40	238	42-353 mg/24h
Urinary P/24 h	0,62	0.63	1.065		**1.5**	**1.6**	1.06	**1.53**	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.

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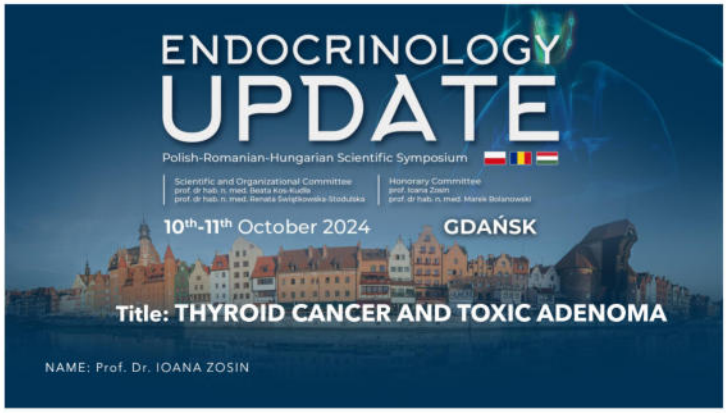
Take home messages

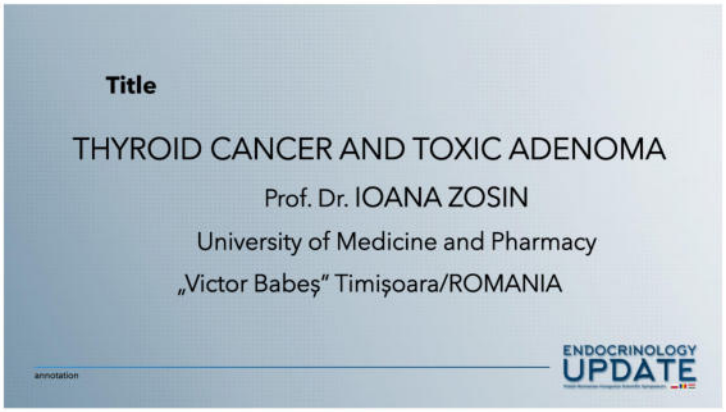
- Being so rare, XLH as a cause of short stature can be easily overlooked.
- **X linked - hypophosphatemia rickets** can be **diagnosed** even in **adulthood**.
- Any patient with **undocumented** short stature **should be investigated,** regardless their age.
- There are newly approved medication for 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.**

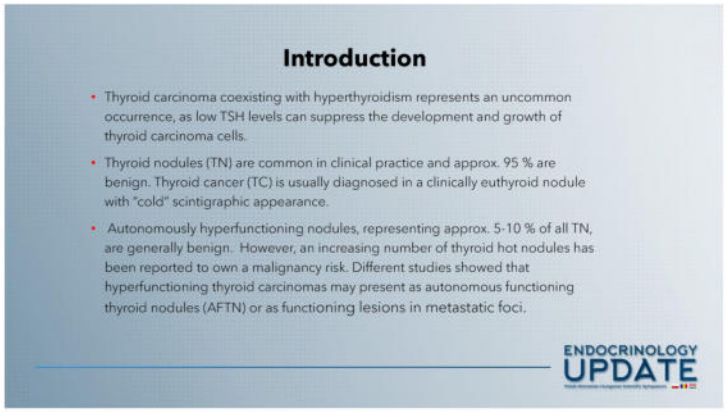
ENDOCRINOLOGY UPDATE

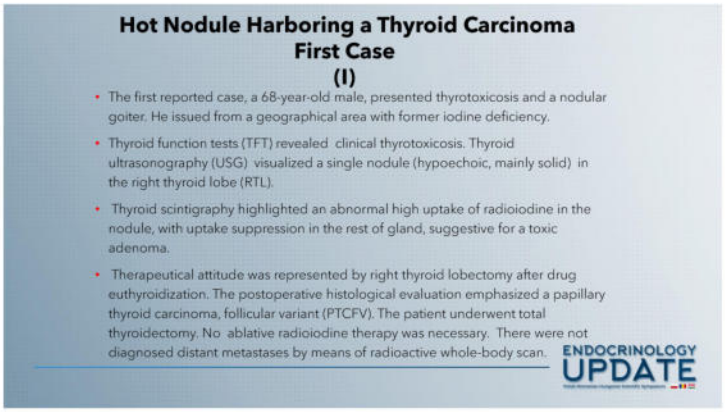
Thyroid cancer and toxic adenoma

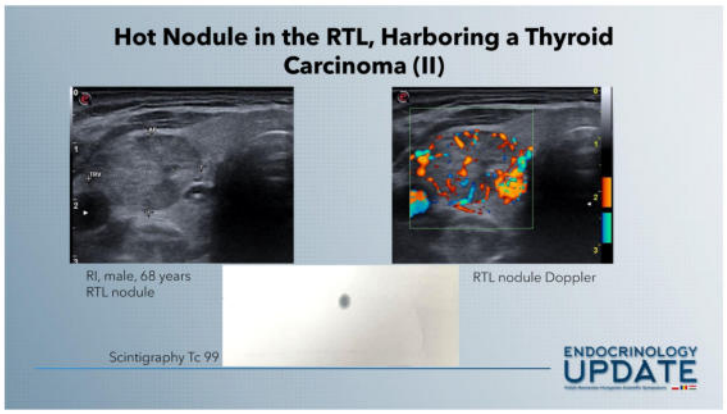
Professor Ioana Zosin

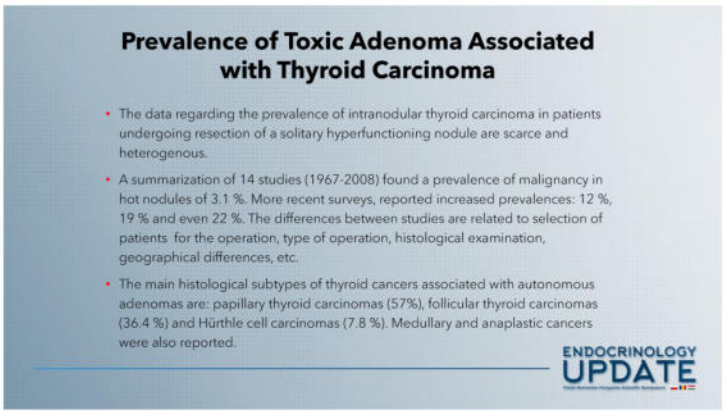












Thyroid cancer and toxic adenoma

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 diffent thyroid cancers, history of head and neck irradiation, some clinical peculiarities (rapid growth of the nodule, cervical adenopaty, 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.

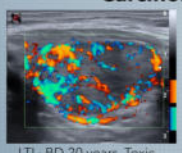
ENDOCRINOLOGY UPDATE

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

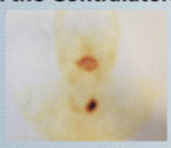
- The second case was represented by a young female patient with thyrotoxicosis and a left TN. USG revealed a hypoechoic solid nodule. Scintgraphically, the nodule was a „hot" one. In the RTL, two small cysts were visualized. The patient was no more evaluated 2 years because of COVID pandemia.
- At the 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

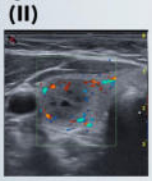
Hot Nodule in one Thyroid Lobe (LTL), Thyroid Carcinoma in the Contralateral Lobe (II)



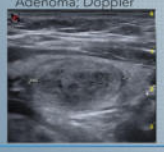
LTL- BD 20 years. Toxic Adenoma; Doppler



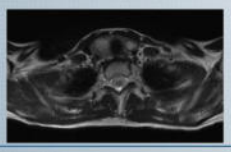
Toxic adenoma Scintigraphy



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 ovalar 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