Diagnostic et prise en charge des phéochromocytomes (PH) et paragangliomes (PG)

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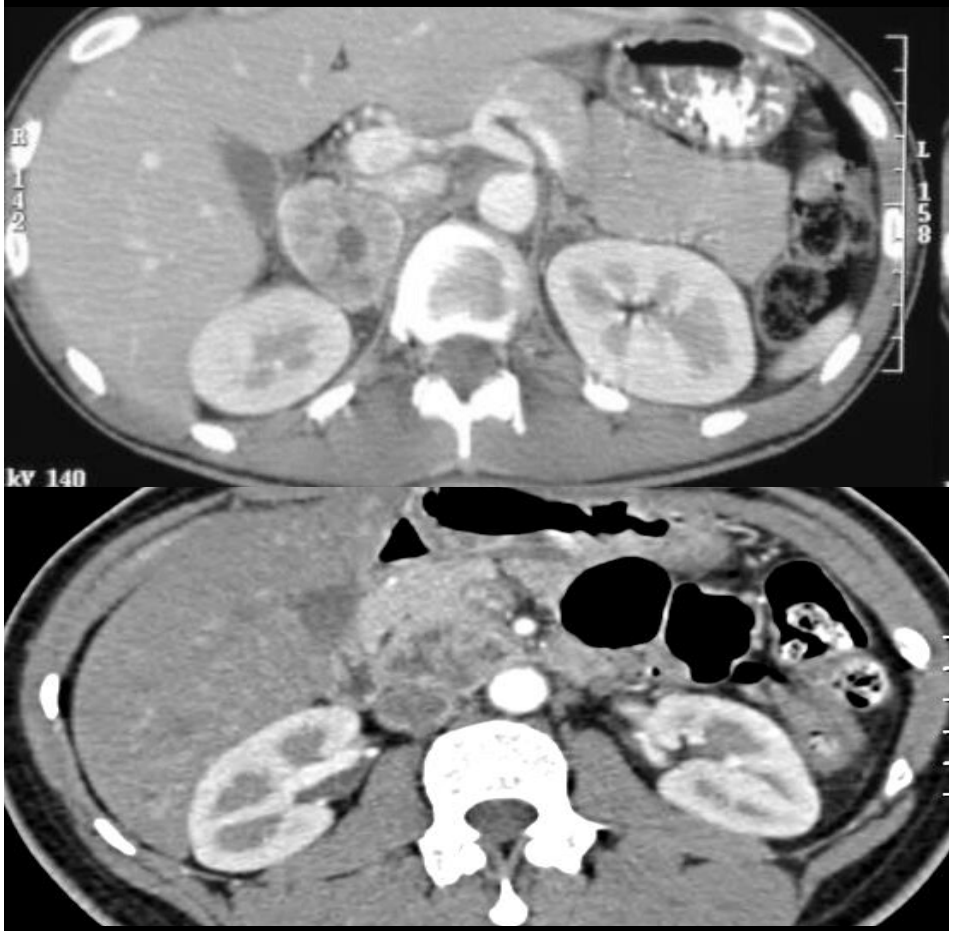
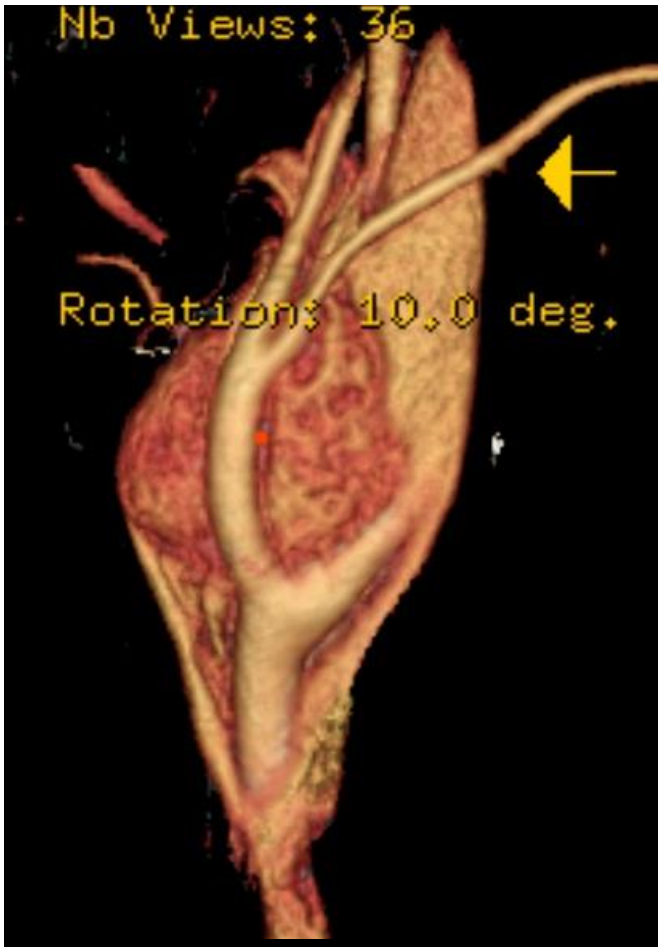
Chromaffin tumors: PH and PG

PH proper

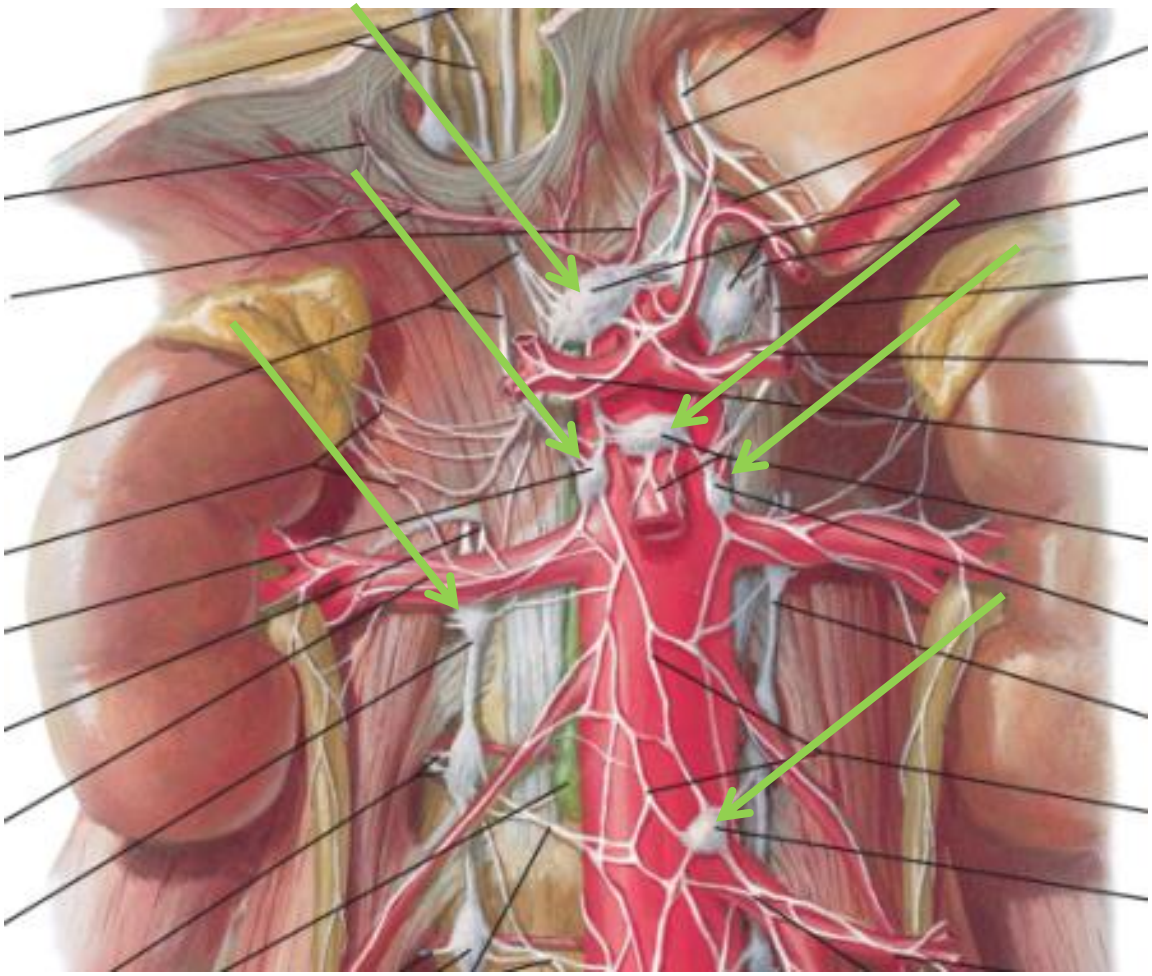


Functioning PG

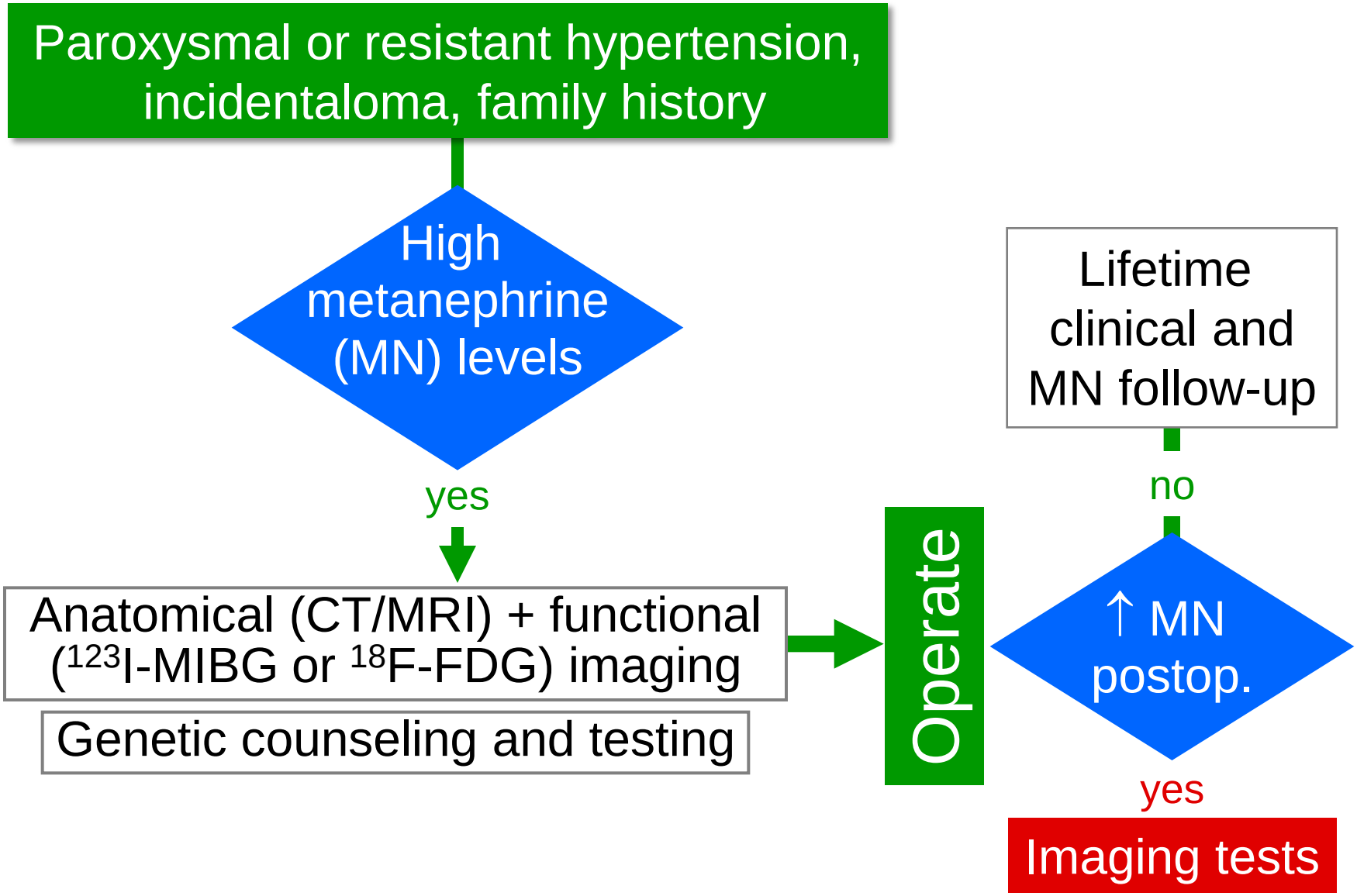


Head and neck PG

Paraaortic bodies



MESH: small masses of chromaffin cells found near the sympathetic ganglia along the abdominal aorta, also called the organs of Zuckerkandl

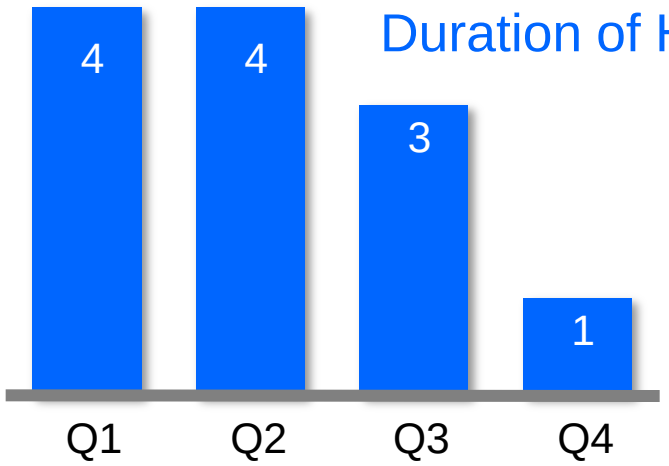

Paroxysmal or resistant hypertension, incidentaloma, family history
High metanephrine (MN) levels
yes
Anatomical (CT/MRI) + functional (^{123}I-MIBG or ^{18}F-FDG) imaging
Genetic counseling and testing
Operate
Lifetime clinical and MN follow-up
no
↑ MN postop.
yes
Imaging tests

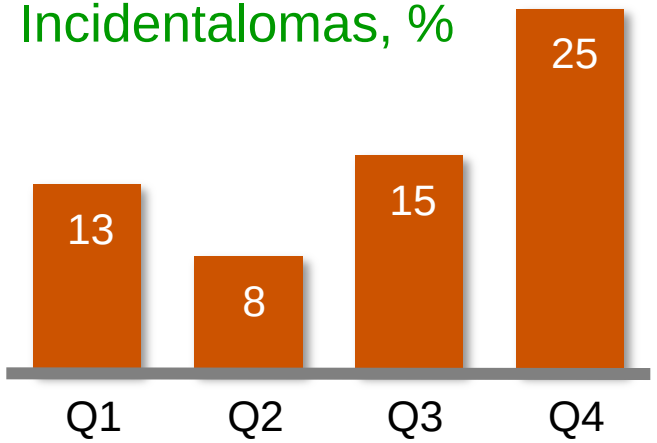
When to screen for a PH/PG

- Paroxysmal hypertension and/or hypertension with adrenergic symptoms
- Drug-resistant hypertension
- Hypertension + diabetes and BMI <25 kg/m^2 in patients <50 years*
- Positive family history or syndromic presentation
- Incidentaloma

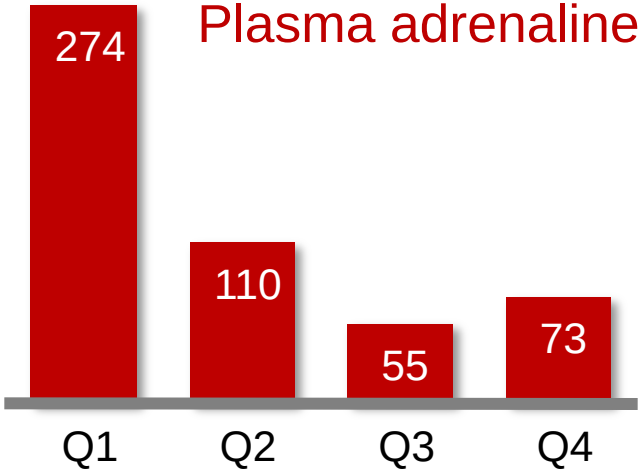
* La Batide Alanore et al, J Hypertens 2003;21:1703 [OR 19]

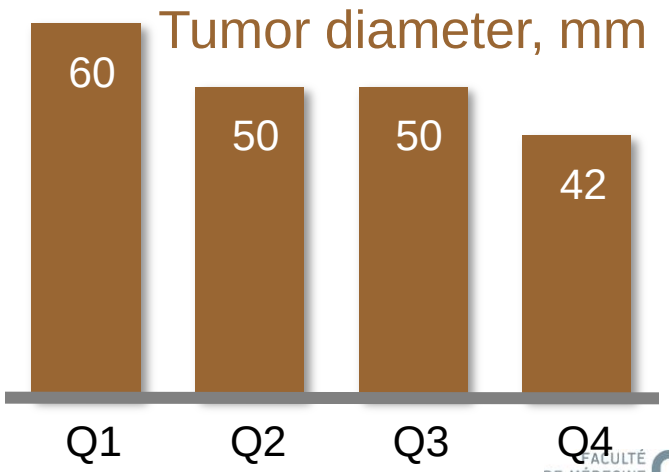
Presentation by quartile of date of operation





p for trend <0.01





Amar L et al, J Clin Endocrinol Metab 2005;90:2110

Metanephrine determinations

Adrenaline → Metanephrine (COMT)

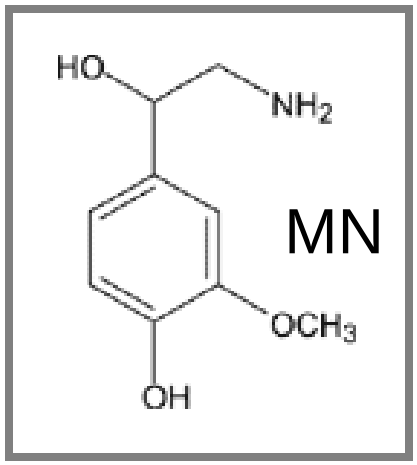
NorA → NorMN (COMT)

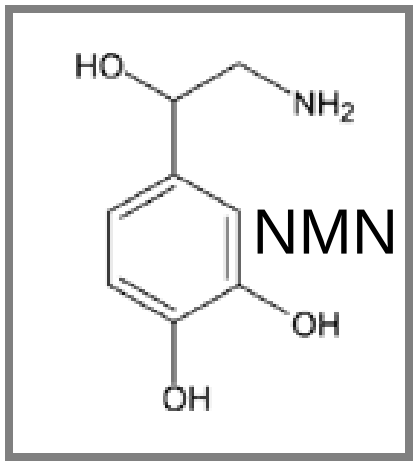
Metanephrine → MN sulfate (SULT1A3)

NorMN → NorMN sulfate (SULT1A3)

Free

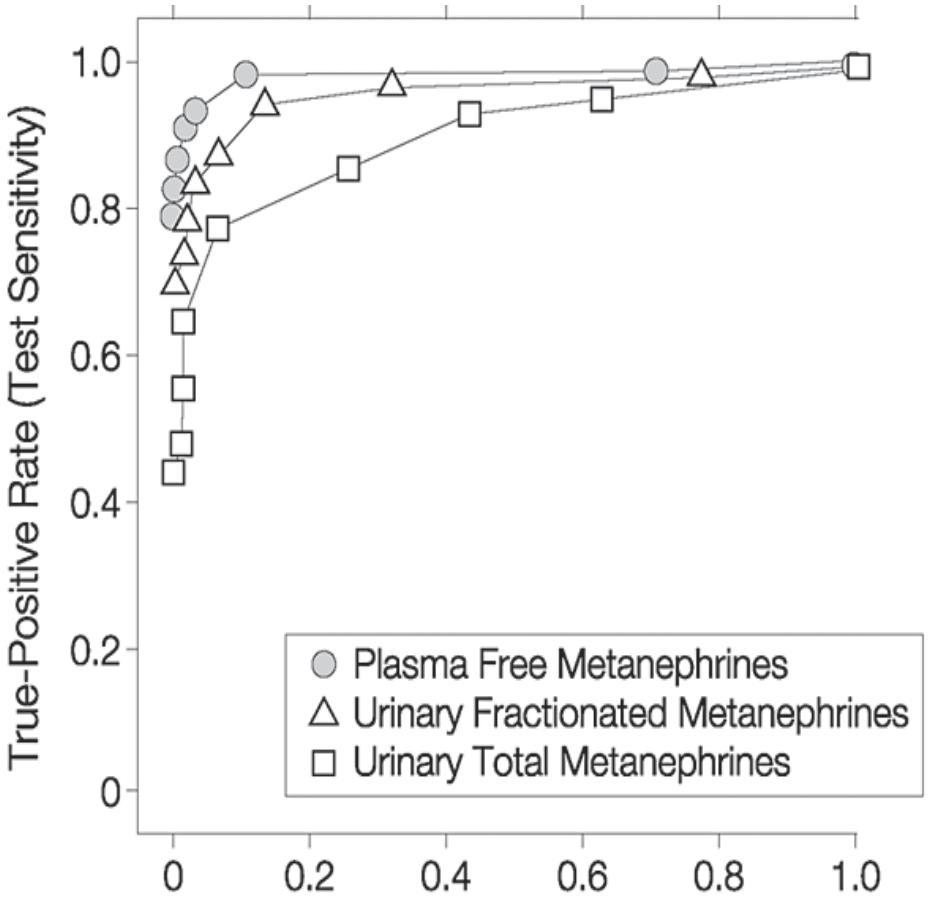
Total





Plasma free MN or urinary MN excretion?

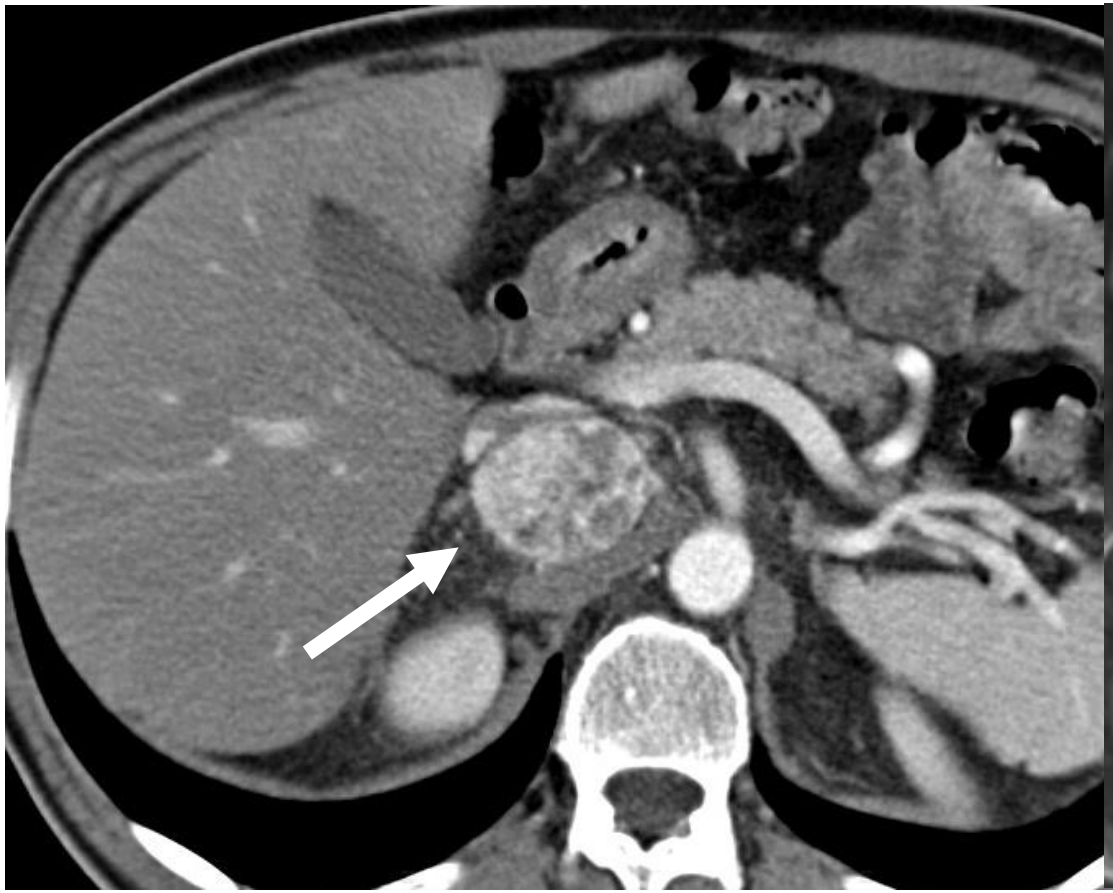
MNs are continuously produced by the tumor
Total MNs include conjugated MNs produced by a gut sulfo-transferase
Free MNs mostly have an extra-renal clearance

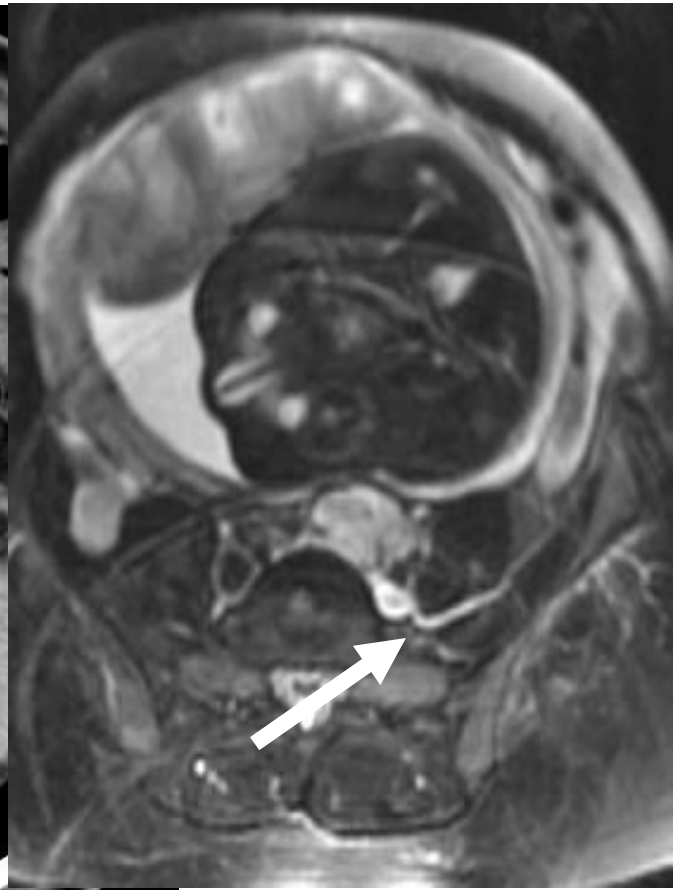


Eisenhofer G et al, JCEM 1998;83:2175
Eisenhofer G, Clin Chem 2001;47:988

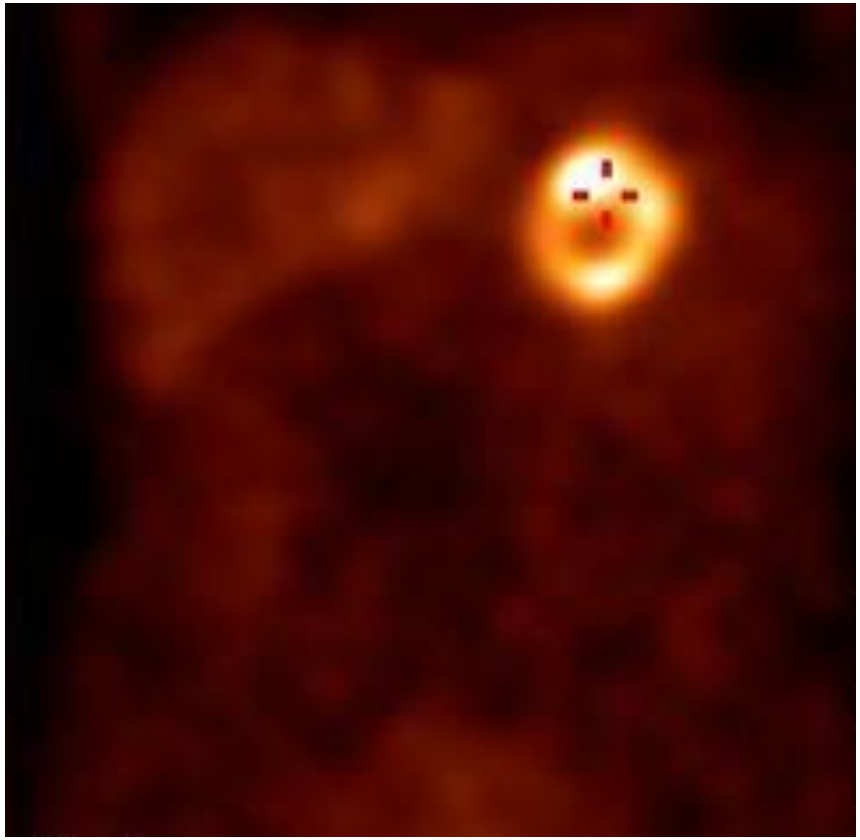
Lenders J et al, JAMA 2002;287:1427

Anatomical imaging: CT, MR

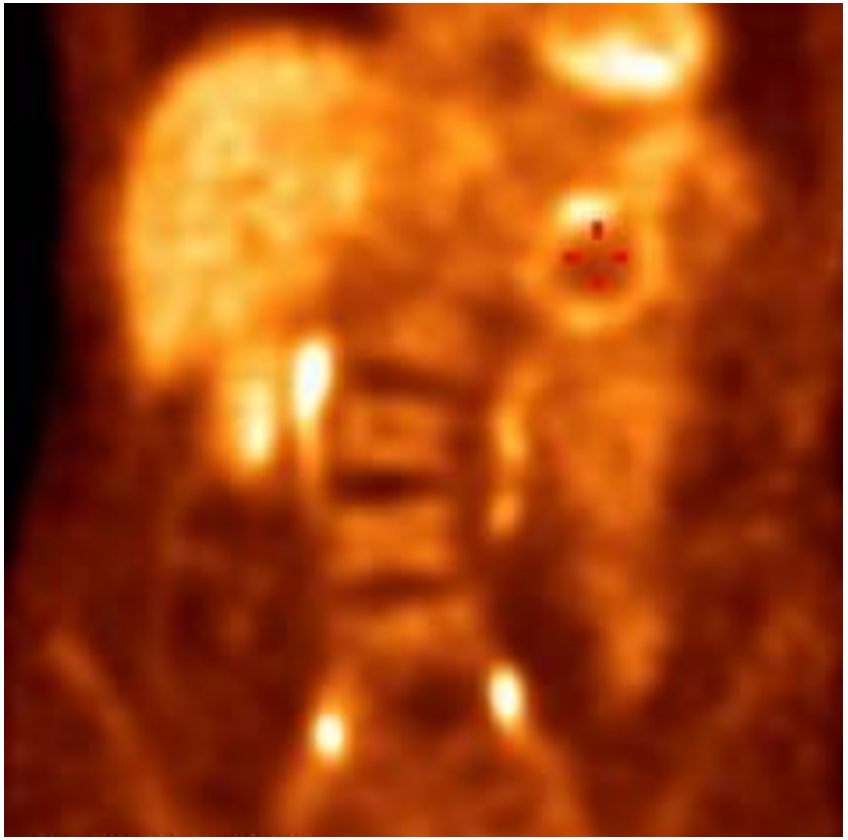




Functional imaging

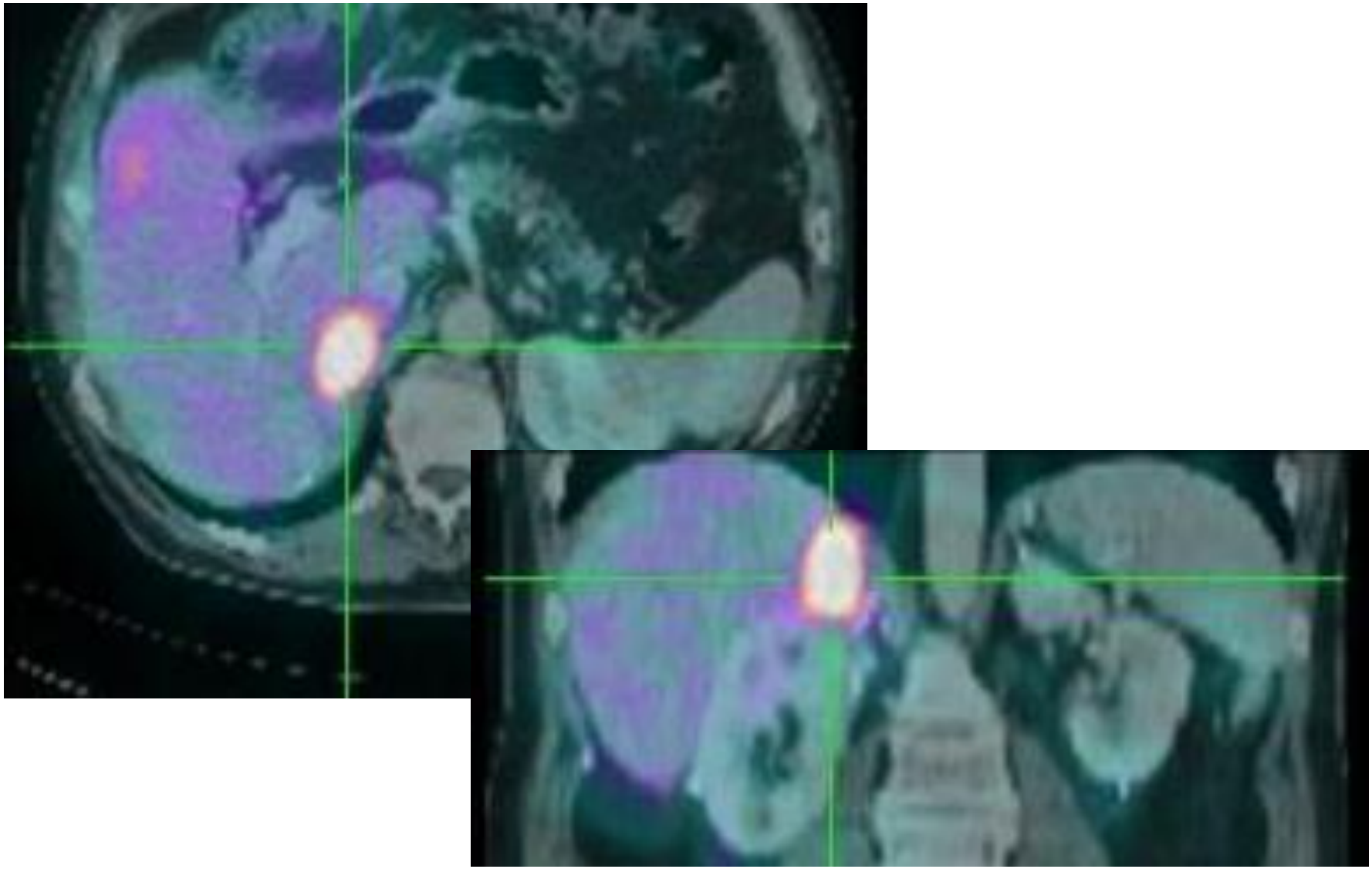


Specific: ^{123}I-MIBG, FDA-PET

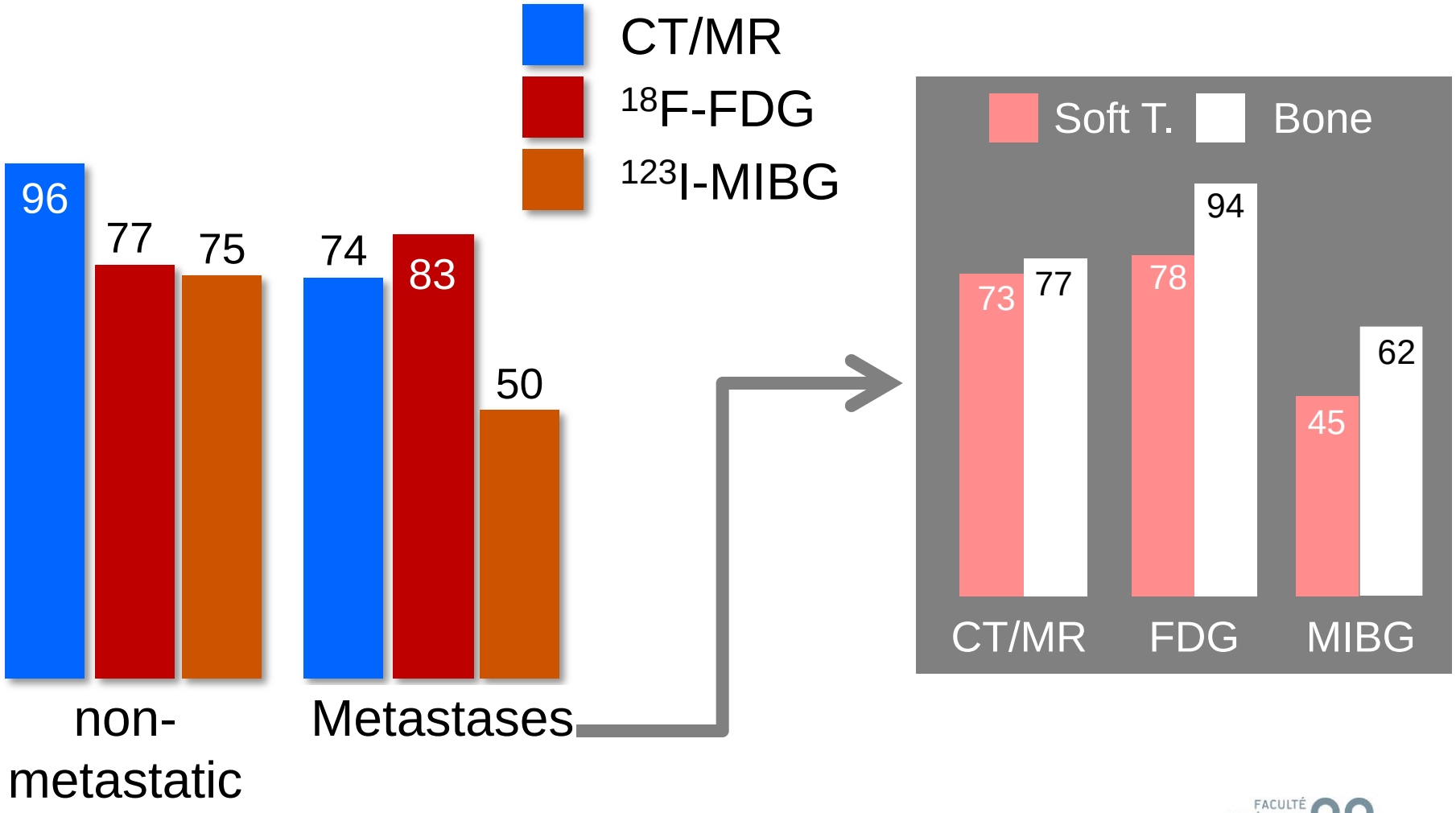


Nonspecific: ^{18}F-FDG-PET
DOPA-PET, Octreoscan

Image fusion



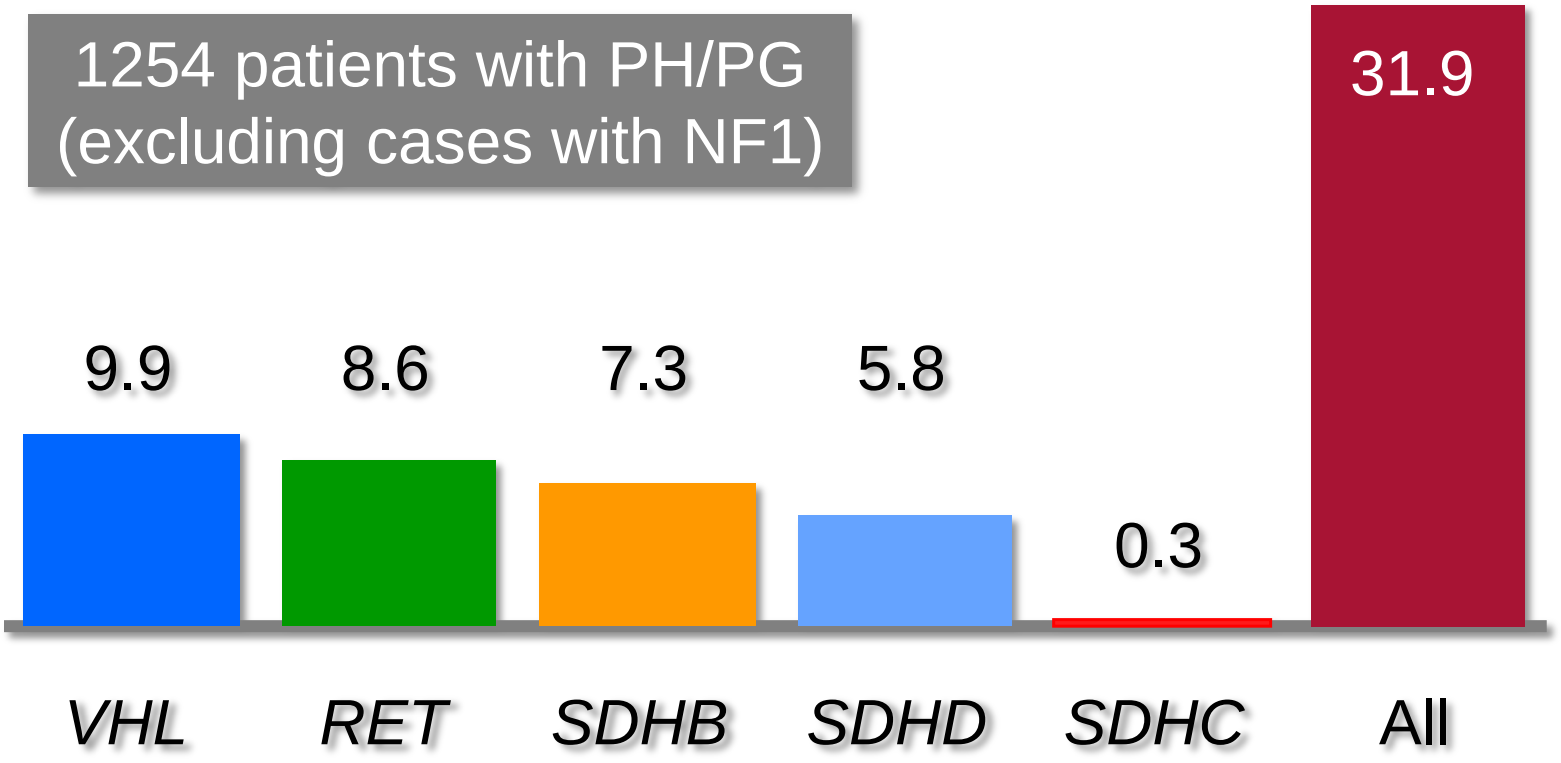
Sensitivities (%) of imaging tests



Timmers HJ et al, J Natl Cancer Inst 2012;104:700

Inherited PH/PG (%) in 4 European series

1254 patients with PH/PG (excluding cases with NF1)

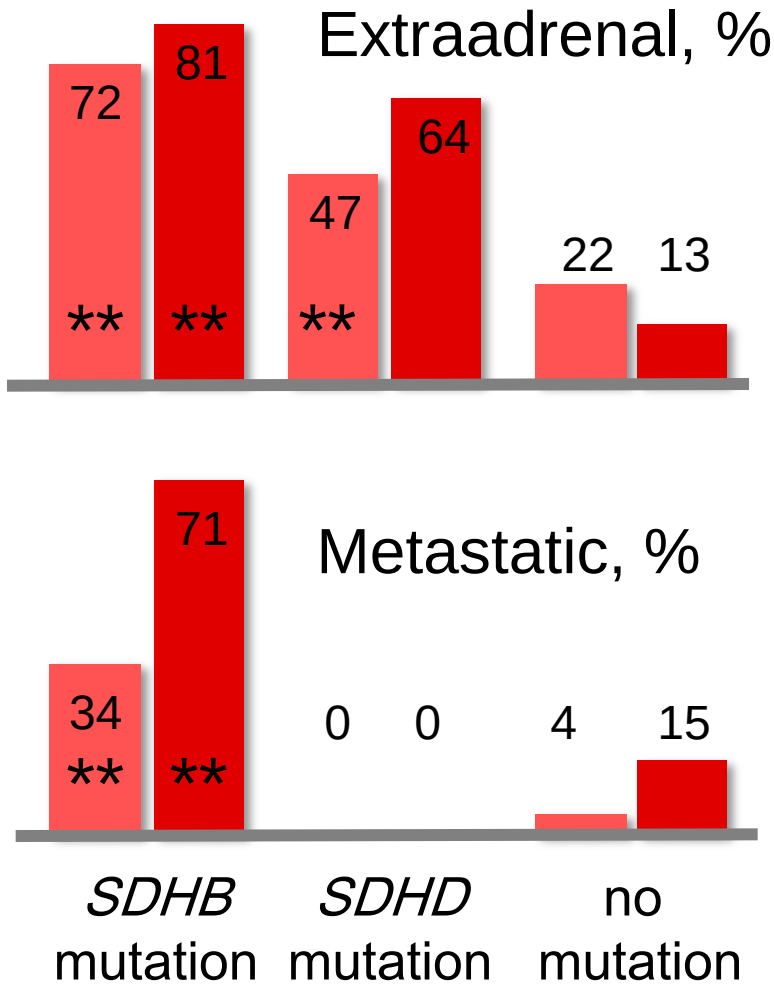


Spain, n=192 — Cascon A et al, J Clin Endocrinol Metab 2009;94:1701
Germany, n=271 — *in:* Gimenez-Roqueplo AP et al, Clin Endocrinol 2006;65:699
France, n=301 — Amar L et al, J Clin Oncol 2005;23:8812
Italy, n=490 — Mannelli M et al, J Clin Endocrinol Metab 2009;94:1541

Tumor features in *SDH* mutation carriers

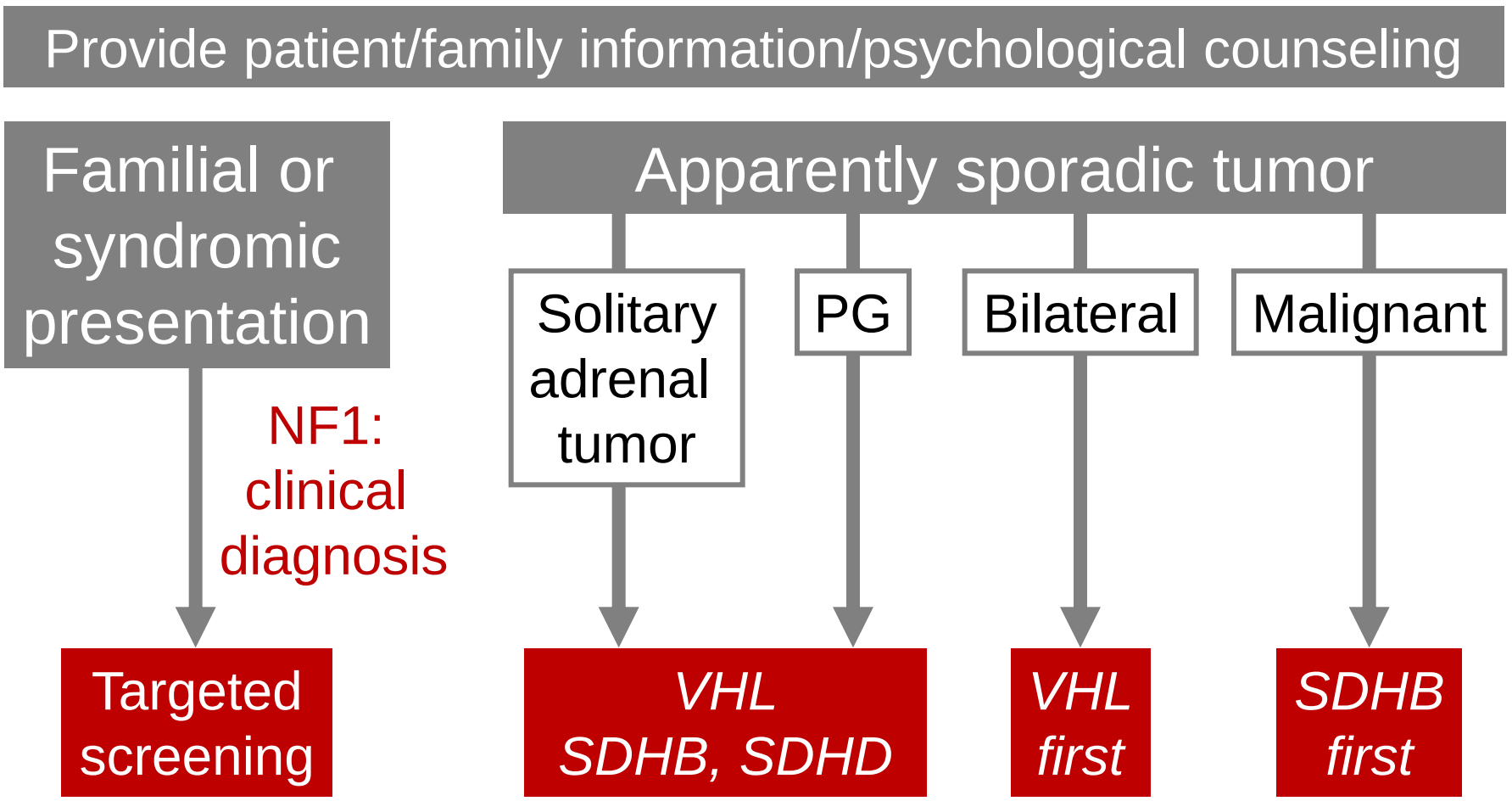
SDHB mutations and odds ratio for:	
Extraadrenal tumor	18.9
Metastatic or recurrent tumor	19.8

Gimenez-Roqueplo AP et al,
Cancer Res 2003;63:5615



Neumann H et al, JAMA 2004;292:943
Amar L et al, J Clin Oncol 2005;23:8812

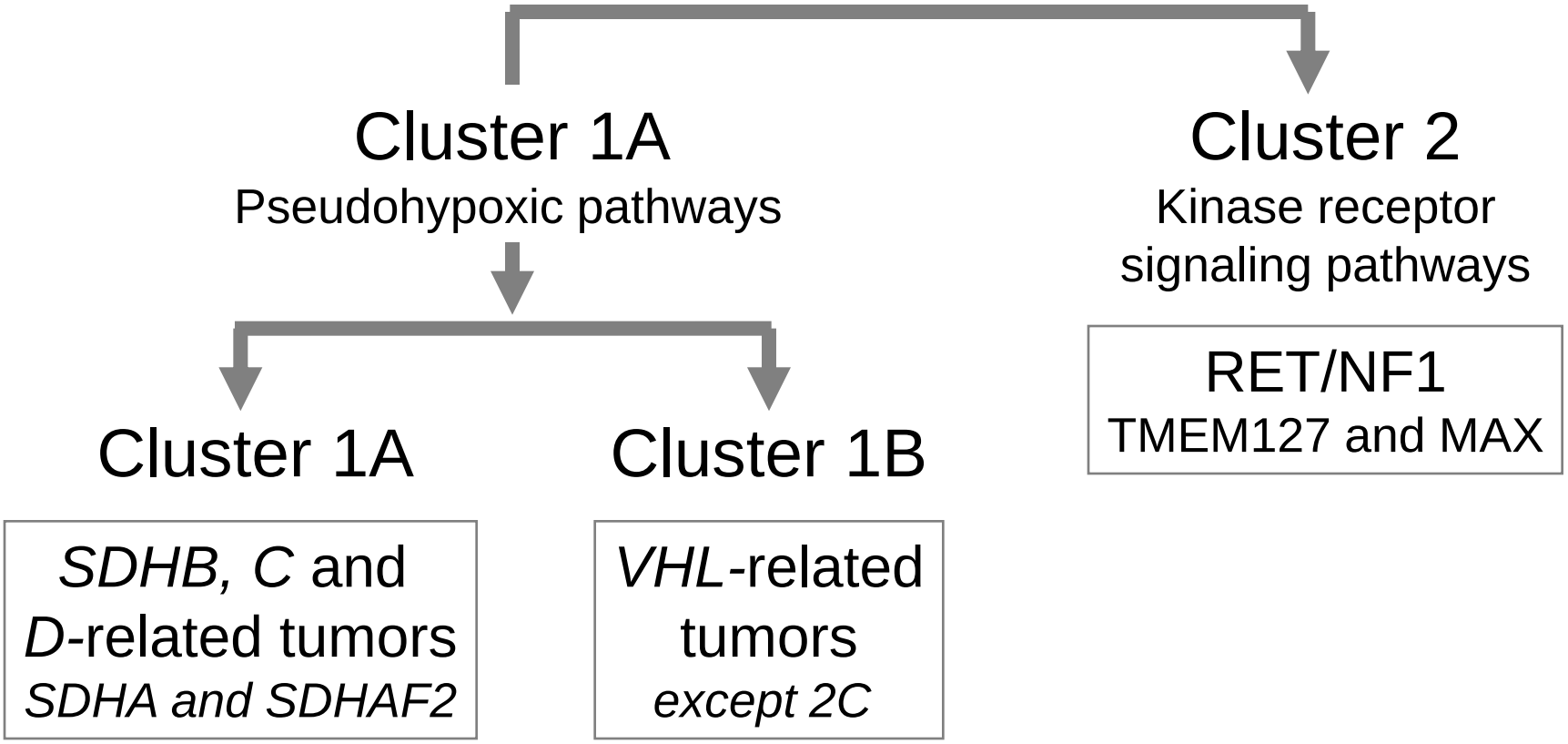
Suggested screening



SDHB immunostaining facilitates genetic screening

Recent reports of mutations in *TMEM127, SDHAF2* and *SDHA*

Transcription-based classification



Cluster 1 tumors synthetize noradrenaline, uptake FDG, and could respond to antiangionenic Rx

Gimenez-Roqueplo AP, Dahia P, Robledo M. Horm Metab Res 2012;44:1

Preoperative control of BP

Use	Do not use
α-blockade then β-blockade	β-blockade alone
Plasma volume expansion	Diuretics
Calcium-channel blockers (renin-angiotensin antagonists)	Drugs that affect catecholamine turnover

Unopposed β-blockade can induce acute crises in Pheo

Sibal L et al, Clin Endocrinol 2006;65:186

Drugs that can induce PH crisis

D2 receptor antagonists

metoclopramide, chlorpromazine, droperidol

Monoamine oxidase inhibitors

Non cardio-selective β-blockers

Noradrenaline and serotonin reuptake inhibitors

Peptides: ACTH, glucagon

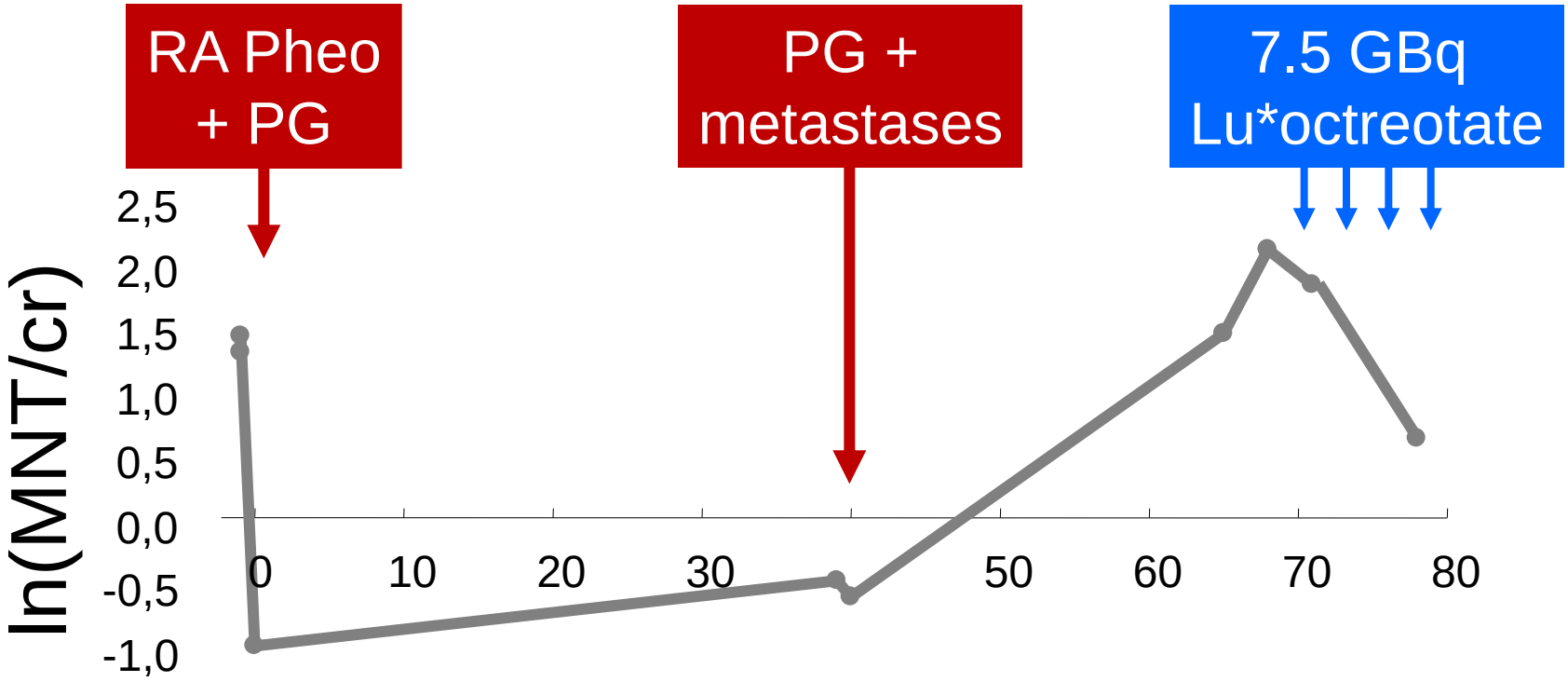
Steroids in high doses

Postoperative follow-up: rationale

Total number	1486	
with malignant primary tumor	83	5.6%
No. with follow-up (2-15 years)	991	
with malignant recurrence	112	11.3%
with new tumor	44	4.4%
with any tumoral event	156	15.7%
Malignant at any time	195	>13.1%

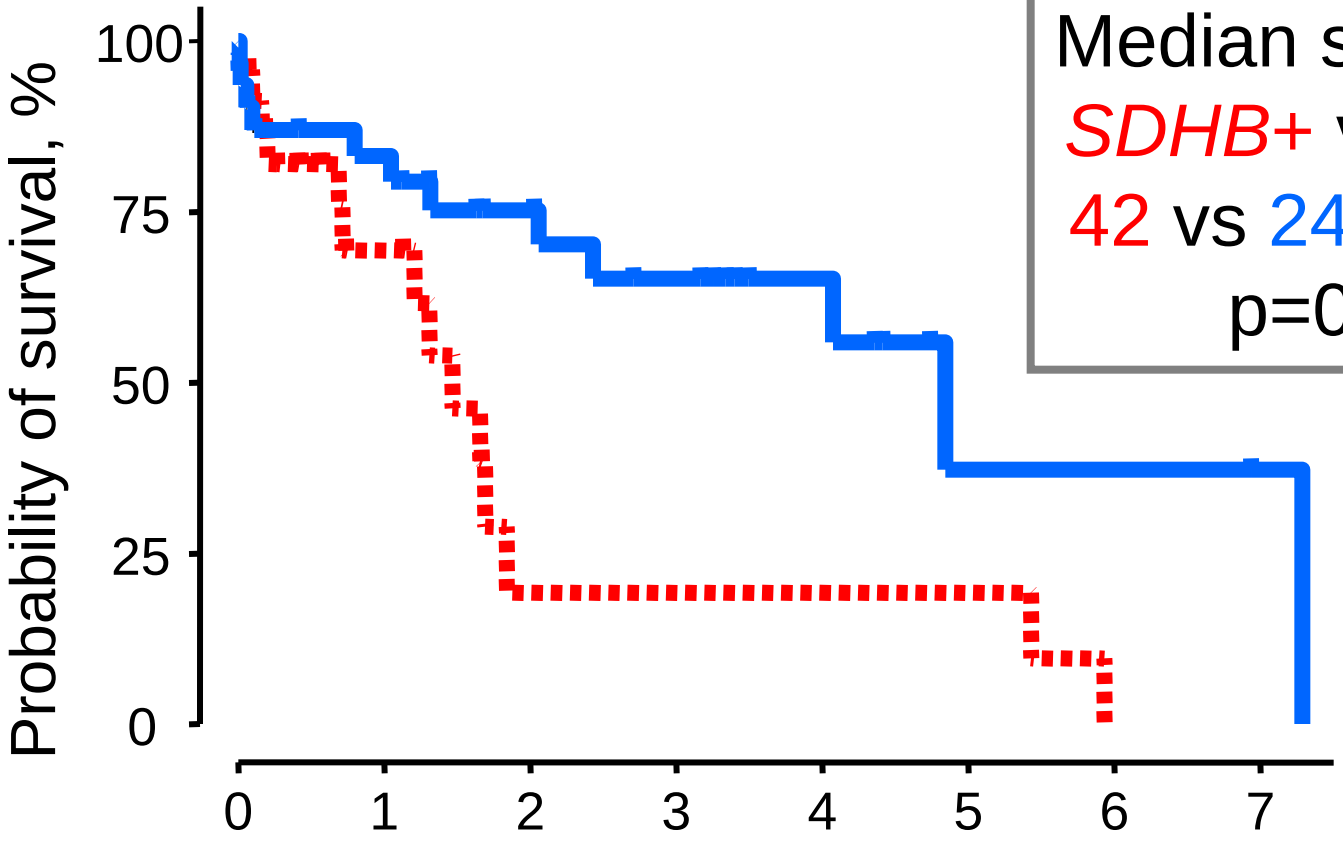
Amar L et al, Horm Metab Res 2012;44:385

Follow-up of a patient with *SDHB* mutation



Survival in malignant PH/PG

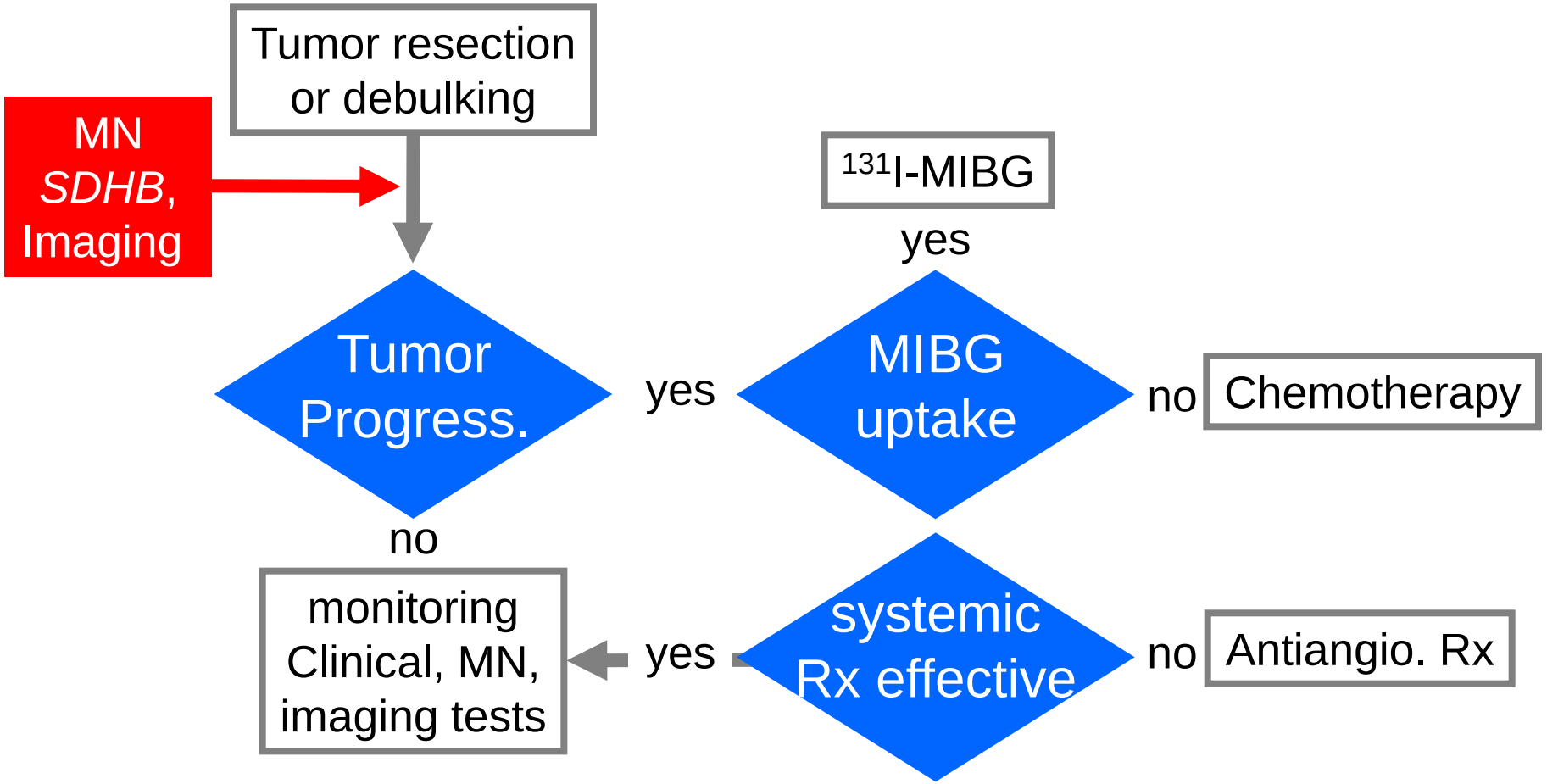
54 malignant tumors including 23 with *SDHB* mutations



Median survival in *SDHB+* vs *SDHB-*
42 vs 244 months
p=0.012

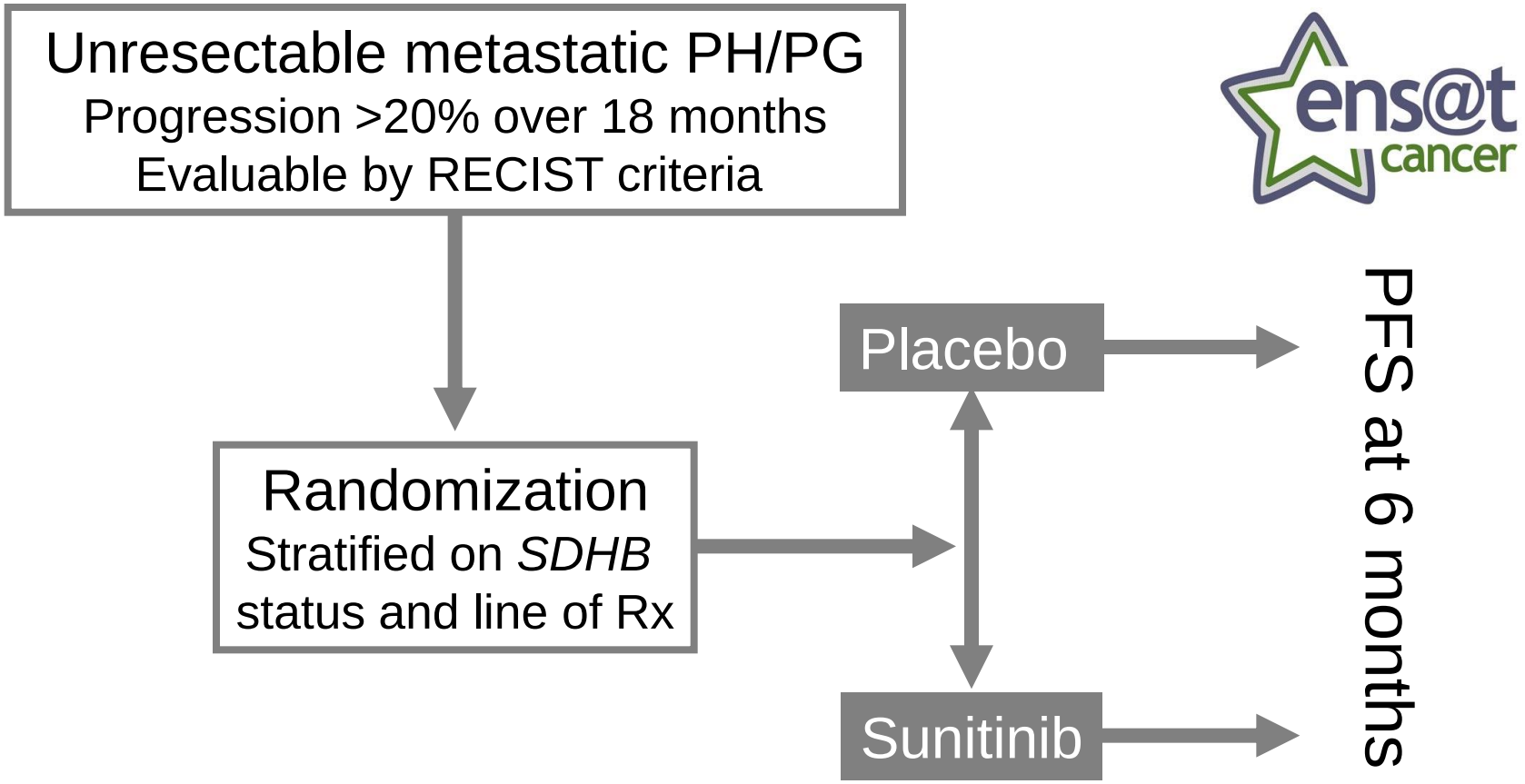
Amar L et al, J Clin Endocrinol Metab 2007;92:3822

Proposed management following 1st metastasis



Antiangiogenic Rx in metastatic PhH/PG

FIRSTMAPPP, a randomized phase II multicenter trial



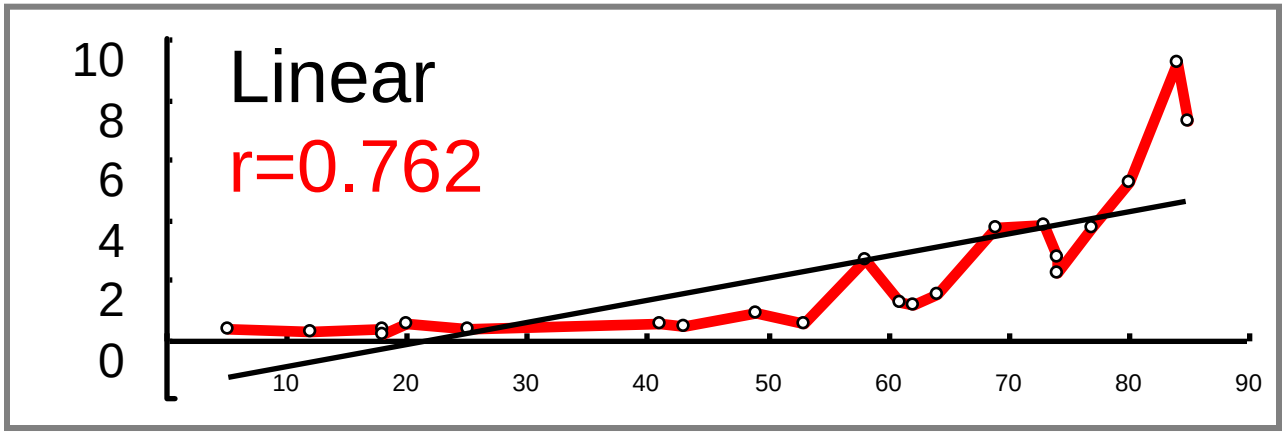
ENS@T-Cancer is funded by the European Commission within the 7th Framework Programme

Summary

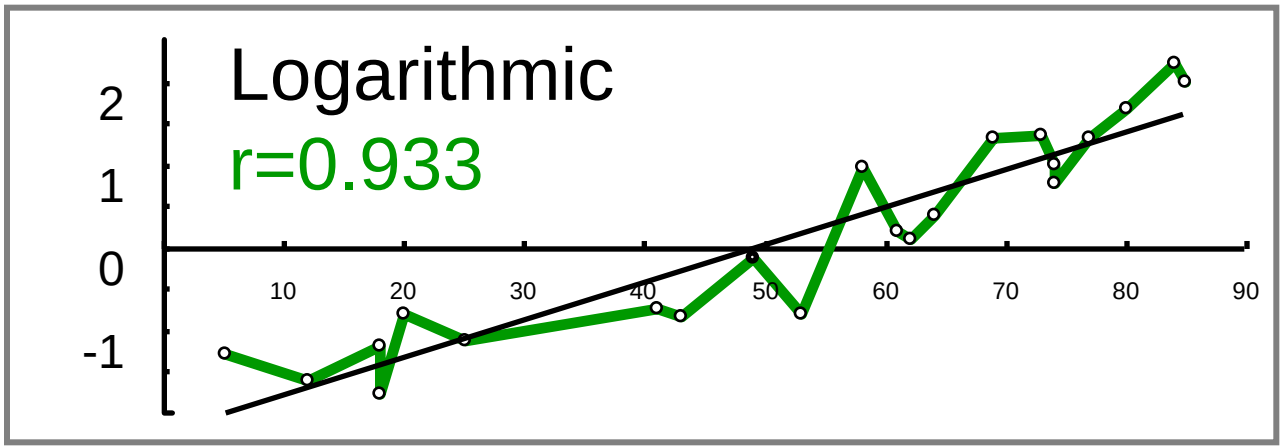
- The most specific and sensitive diagnostic test for PH and functional PG is the determination of metanephrines
- Tumors are located by CT/MR and MIBG or FDG
- Targeted genetic testing should be offered to patients with evidence of syndromic or familial disease, and testing for VHL and SDHx mutations should considered in patients with apparently sporadic tumors
- *SDHB* mutations are associated with a risk of malignancy
- Patients, especially those with familial, extra-adrenal or large (>6 cm) tumors, should be followed-up indefinitely

MN/Cr rises exponentially in malignant T

MN/cr

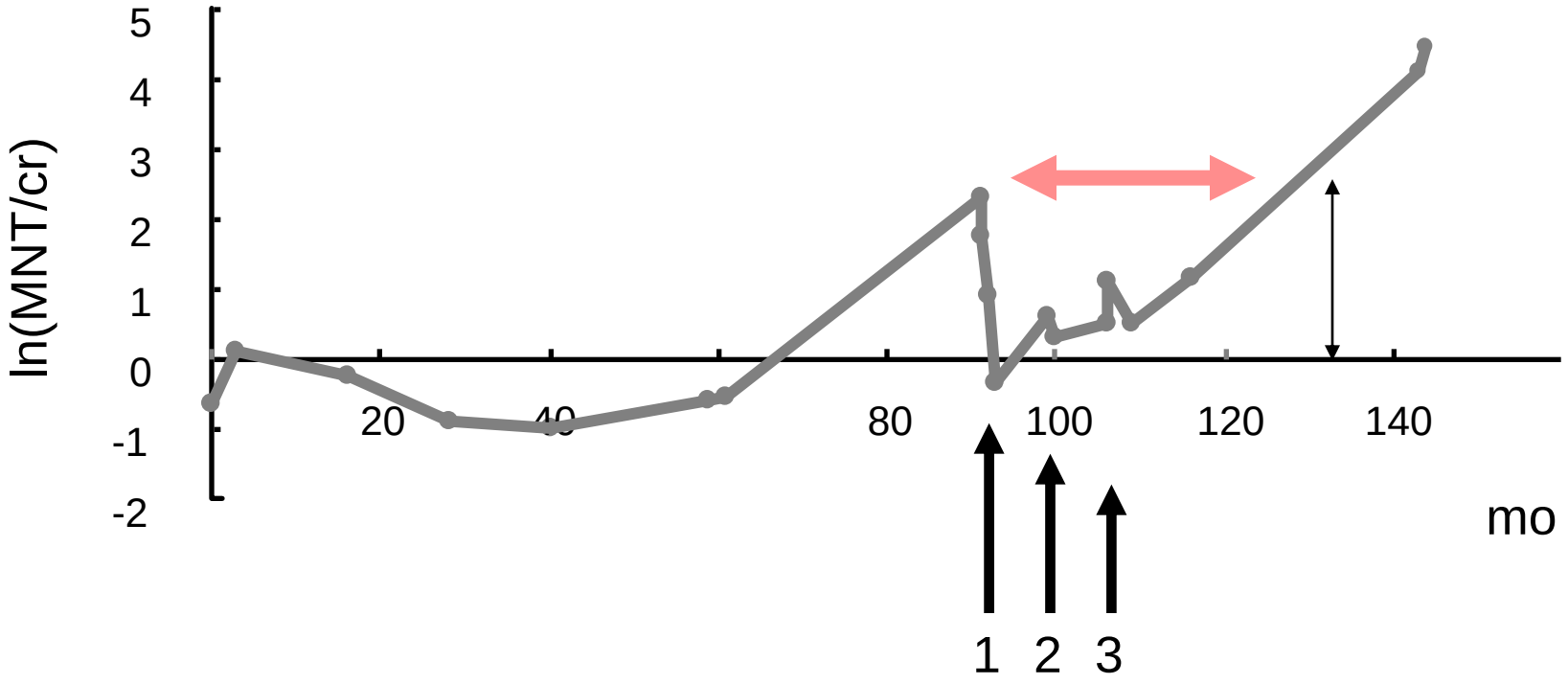


ln(MN/cr)



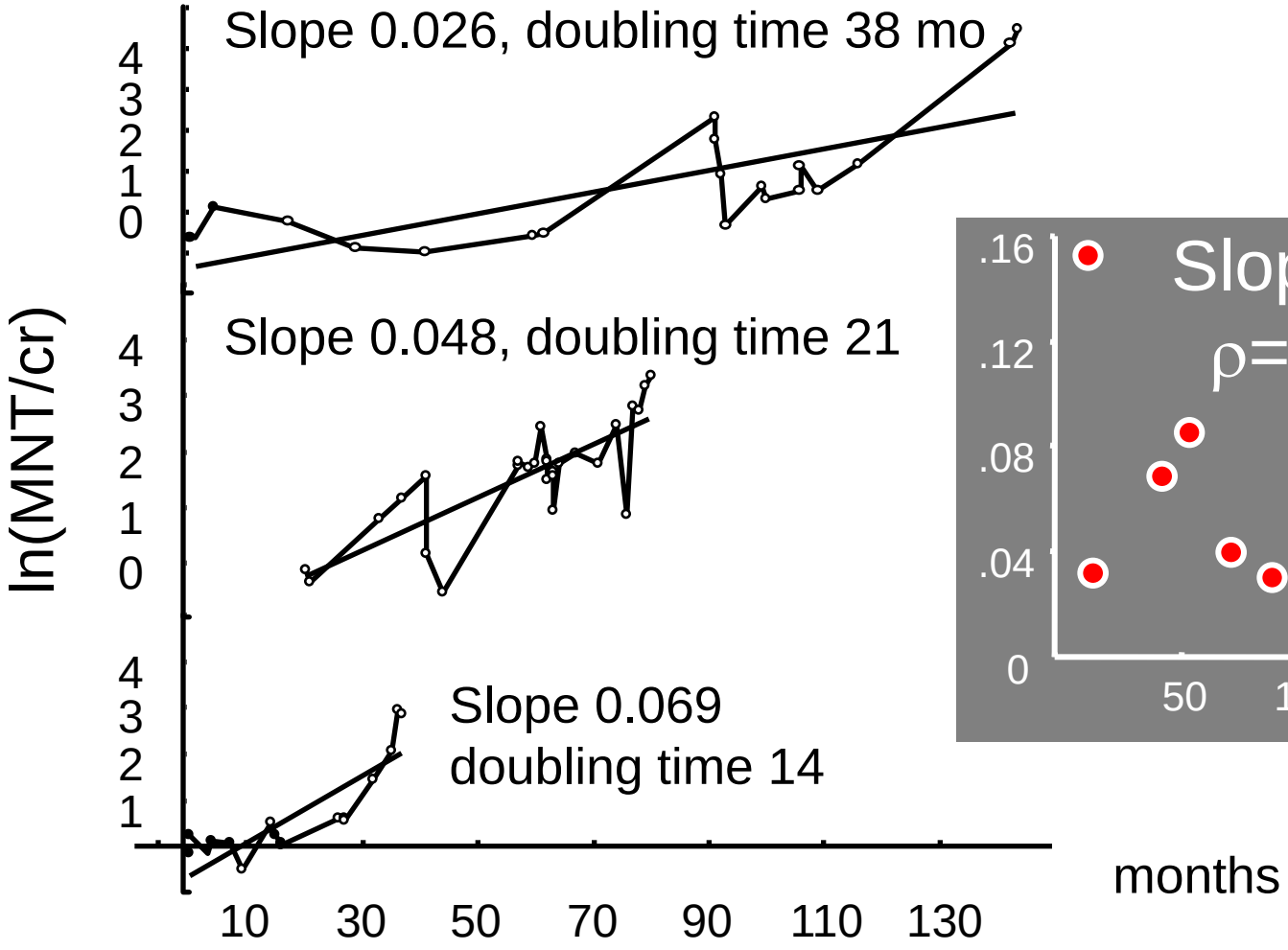
Amar L et al, Ann NY Acad Sci 2006;1073:383

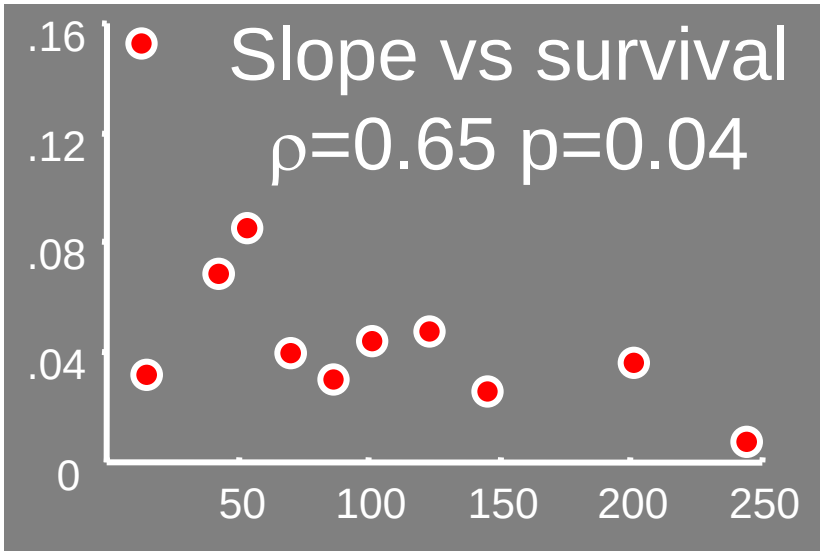
Effect of tumor embolization



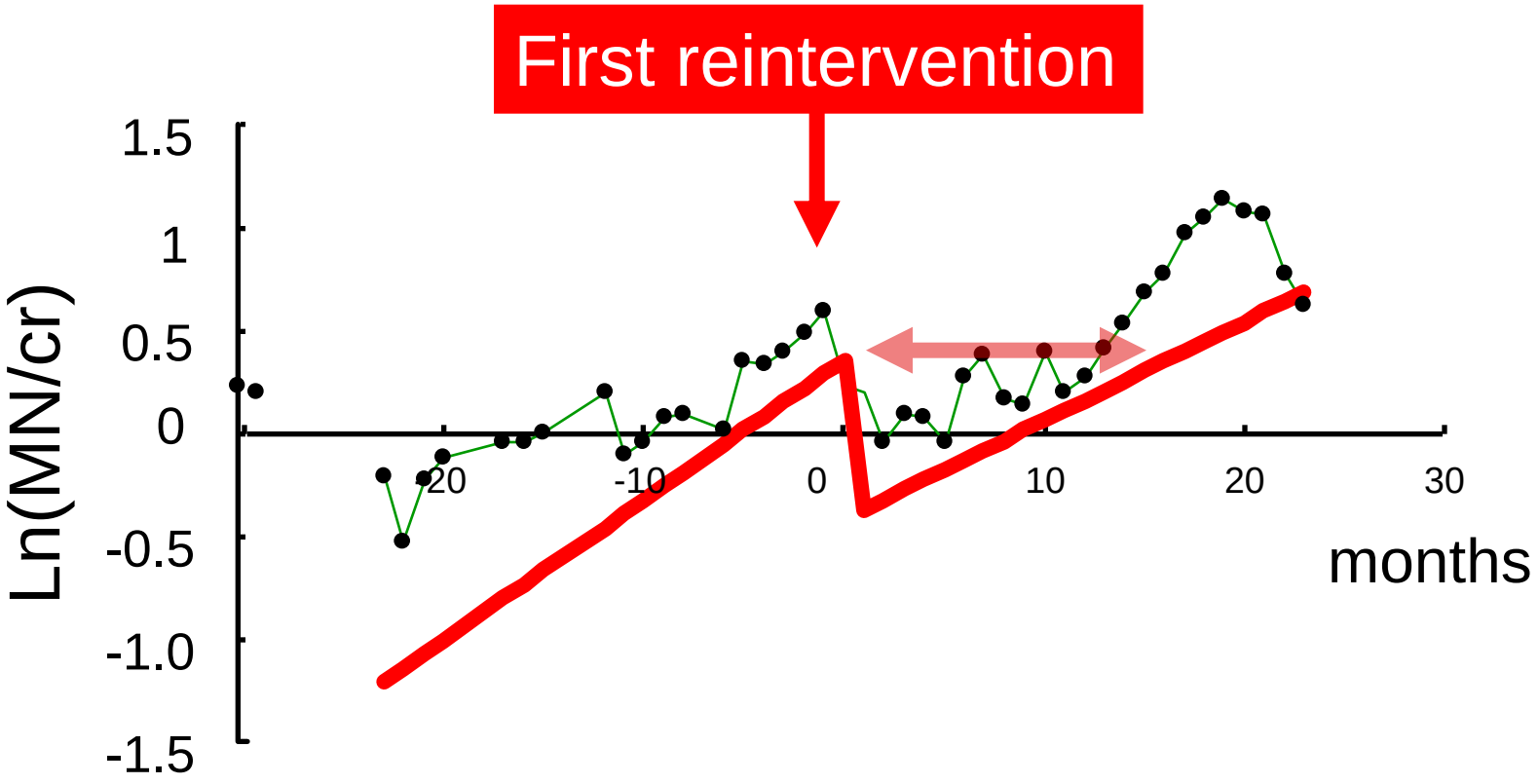
Embolisations of liver metastases

MN/Cr doubling time and survival





Effect of tumor debulking on survival



Reintervention reduced the MN/Cr ratio
and apparently delayed tumor growth by 18 months
(n=20, 95% CI: 16.0-18.0 mo, p<0.001)

CT/MRI vs ^{123}I-MIBG and ^{18}F-FDG

For nonmetastatic tumors

CT/MR have a sensitivity of 96% and a specificity of 90%

^{123}I-MIBG and ^{18}F-FDG have lower sensitivities (75% and 77%) and similar specificities (92 and 90%)

FDG uptake is higher in SDH/VHL-related that in MEN2-related tumors

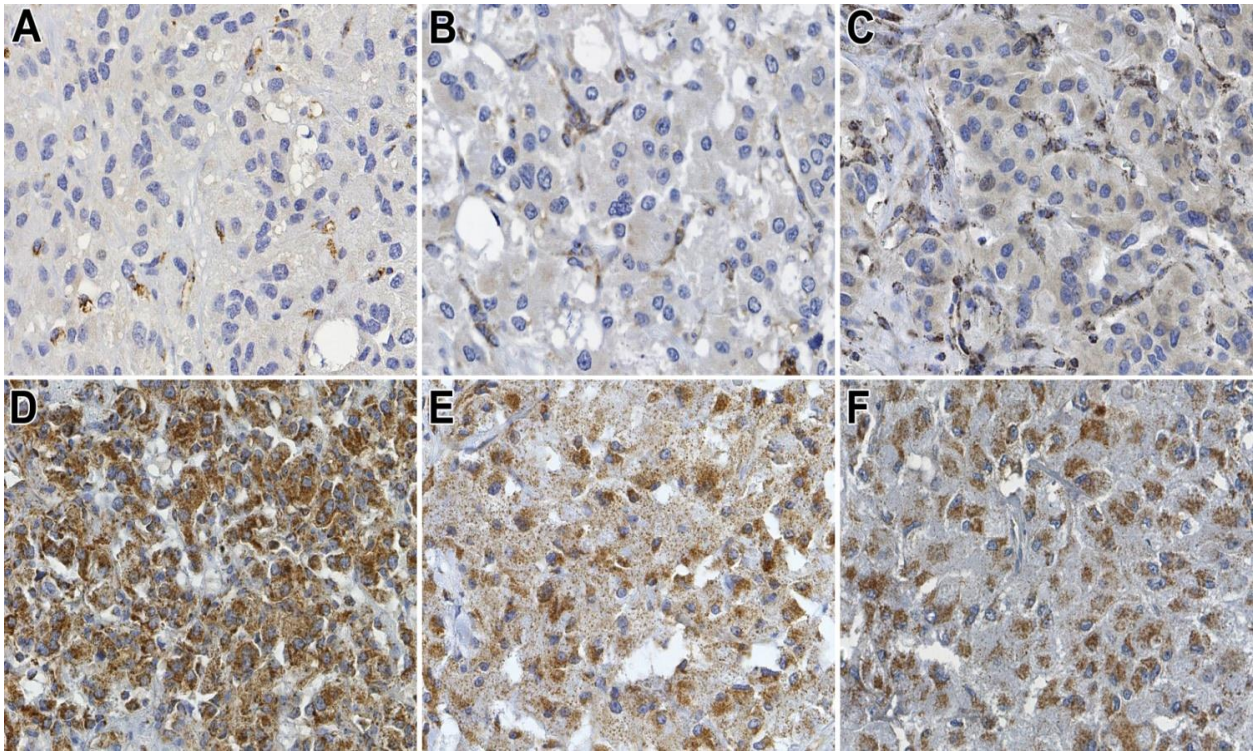
For metastases

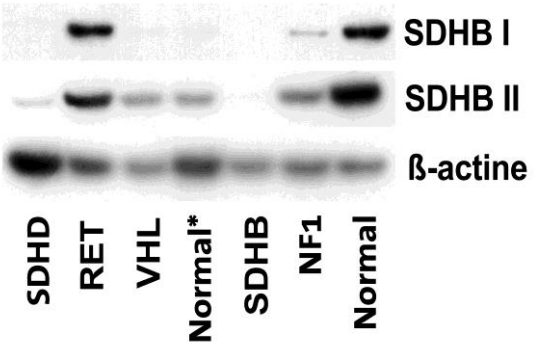
Sensitivity is 83% for ^{18}F-FDG, 74% for CT/MR, 50% for ^{123}I-MIBG (FDG vs MIBG and CT/MR vs MIBG, $p < 0.001$)

Timmers HJ et al, J Natl Cancer Inst 2012;104:700
216 patients including 155 with PH/PG

Destabilization of the complex II in SDH tumors

SDHB *SDHC* *SDHD*





VHL *RET* *NF1*

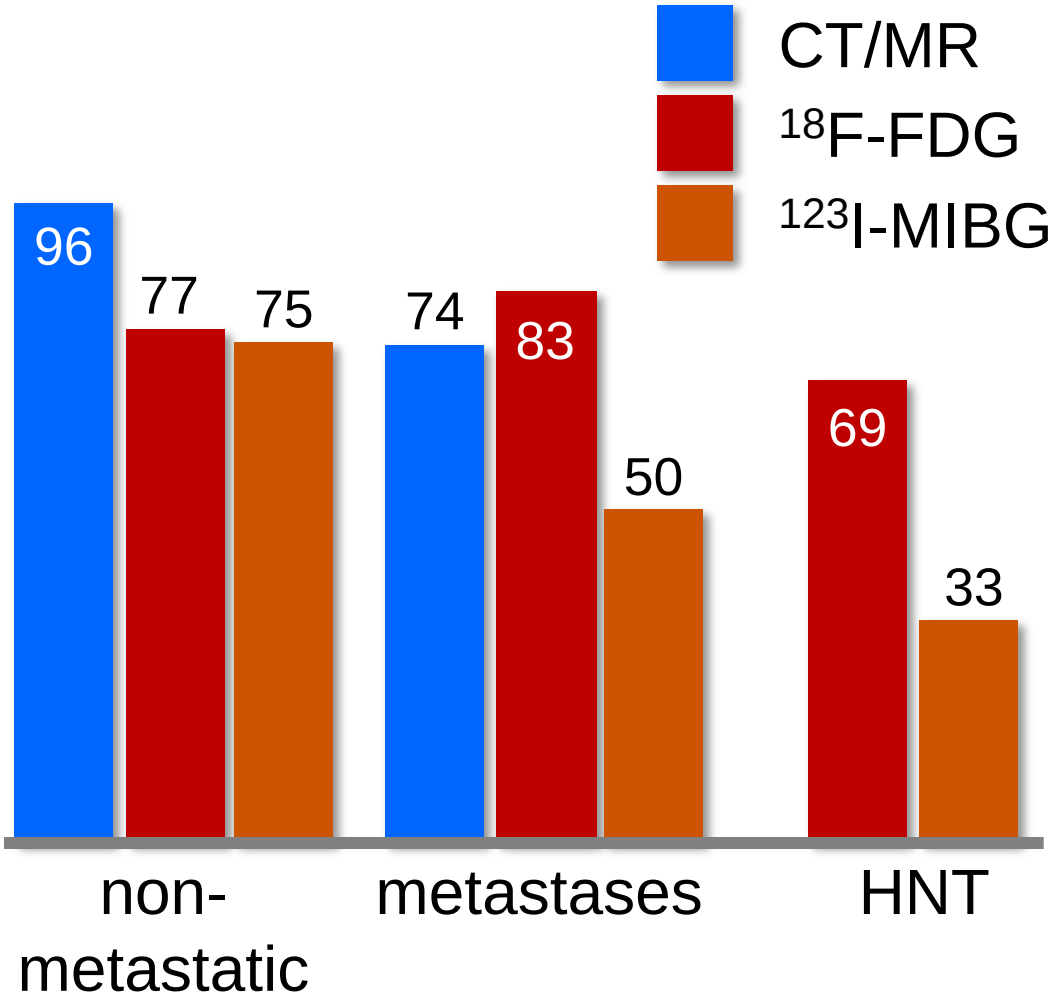
Van Nederveen F et al, Lancet Oncol 2009;10:764

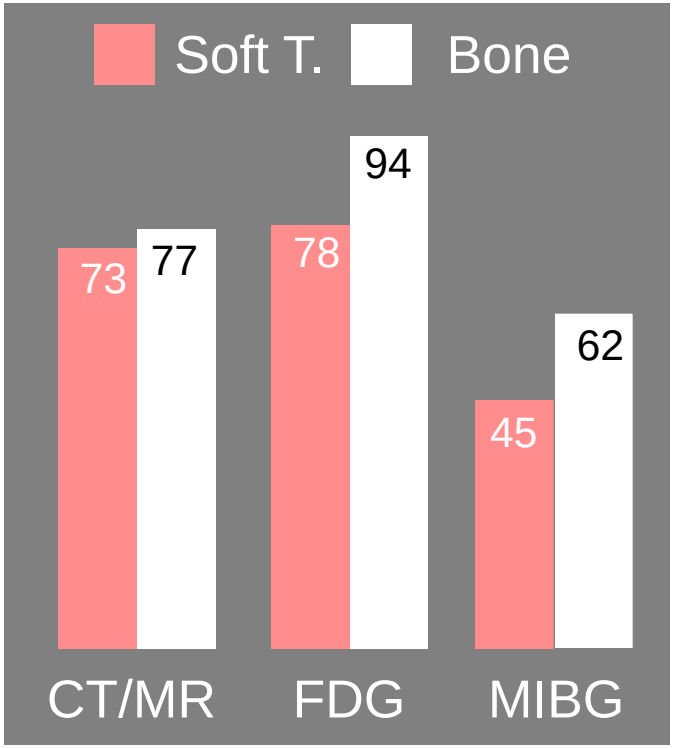
Clinical Signs

Symptoms	Frequency
– HTN	50-60 %
– Paroxysmal HTN	30 %
– Orthostatic Hypotension	10-50 %
– Hyperglycemia	40 %
– Headaches	60-90 %
– Sweating	55-75 %
– Palpitations	50-70 %
– Palor	40-45 %
– Perte de poids	20-40 %

Lenders, Lancet 2005

Sensitivities (%) of imaging tests





Timmers HJ et al, J Natl Cancer Inst 2012;104:700