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21th PostADA / PostENDO – Symposium Endocrine Tumors and Adrenals

Svenja Nölting, Felix Beuschlein

Overview:

Benign adrenal tumors

(OR29) Comprehensive Steroid And Global Metabolome Analysis By Mass Spectrometry And Machine Learning To Understand **Metabolic Risk In Benign Adrenal Tumours With Mild Autonomous Cortisol Secretion**

Pheochomocytoma/Paraganglioma (PPGL)

(OR29) **High-specific-activity Iodine 131 Metaiodobenzylguanidine** For The Treatment Of Advanced Pheochromocytoma And Paraganglioma: A Real-world Study

(OR12) **Long-term Follow-Up** of Pheochromocytoma/Paraganglioma (PPGL) after first diagnosis: a retrospective single-center study of 173 patients

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Benign adrenal tumors

(OR29) Comprehensive Steroid And Global Metabolome Analysis By Mass Spectrometry And Machine Learning To Understand Metabolic Risk In Benign Adrenal Tumours With Mild Autonomous Cortisol Secretion

Alessandro Prete, MD (….) Wiebke Arlt, MD, Birmingham, U.K.

Background: Benign adrenal tumors are found in 3-10% of adults and can be non-functioning (NFAT) or associated with adrenal hormone excess.

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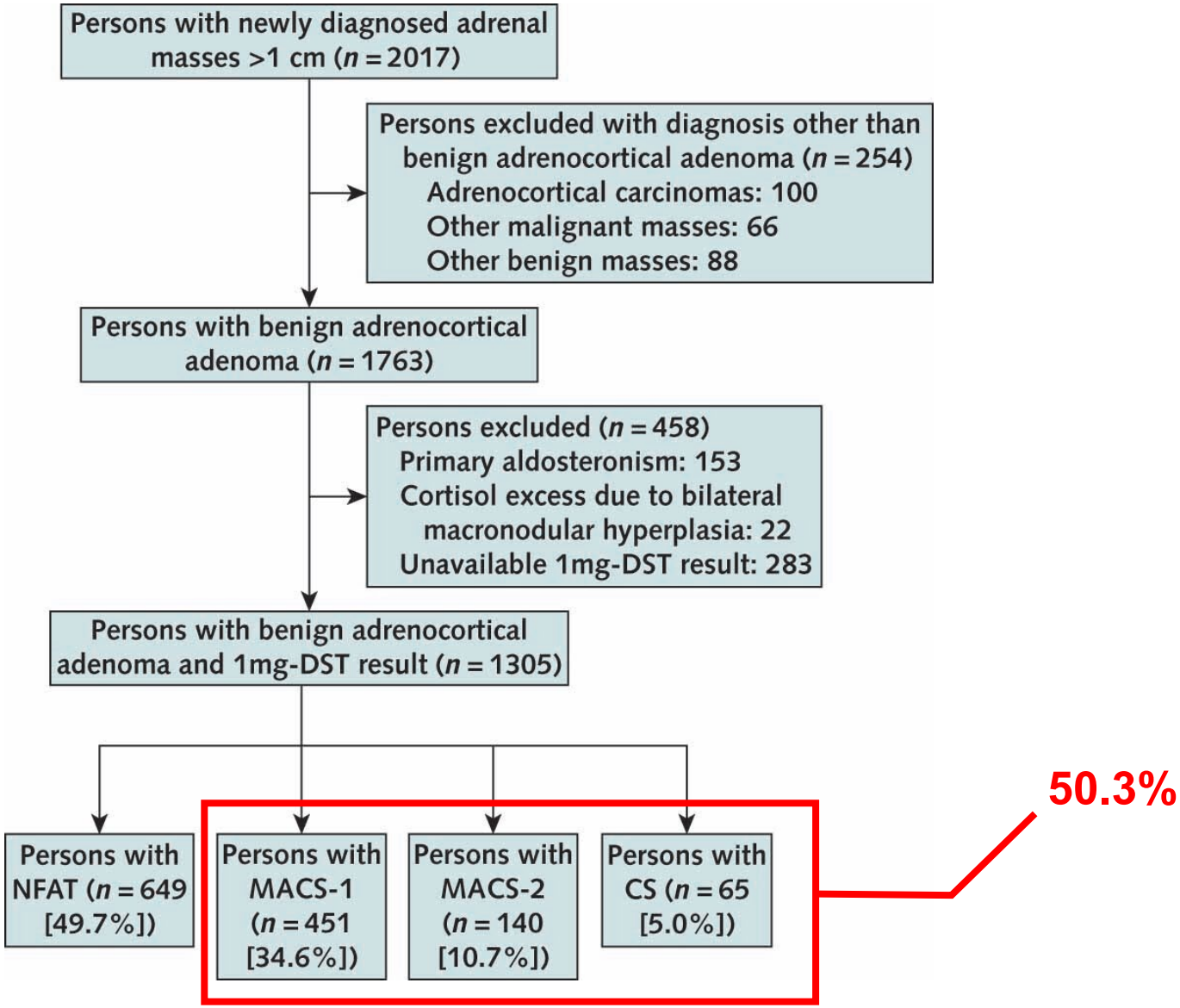
Cardiometabolic Disease Burden and Steroid Excretion in Benign Adrenal Tumors



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Prete A et al., Ann Intern Med. 2022 Jan 4

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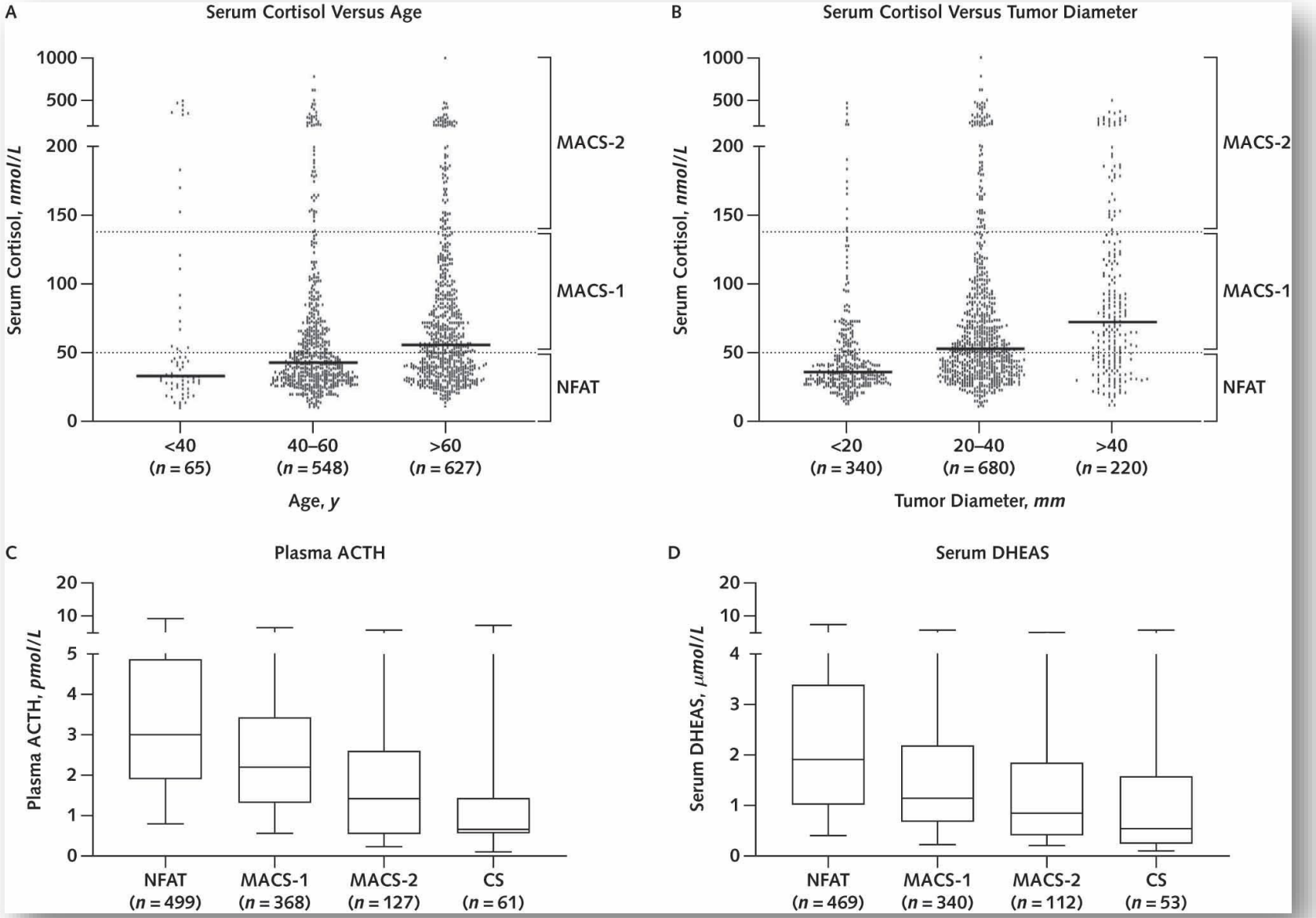

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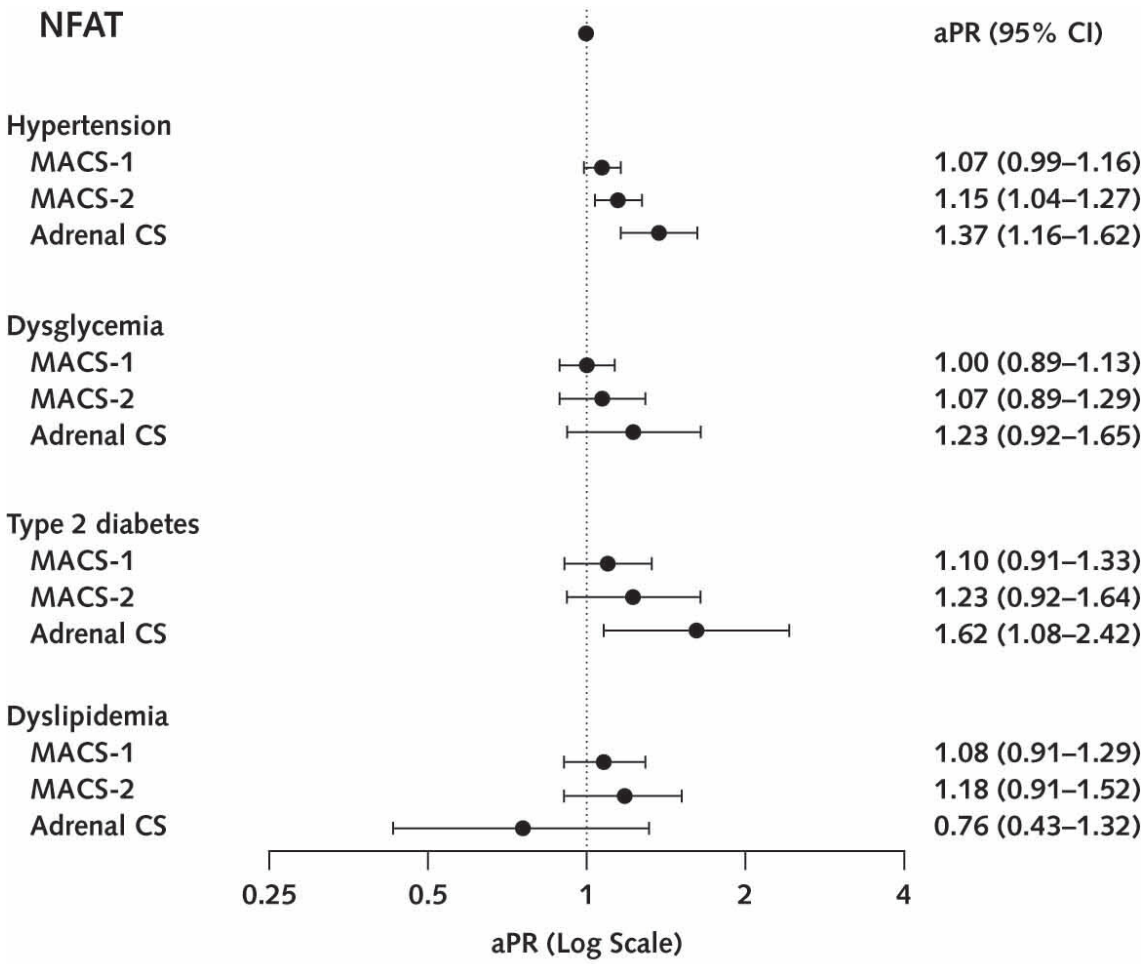

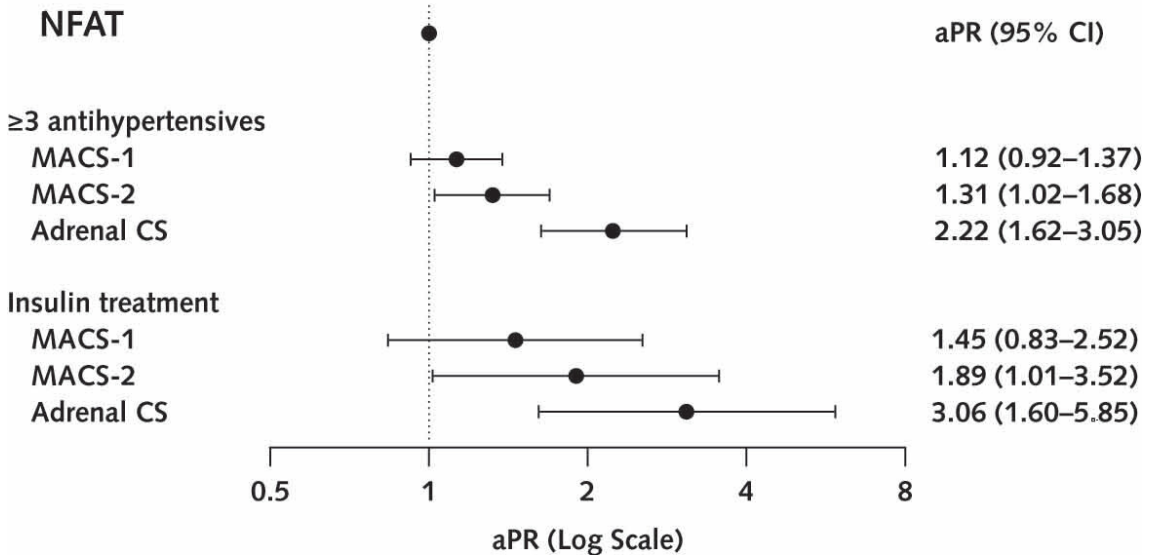

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(OR29) Comprehensive Steroid And Global Metabolome Analysis By Mass Spectrometry And Machine Learning To Understand Metabolic Risk In Benign Adrenal Tumours With Mild Autonomous Cortisol Secretion

Alessandro Prete, MD (….) Wiebke Arlt, MD, Birmingham, U.K.

Methods:

Multi-steroid profiling from 24-h urine samples from 1305 patients (649 NFAT, 591 MACS, 65 CS) using a liquid chromatography-tandem mass spectrometry (LC-MS/MS)

Non-targeted serum metabolome analysis in a representative sub-cohort (104 NFAT, 140 MACS, 47 CS) employing two complementary LC-MS assays, HILIC and C^{18}-lipidomics.

The steroid and global metabolome data were analyzed by two supervised machine learning approaches, generalized matrix learning vector quantization and ordinal regression, to identify the most relevant metabolic changes.

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Findings:

Urine steroid metabolome analysis revealed an increase in glucocorticoid excretion from NFAT over MACS to CS, whereas androgen excretion decreased.

Increased glucocorticoid metabolites were also the major differentiators between MACS patients with and without type 2 diabetes and hypertension, respectively.

Lipidome analysis by machine learning identified glycerophospholipids, lysoglycerophospholipids, triacylglycerides, ceramides, sphingolipids, and acylcarnitines as the most relevant metabolite classes exhibiting gradually progressive changes with increasing cortisol excess (NFAT).

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Conclusion:

Gradual change in the lipidome towards lipotoxicity with increasing cortisol excess.

MACS patients with type 2 diabetes and hypertension had higher glucocorticoid output than other MACS patients, suggestive of a causative contribution of cortisol excess to their increased cardiometabolic burden.

Possible risk stratification in MACS, a highly relevant and previously largely overlooked metabolic risk condition.

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Pheochomocytoma/Paraganglioma (PPGL)

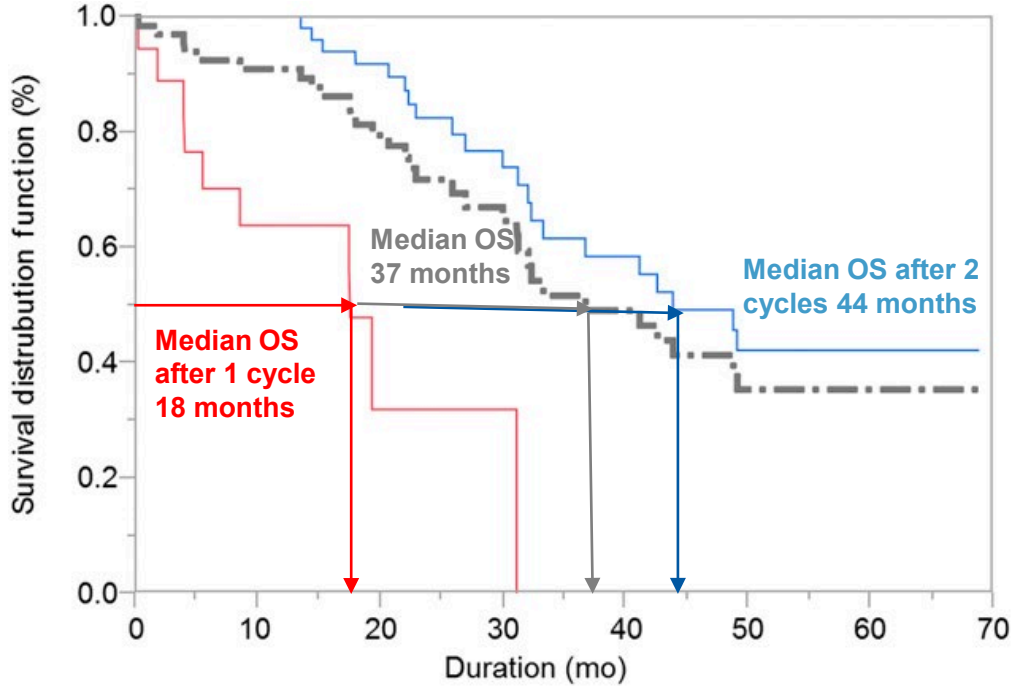
(OR29) High-specific-activity Iodine 131 Metaiodobenzylguanidine For The Treatment Of Advanced Pheochromocytoma And Paraganglioma: A Real-world Study

Ruaa Al-ward et al. (MD), Baylor College of Medicine, Houston, US

Background:

- High-specific-activity ^{131}I-meta-iodobenzylguanidine (HSA ^{131}I-MIBG) is the **only approved systemic therapy for metastatic (m)PPGLs**.
- **Prospective phase II study on HSA [^{131}]MIBG (n=68, evaluable n=64)** (Pryma et al., J Nucl Med. 2019)

Complete response 0%	Partial response 23%	Stable disease 69%	Disease control rate (DCR) 92%	Overall survival (OS) 37 months: 18 months after one cycle / 44 months after two cycles



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Methods:

- **Retrospective cohort study in mPPGL treated with HSA ^{131}I-MIBG at a tertiary cancer center (n=24, evaluable n=23)**
- **Primary endpoint:** Radiographic treatment response: CT/MRI according to RECIST v1. and ^{123} I-MIBG scan
- **Secondary endpoints:** Blood pressure changes, HSA ^{131}I-MIBG related adverse events
- **Exploratory endpoint:** Correlation of responses with the genetic background

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Results (1):

- **N=24 patients (15 men, 62%)**. Median age: 44 y (range 18-82)
- **N=23 with metastases, n=1 unresectable primary tumor**
- N=17 (70%) hormonally active tumors, n=17 (70%) on antihypertensive medications before treatment
- N=13 (54%) previous antineoplastic treatment
- N=11 (46%) one dose of HSA ^{131}I-MIBG, n=13 (54%) two doses
- **Median duration of follow-up:15 months (range 2-52)**

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Results (2):

- **N=23 evaluable: Radiographic responses:**
  - **2 (9%) complete responses (CR)**
  - **10 (44%) partial responses (PR)**
  - **8 (35%) stable diseases (SD)**
  - **2 (9%) mixed responses (MR**
  - **1 (4%) progressive disease (PD)**
  - **Disease control rate (DCR) of 87%**
- Median time to response:12.5 months (95% CI, 4.6 to 25.1)
- Progression status prior to therapy unclear

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Results (3):

Radiographic responses - correlation with genetics:

- **Sporadic disease** (n=11, 48%): **DCR 82%**
- **Genetic mutation** (n=12, 52%) (*SDHB*, *VHL*, *RET*): **DCR 92%**

- N=17 (70%) hormonally active: Plasma metanephrines normalized n=3 (18%), improved by 50% n=5 (29%), stable levels n=1 (6%), no repeat levels n=4 (24%), increased n=4 (24%)

- N=22 (92%) blood pressure evaluable: Normalized n=9 (41%), improvement n=1 (5%)

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Results (4):

- **Most common adverse events:** Grade I/II nausea/vomiting and transient bone marrow suppression
- **Less common adverse events:** N=1 premature ovarian failure, n=3/24 (12%) grade III/IV myelosuppression, n=1 fatal pneumonitis, n=1 fatal gastrointestinal bleeding a month after treatment with unclear attribution to HSA ^{131}-I-MIBG

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Conclusions:

- **High DCR (87%) rega**
- **Severe adverse event**

AE Incidence Among 68 Patients with Unresectable Advanced PPGL Who Received Any Therapeutic Dose of HSA ^{131}I-MIBG

AE by preferred term	Treatment-related AE, all grades	Treatment-related AE, grades 3–5	Any AE, all grades
Nausea	52 (76)	1 (1)	53 (78)
Thrombocytopenia	49 (72)	28 (41)	49 (72)
Anemia	40 (59)	14 (21)	43 (63)
Leukopenia	41 (60)	28 (41)	41 (60)
Fatigue	32 (47)	7 (10)	41 (60)
Neutropenia	39 (57)	26 (38)	39 (57)
Vomiting	33 (49)	1 (1)	36 (53)
Dry mouth	27 (40)	0	28 (41)
Dizziness	16 (24)	1 (1)	27 (40)
Headache	15 (22)	0	21 (31)
Hypotension	8 (12)	1 (1)	18 (26)
Decreased appetite	14 (21)	1 (1)	17 (25)
Diarrhea	11 (16)	2 (3)	16 (24)
Constipation	4 (6)	1 (1)	16 (24)

Data are numbers followed by percentages in parentheses.
Grade 1 = mild AE; grade 2 = moderate AE; grade 3 = severe AE; grade 4 = life-threatening or disabling AE; grade 5 = death related to AE.

Pryma et al., J Nucl Med. 2019

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(OR12) Long-term Follow-Up of Pheochromocytoma/Paraganglioma (PPGL) after first diagnosis: a retrospective single-center study of 173 patients

Raphael Schendl (MD) et al., Medical University of Vienna, Austria

Background:

- **Long-term follow-up (FU)** and **genetic testing** recommended in all PPGL patients
- **Questions to answer:**
  - The most suitable duration of FU
  - The prognostic value of genetic mutations and clinical, biochemical or radiological findings during FU, of the incidence of tumor-recurrence (TR) after recommended 10 years FU of low-risk sporadic Pheos, or of TR on morbidity and mortality

(OR12) Long-term Follow-Up of Pheochromocytoma/Paraganglioma (PPGL) after first diagnosis: a retrospective single-center study of 173 patients

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Objective, patients, and methods:

- **Retrospective analysis** of the **overall survival (OS), progression-free survival (PFS) and tumor-recurrence (TR)**
- **N=173 PPGL** patients initially operated, followed-up at a single tertiary referral center **1988-2020** by Kaplan-Meier Estimates
- Assessment of **age, sex, hormonal activity, tumor size, metastatic spread at first diagnosis, pathohistological PASS score, mutation-positive PPGLs, tumor-recurrence, comorbidities (associated with increased cardiovascular risk)** as **independent prognostic markers** by multivariate Cox-regression. Certificats of the Austrian death registry were obtained.

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Results (1):

- No FU n=8 (5%), but death was certified 65±28 months/5.4±2.3 yrs after first diagnosis
- The remaining **n=165:** Mean age 49 (±16) yrs (43.9% female)
  - **94.5% Pheos, 3.0% multiple PGLs, 2.5% head-and-neck PGLs**
  - **Mean (range) FU 90 (3-537) months/7.5 yrs**

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Results (2):

- **93 (54%) genetic testing**
  - **37 (40%**, 21% of entire cohort) **mutation-positive** (**mean±SD age 33.8±13.2 yrs**, **OS 391 months/32.6 yrs**)
  - **56 (60%) mutation-negative** (**mean±SD age 53.3±14.8 years, OS 190 months/15.8 yrs**)
  - **Mutation-positive patients significantly younger versus mutation-negative ones (p<0.01)**
  - **OS of mutation-positive patients significantly longer versus mutation-negative ones (p=0.03)**

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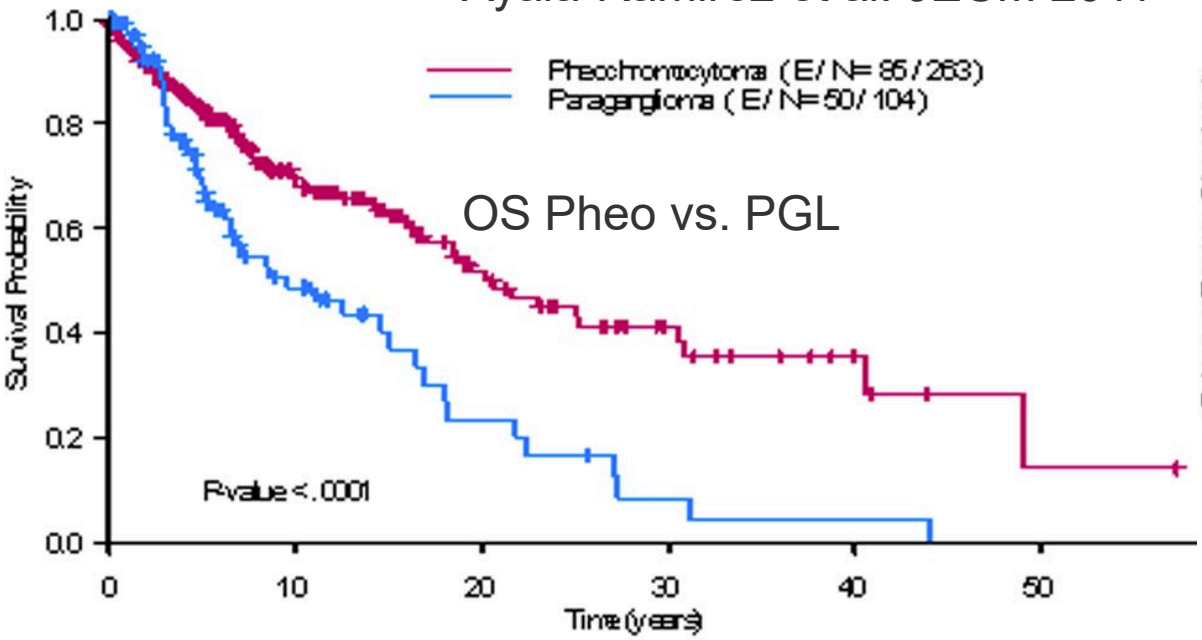
Results (3):

- **Independent negative predictors of OS by univariate analysis: Male sex, higher age, presence of comorbidities, primary metastatic disease, but by multivariate analysis only age and metastatic disease significant**

- **Independent negative predictors of PFS by univariate analysis: Higher age and no hormonal activity (but not by multivariate analysis !)**

A

Ayala-Ramirez et al. JECM 2011



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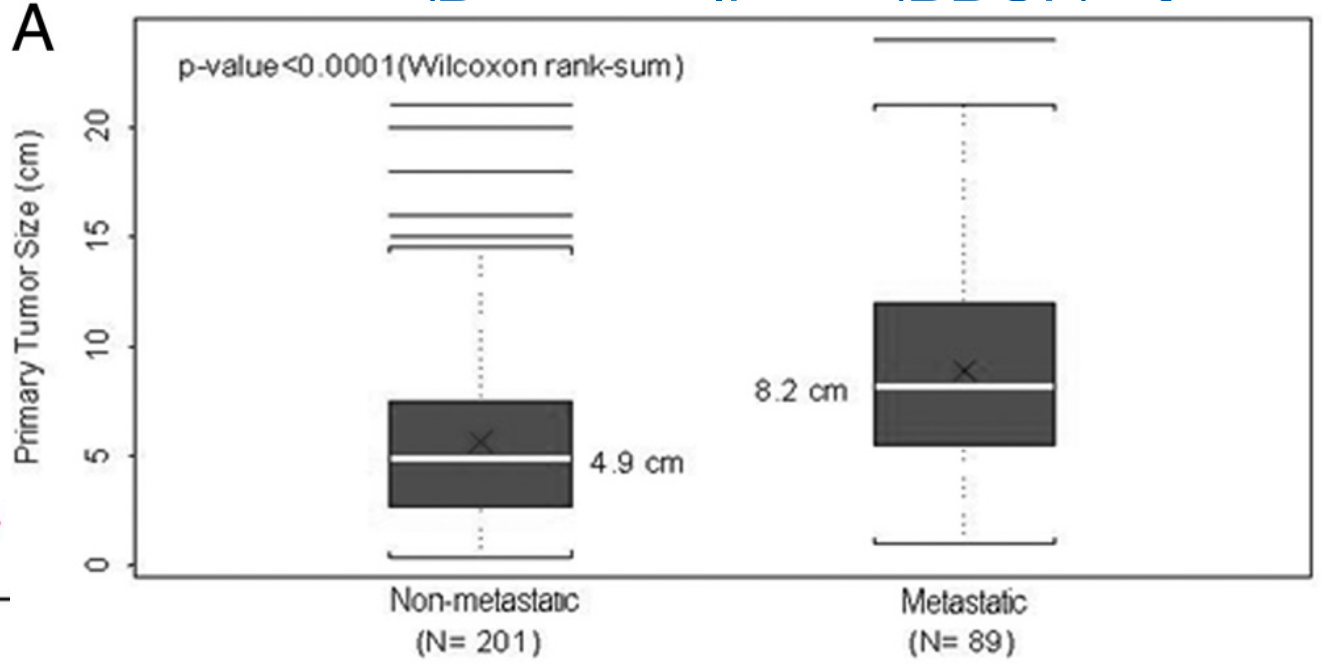

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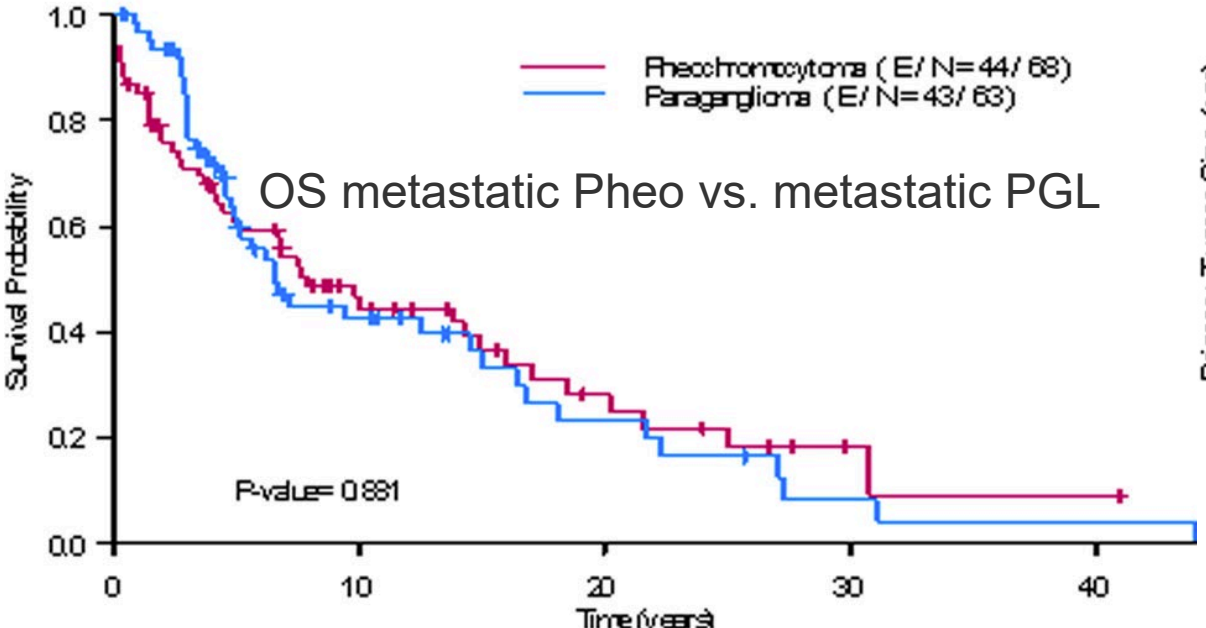

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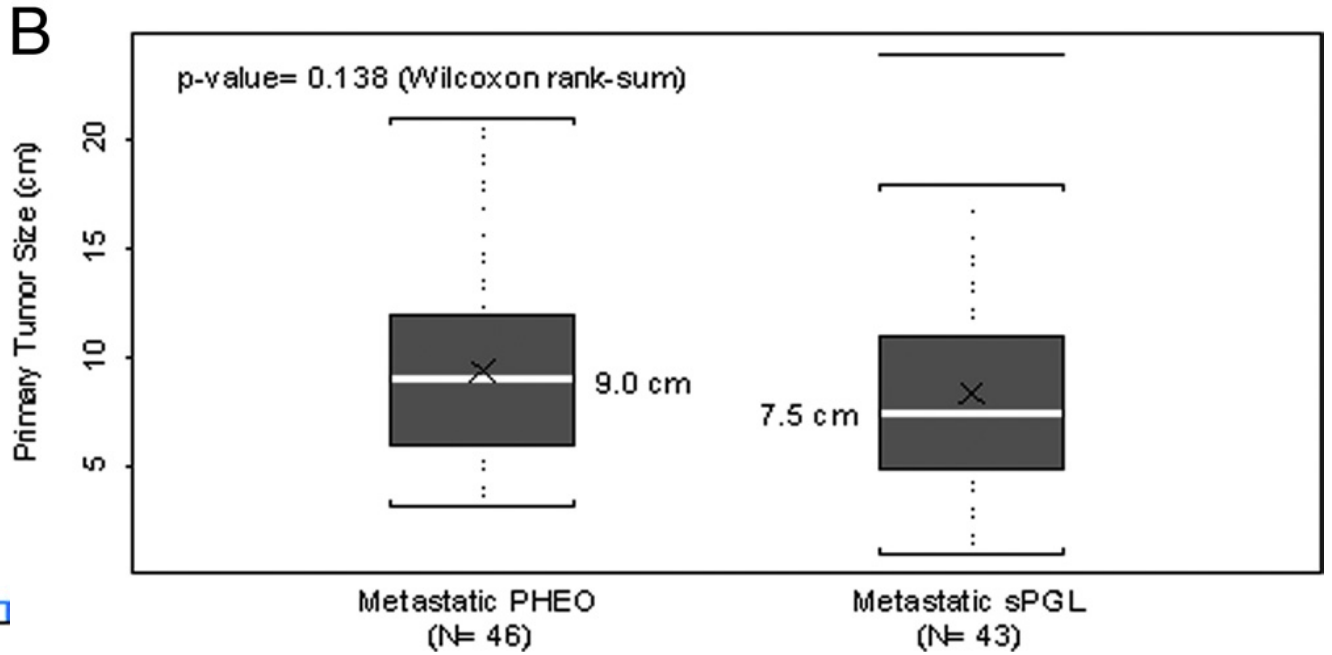

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Conclusions:

- **Shorter Overall Survival** of PPGL **with higher age and metastatic disease at first diagnosis**
- **However, tumor size, presence of sympathetic PGL, sex, hormonal activity, pathohistological PASS score, genetic mutations, presence of comorbidities, or tumor recurrence may not be predictive**

Outlook:

- **A multi-center study approach**, **prospective long-term follow-up,** and **genetic testing** in **every patient** may identify more independent **prognostic risk factors for long-term Overall Survival or Progression Free Survival**

➢ **Recruiting MUPPET/PROSPHEO study (current n=271)**

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Thank you!

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ENS@T registry and **PROSPHEO/MUPPET** project leader

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