

Istituto Oncologico della Svizzera Italiana
Servizio Cantonale di Medicina Nucleare e Centro PET/CT
Primario: Dr.med. Luca C. Giovanella

Marcatori neuroendocrini circolanti

Dr. med. Luca C. Giovanella



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“Il nostro scopo non è di vedere solo nuove cose ma, soprattutto, di guardare con nuovi occhi quello che è già stato visto”

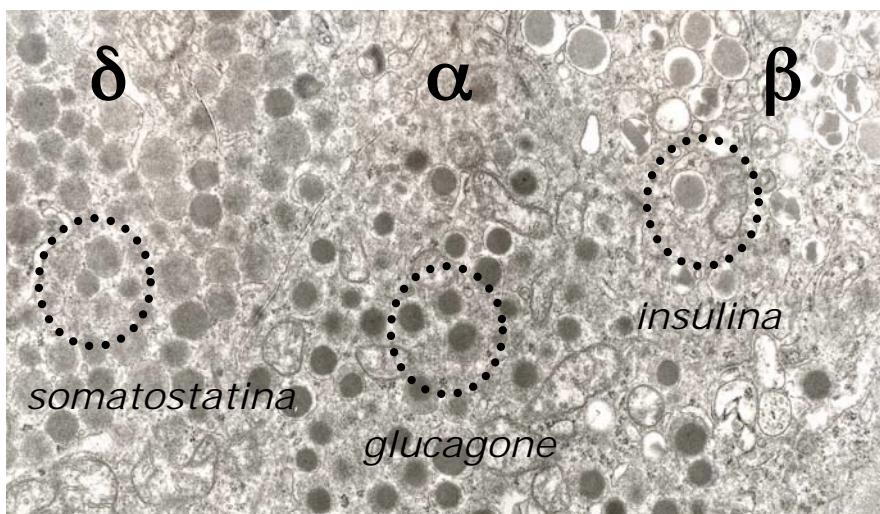
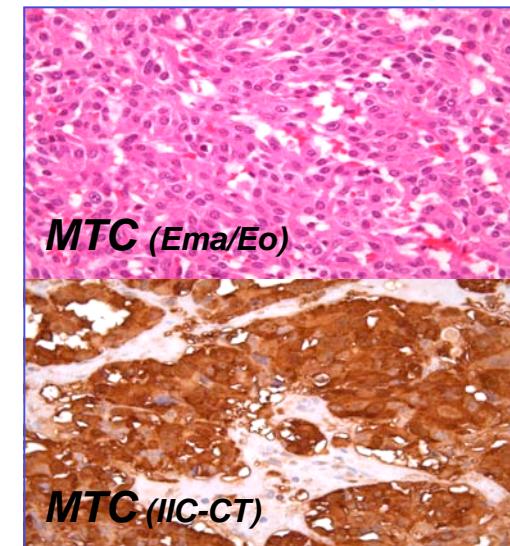
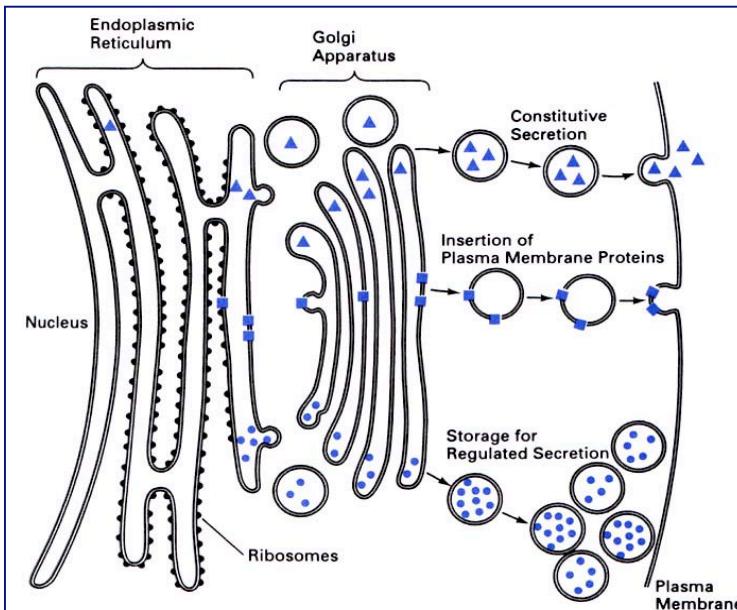
B.Spinoza (1632-1677)

Marcatori neuroendocrini

- **Biologia (cenni)**
- **Applicazioni cliniche**
- **Fattori interferenti**
- **Marcatori/imaging**

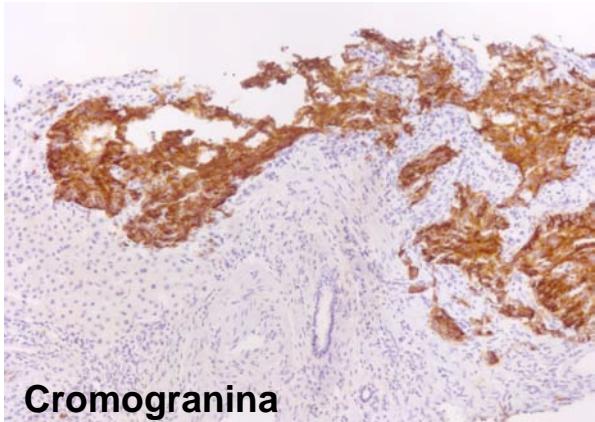
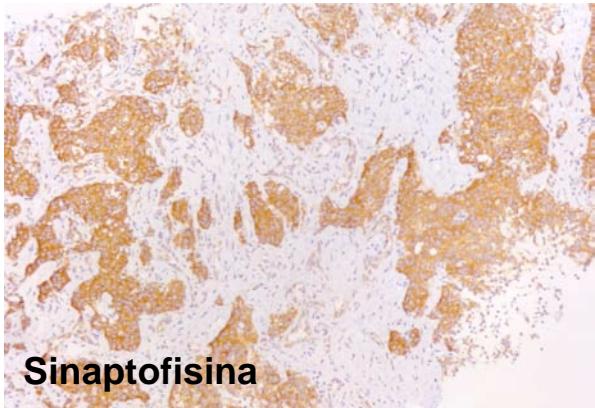


Marcatori neuroendocrini specifici



| Cells | Secretion Product |
|------------------------|--|
| Pituitary | ACTH, GH, FSH, LH, PRL, TSH |
| Parathyroids | PTH |
| C-cells (thyroid) | CT, somatostatin, CGRP |
| Bronchial tract | bombesin, 5HT, CT, ACTH, enkefalin |
| Gastrointestinal tract | 5HT, gastrin, SS, secretin, PP, CCK, glicentin, motilin, neuropeptid Y (PPY) |
| Pancreas | Insulin, PP, glucagon, SS |
| Adrenal Medulla | Catecholamines, enk, VIP, SS |
| Paraganglia | Catecholamines, enk, VIP, SS |

Marcatori neuroendocrini aspecifici

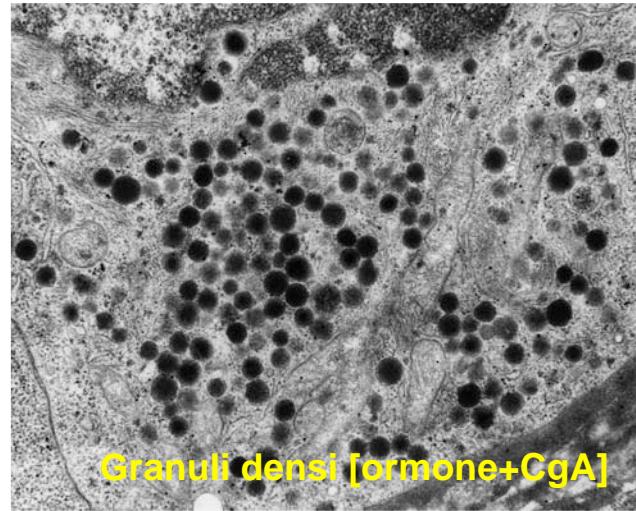


Cytoplasm

- Neuron-Specific Enolase
- Synaptophysin
- Synaptobrevin
- Protein S-100
- Intermediate filaments

NE Granules

- Chromogranin A
- Chromogranin B
- Chromogranin C
- Pancreastatin
- Vasostatin



©Stefano La Rosa MD, Department of Pathology Ospedale di Circolo e Fondazione Macchi-Varese



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BA-NET

BI-NET

-NET/intestino

Serotonin

- Sindrome da carcinoide

-NET/pancreas

Gastrina

- sindrome di Zollinger-Ellison

Insulina

- sindrome ipoglicemica

Glucagone

- eritema necrolitico migrante

Somatostatina

- DM, colelitiasi

VIP

- sindrome di Verner e Morrison

-NET/cromaffine

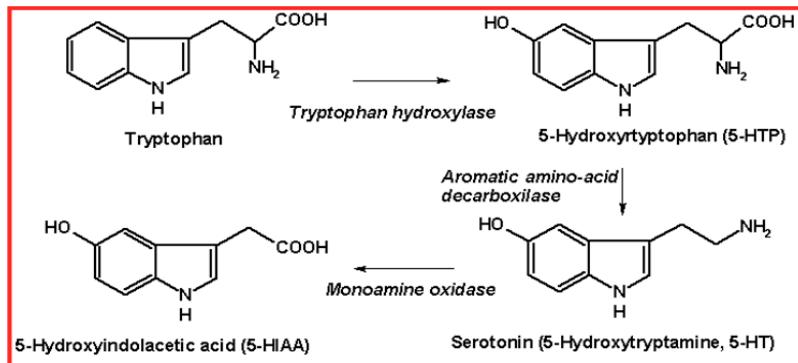
Catecolamine

- sindrome da feocromocitoma



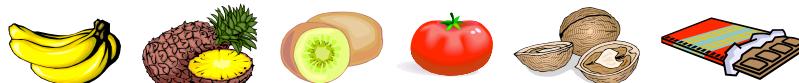
NET/tratto GE

- sindrome da carcinoide



Interferenze

Cibi: avocado, banane, kiwi, mele, ananas, noci, pomodori, nocciole, caffè, cioccolato...

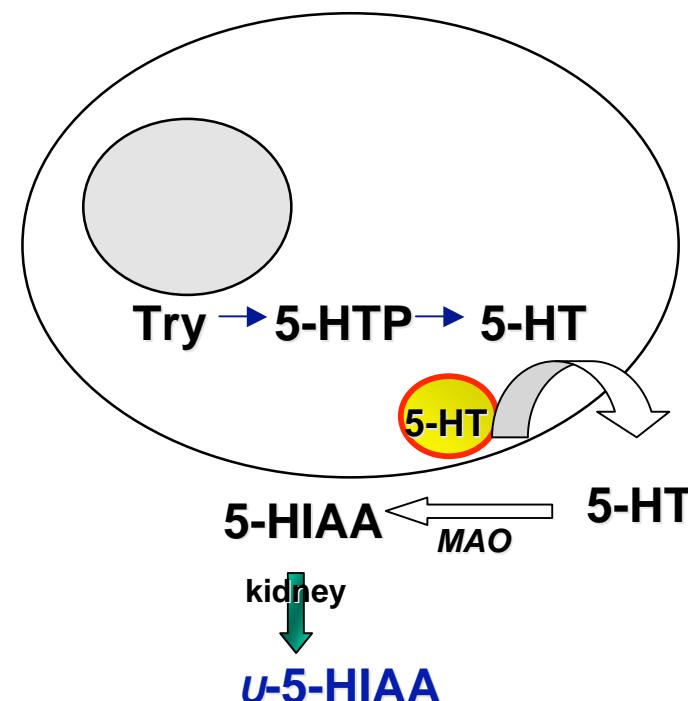


Farmaci: ASA, caffina, paracetamolo, eparina, MAO-I, clorpromazina, metil-DOPA, levo-DOPA, reserpina...

Malattie: morbo celiaco, occlusione intestinale, insufficienza renale e/o epatica

Metodologia

- raccolta urine/24 hrs
- metodo HPLC-ECD / (RIA)

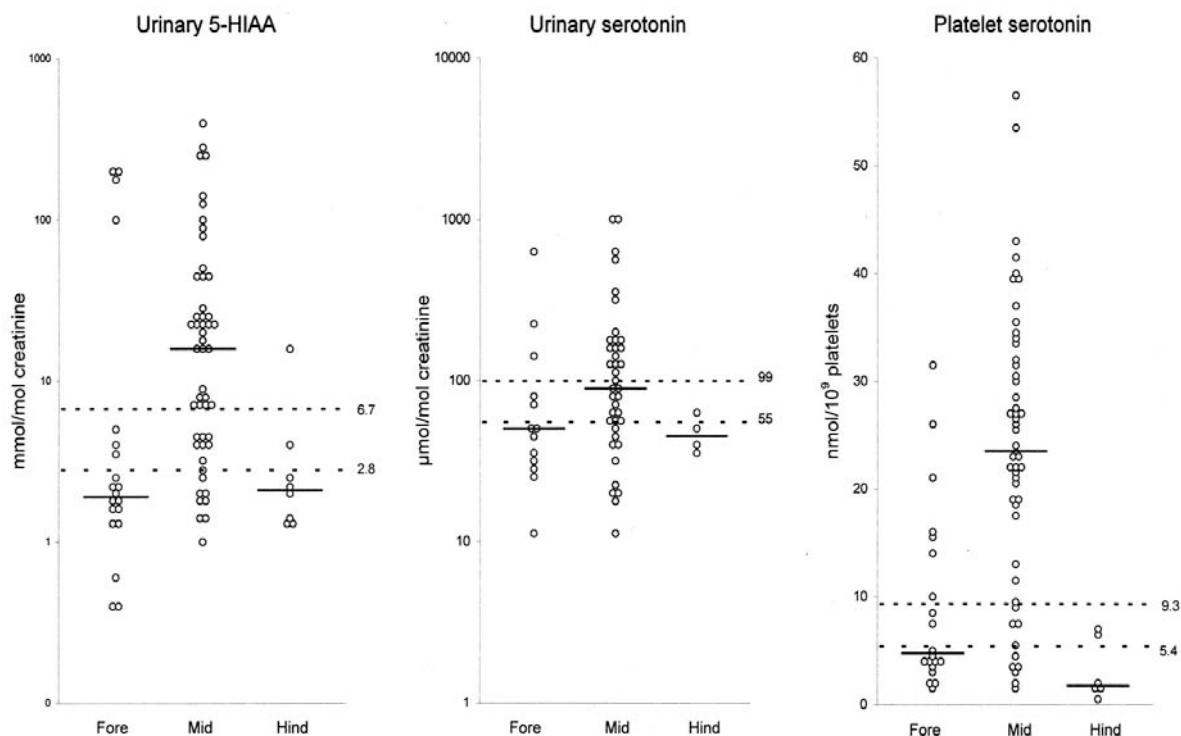


| pts | cut-off | sens% | spec% | PPV% | NPV% |
|-----|---------|-------|-------|------|------|
| 519 | 2.8 | 68 | 89 | 58 | 93 |
| | 6.7 | 52 | 98 | 87 | 90 |

24 hrs urine 5-HIAA (mmol/mol creatinine)

5-HIAA / NET intestinale

Meijer WG et al. Clin Chem 2000; 46: 1588-1596



| pts | sens % | [CgA] | |
|----------------|----------|----------------|------------------------------|
| GE-NET | 58% | 256 | |
| active | 70% | 323 | |
| inactive | 46% | 127 | |
| | | | CgA / NET intestinale |
| | GE-NET | sens % | [CgA] |
| limited | | 38% | 174 |
| extensive | | 69% | 385 |
| very extensive | | 100% | 1290 |
| <i>p</i> | | | <0.001 |
| | GE-NET | FU concordance | |
| | CgA | 81% | |
| | 5-HT | 54% | |
| | <i>p</i> | | <0.001 |

Nahar D et al. Clin Endocrinol 2004; 60: 644-652

Pirker RA et al. Clin Chem Lab Med 1998; 36: 837-840

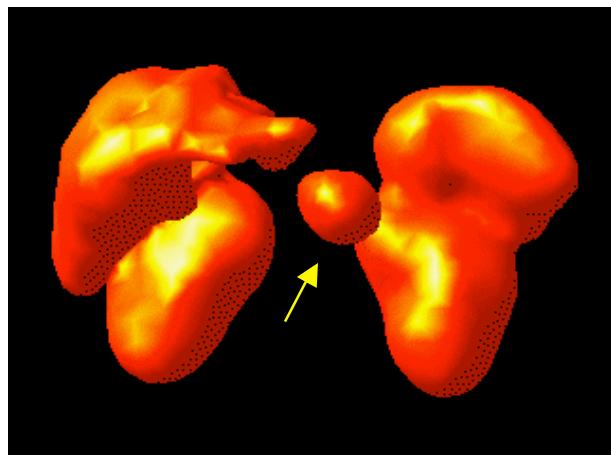


| pts | sens % | [CgA] |
|----------|--------|-------|
| P-NET | 62% | 358 |
| active | 78% | 564 |
| inactive | 44% | 112 |

NET pancreas

| | sens % |
|-------------|--------|
| gastrinoma | 100% |
| glucagonoma | 100% |
| insulinoma | 20% |

Nahar D et al. Clin Endocrinol 2004; 60: 644-652

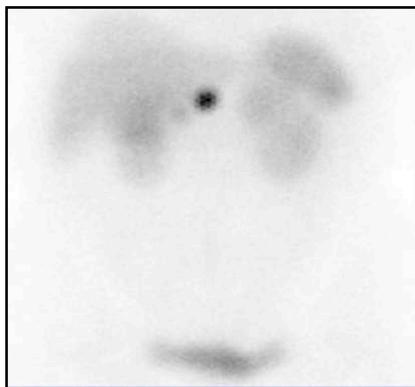


Insulinoma

- Test del digiuno standardizzato
- Insulina, C-peptide, Proinsulina

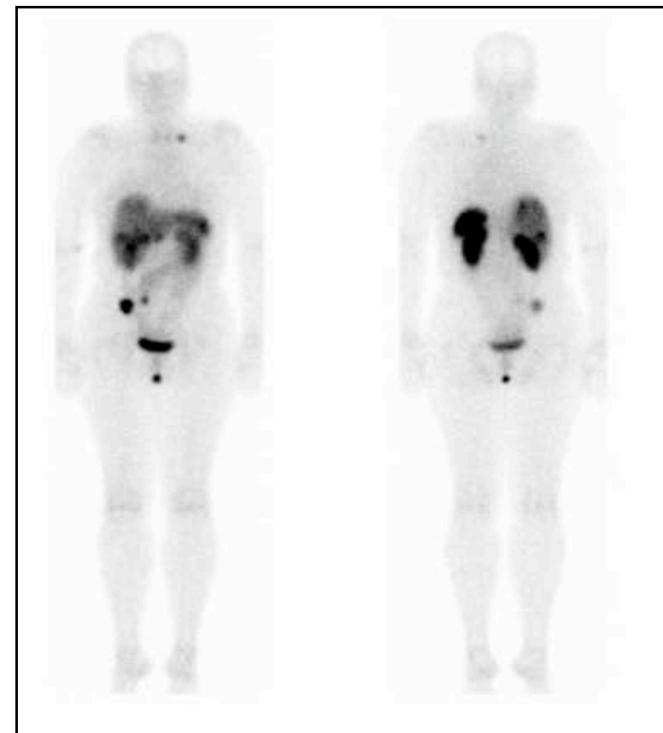


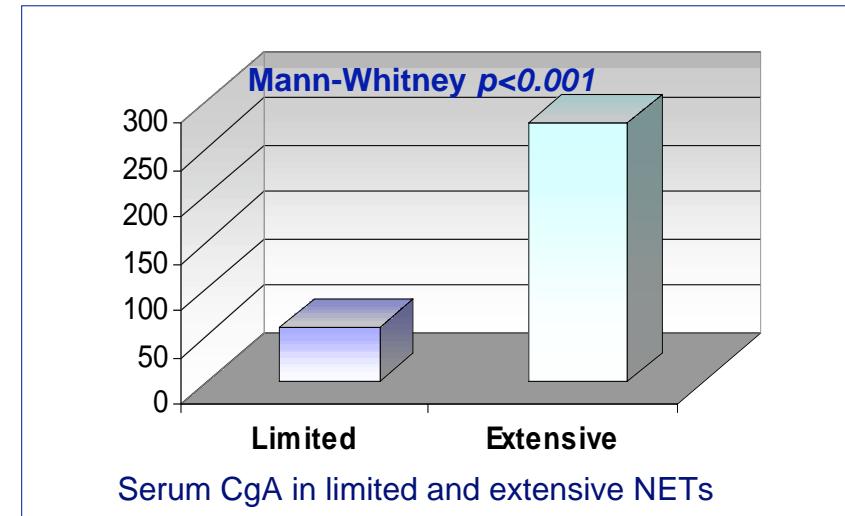
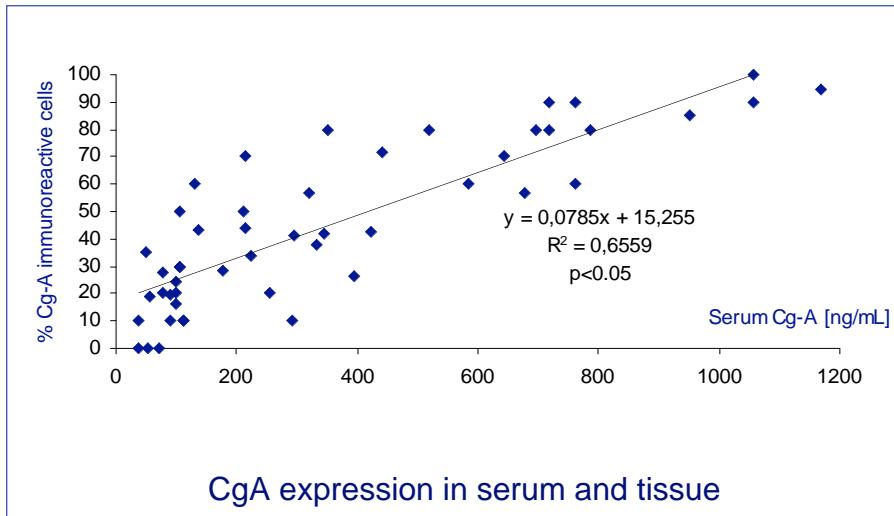
CgA ed estensione di malattia



| NET | CgA |
|---------------------|--|
| M+ (n=97) | 3444 ± 12256 |
| M- (n=27) | 174 ± 233 |
| p | <0.001 |

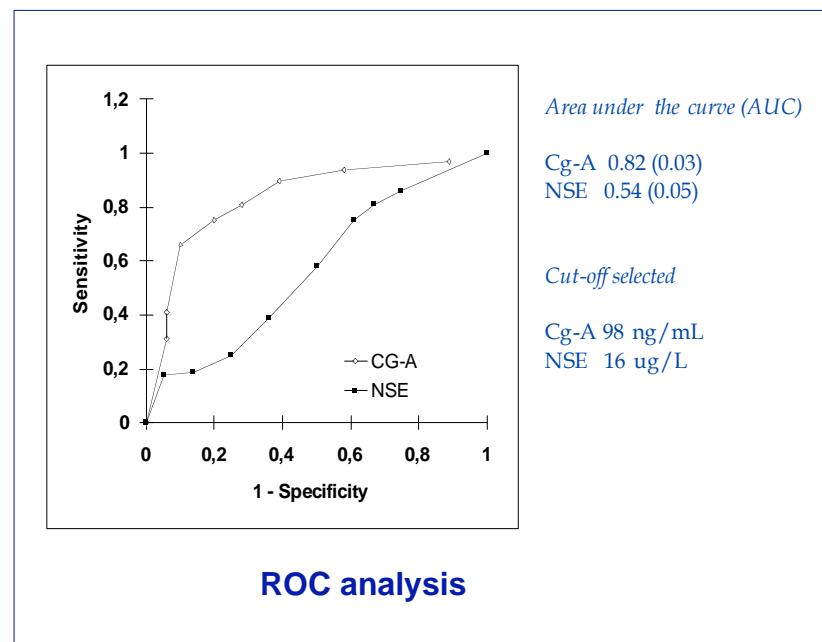
Nehar D et al. Clinical Endocrinology (2004)





| | CgA | NSE |
|---|-----------------------------|----------------------------|
| Sensitivity (positives/64 NET) | 40 (0.62) | 18 (0.28) |
| Specificity (negatives/100 ctr) | 82 (0.82) | 78 (0.78) |
| Accuracy (TP+TN/164) | 122 (0.74) | 96 (0.58) |

Giovanella L. et al. Int J Biol Markers 1999



CgA in fase diagnostica: bassa sensibilità complessiva

| Sensitivity | Case-mix | Authors | cut-off (ng/mL) |
|-------------|----------|-------------------------|--------------------|
| 47-61 | NET | Baudin et al.1998 | 100 |
| 62 | NET | Giovanella L et al.1999 | 100 |
| 63 | NET/MEN1 | Nehar C et al.2003 | 130 |

Interferenze (falsi positivi)

Insufficienza renale

Ipo/acloridria

- Gastrite cronica atrofica
- IPP

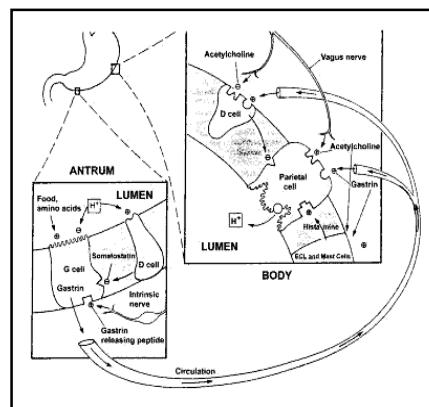
Altre cause

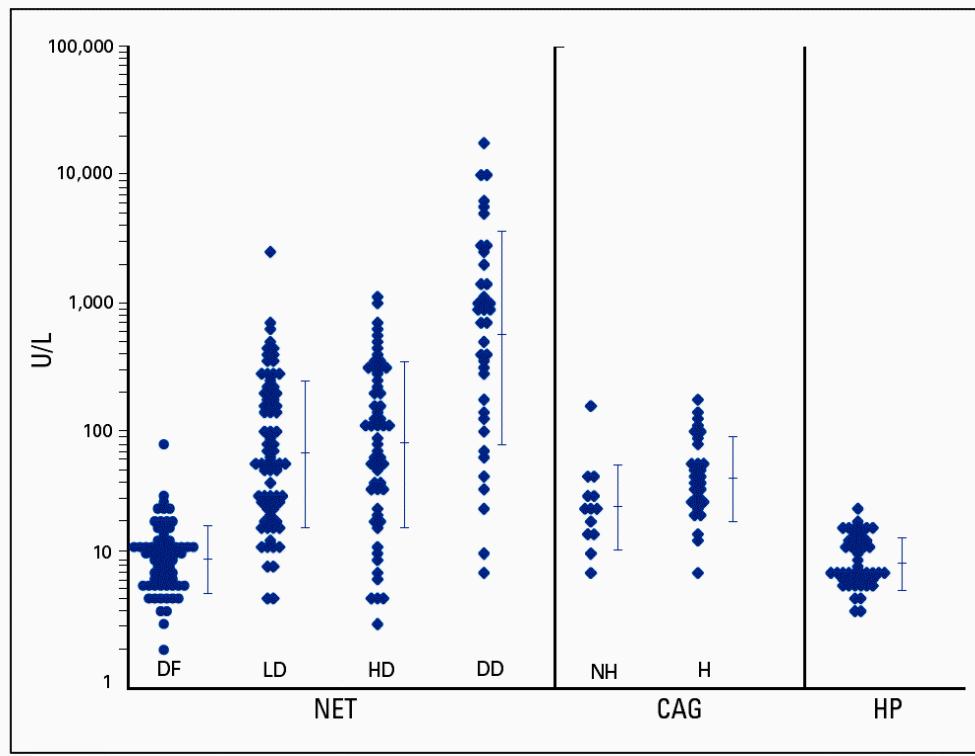
Terapia steroidea

Gravidanza

Insufficienza epatica

Morbo di Parkinson





- CgA < 18 U/L

STOP

CgA 18-84 U/L

EXCLUDE INTERFERENCES

CgA > 84 U/L

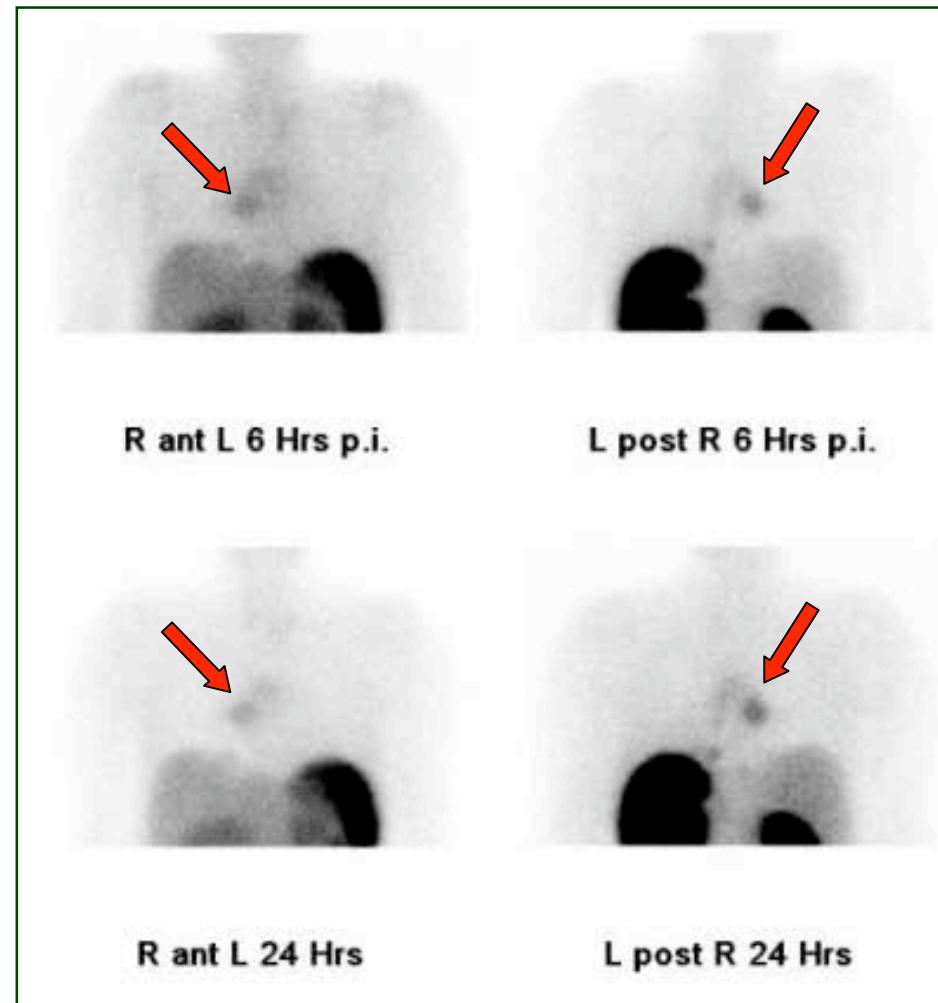
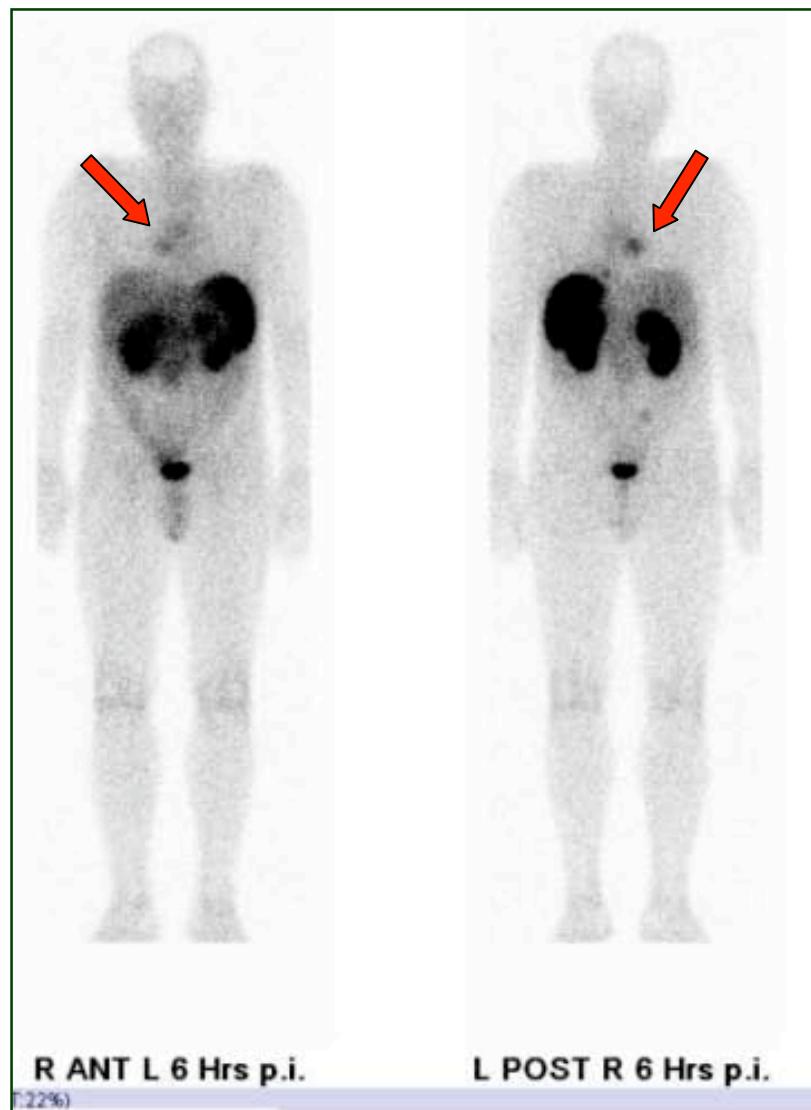
NET WORK-UP

ELISA Dako Assay

Campana et al. J Clin Oncol 2007



CARCINOIDE BRONCHIALE



Marcatori neuroendocrini e NET-GEP

-Sindrome da carcinoide

- Diagnosi e work-up: 5-HIAA urinario + CgA → **Imaging**
- Follow-up: CgA

-NET gastroenterico e bronchiale (non-sindromico)

- Diagnosi: CgA (considerare bassa sensibilità e NPV)
- Follow-up: CgA (se elevata al work-up iniziale? Se IIC positiva?) → **Imaging**

-NET pancreatico (sindromico)

- ormone specifico+CgA → **Imaging**

-NET pancreatico (non-sindromico)

- CgA(considerare bassa sensibilità e NPV) → **Imaging**



Table 1 Proportion of patients displaying SRS positive and increased level of CgA according to tumour features

| Tumour features | SRS positive | CgA increased | Total patients |
|-------------------------------|--------------|---------------|----------------|
| Overall NETs | 107 (89%) | 95 (79%) | 120 |
| WHO classification | | | |
| WDNETs | 64 (90%) | 57 (80%) | 71 |
| WDNECs | 34 (92%) | 29 (78%) | 37 |
| PDNECs | 9 (75%) | 9 (75%) | 12 |
| Primary origin | | | |
| Foregut | 64 (89%) | 61 (85%) | 72 |
| Midgut | 25 (96%) | 19 (73%) | 26 |
| Hindgut | 11 (73%) | 11 (73%) | 15 |
| Unknown | 7 (100%) | 4 (57%) | 7 |
| Extent of disease | | | |
| Limited disease | 18 (78%) | 16 (70%) | 23 |
| Primary tumour and metastases | 52 (91%) | 44 (77%) | 57 |
| Metastases only | 37 (93%) | 35 (88%) | 40 |
| Function | | | |
| Secretory | 22 (88%) | 24 (96%) | 25 |
| Nonsecretory | 85 (89%) | 71 (75%) | 95 |

SRS Somatostatin receptor scintigraphy, CgA chromogranin A, NETs neuroendocrine tumours, WDNETs well-differentiated NETs, WDNECs well-differentiated neuroendocrine carcinomas, PDNECs poorly differentiated neuroendocrine carcinomas

Table 2 Levels of increased CgA in patients displaying SRS positive and negative according to tumour features

| Tumour features | Median (range) levels of CgA (ng/ml) | |
|-------------------------------|--------------------------------------|-------------------|
| | SRS positive | SRS negative |
| Overall NETs | 954 (100–5,700) | 391 (115–5,400) |
| WHO classification | | |
| WDNETs | 482 (100–3,035) | 310 (170–605) |
| WDNECs | 1,762 (120–5,700) | 1,411 (675–3,900) |
| PDNECs | 1,106 (370–1,250) | 619 (530–710) |
| Primary origin | | |
| Foregut | 1,354 (100–5,700) | 915 (210–3,900) |
| Midgut | 805 (120–4,260) | 210* |
| Hindgut | 372 (155–710) | 267 (115–590) |
| Extent of disease | | |
| Limited disease | 277 (100–700) | 320 (200–425) |
| Primary tumour and metastases | 1,152 (115–5,700) | 616 (530–715) |
| Metastases only | 782 (115–4,300) | 735 (175–5,400) |
| Function | | |
| Secretory | 979 (100–5,700) | 581 (425–710) |
| Nonsecretory | 784 (155–1,820) | 328 (155–710) |

CgA chromogranin A, SRS Somatostatin receptor scintigraphy, WDNETs well-differentiated NETs, WDNECs well-differentiated neuroendocrine carcinomas, PDNECs poorly differentiated neuroendocrine carcinomas
* One patient

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-008-0794-1
ORIGINAL ARTICLE

Concordance between results of somatostatin receptor scintigraphy with ^{111}In -DOTA-DPhe $^1\text{-Tyr}^3$ -octreotide and chromogranin A assay in patients with neuroendocrine tumours

Margarida Rodrigues · Michael Gabriel · Dirk Heute · Daniel Putzer · Andrea Gremmacher · Irene Virgolini

Received: 28 January 2008 / Accepted: 25 March 2008
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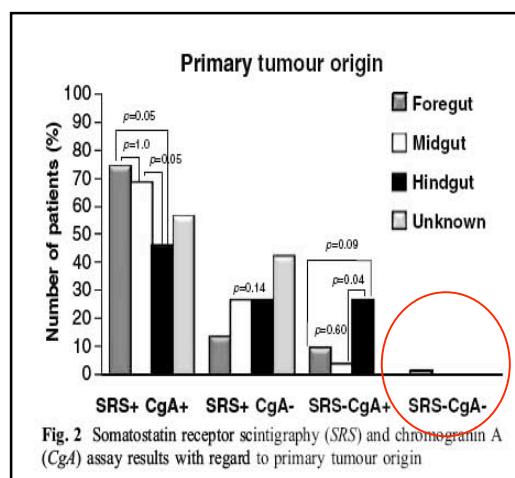


Fig. 2 Somatostatin receptor scintigraphy (SRS) and chromogranin A (CgA) assay results with regard to primary tumour origin

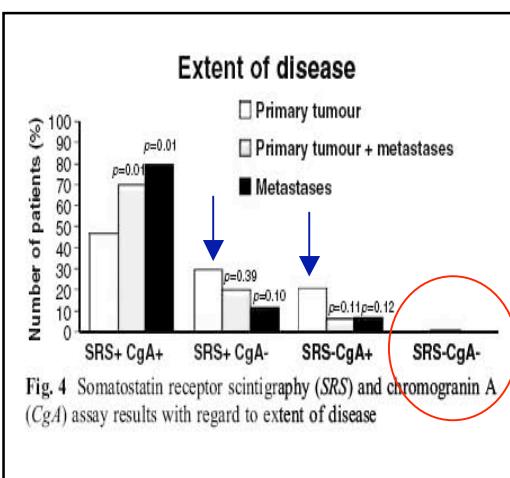


Fig. 4 Somatostatin receptor scintigraphy (SRS) and chromogranin A (CgA) assay results with regard to extent of disease

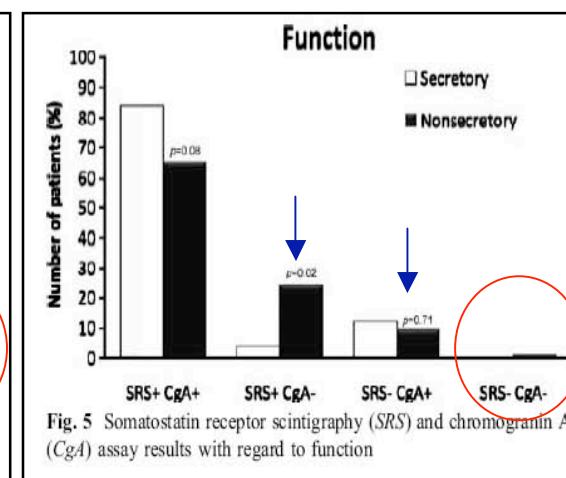


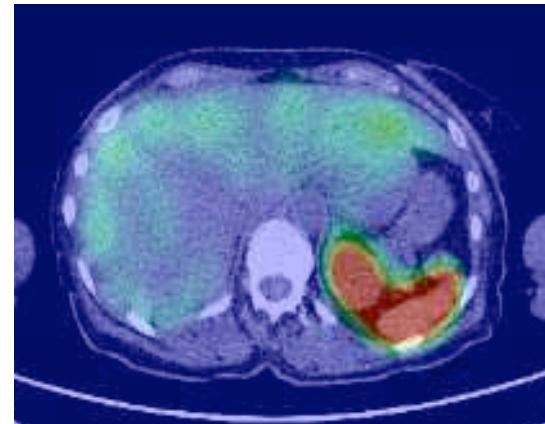
Fig. 5 Somatostatin receptor scintigraphy (SRS) and chromogranin A (CgA) assay results with regard to function



NET ileale sindromico



CgA 1350 ng/mL



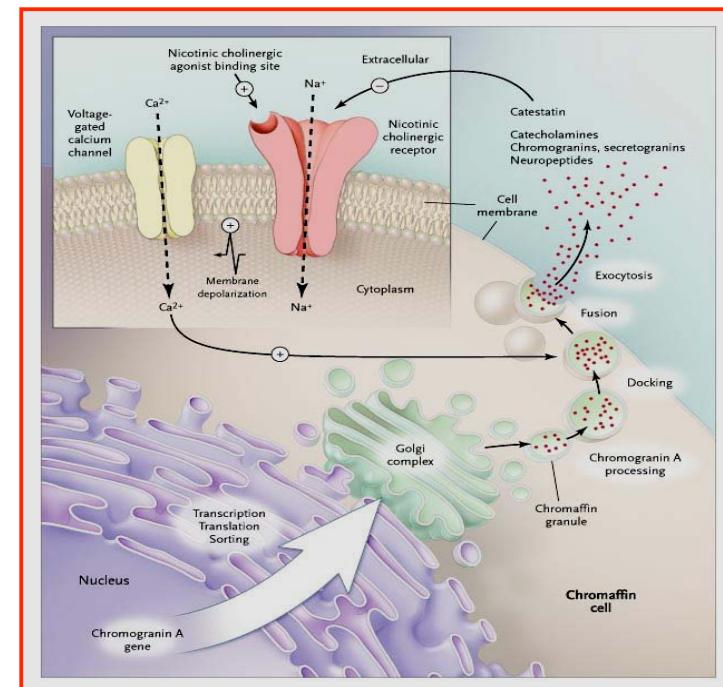
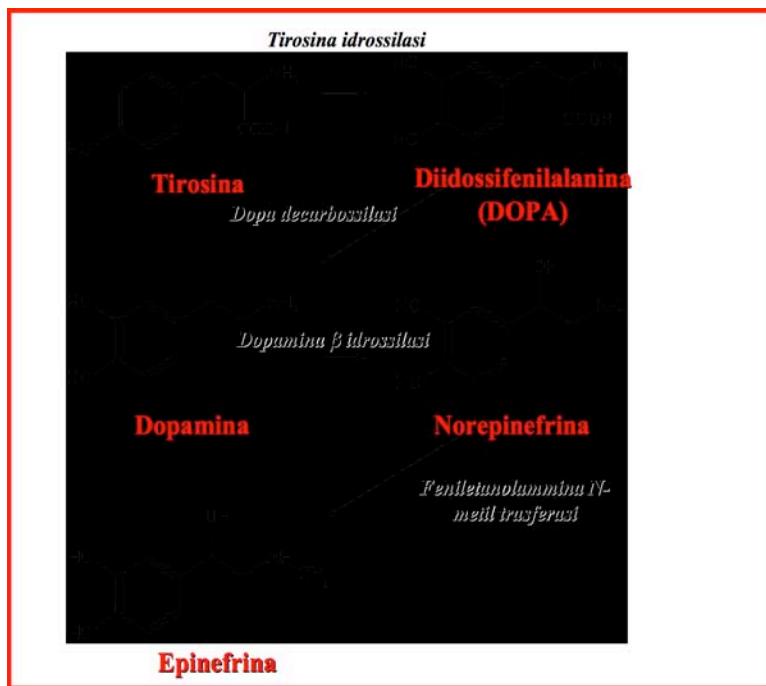
Octreoscan
SPET/CT



18FDG
PET/CT



NET/sistema cromaffine



Heisenhofer G et al. Current progress and future challenges in the biochemical diagnosis and treatment of pheochromocytomas and paragangliomas. *Horm Metab Res* 2008;40:329-337

Conclusions

...measurements of plasma free metanephries provide an overall diagnostic sensitivity of 98% and specificity of 92%. The recommendation that initial testing for the tumor should always include measurements of either plasma or urinary fractionated metanephries results from recognition of the high diagnostic sensitivity of measurements of plasma metanephries.

<http://www.catecholamine.org/labprocedures/procedure/refrange.htm#2metanephries>



NET/sistema cromaffine

| | Sensitivity | Specificity | Accuracy |
|--------------|--------------------|--------------------|-----------------|
| s-CgA | 15/15 (1.00) | 142/148 (0.96) | 157/163 (0.96) |
| u-E | 5/15 (0.33) | 130/148 (0.88) | 135/163 (0.82) |
| u-NE | 8/15 (0.53) | 127/148 (0.86) | 135/163 (0.82) |
| u-VMA | 6/15 (0.40) | 130/148 (0.88) | 136/163 (0.83) |
| u-MNs | 13/15 (0.86) | 132/148 (0.89) | 145/163 (0.89) |

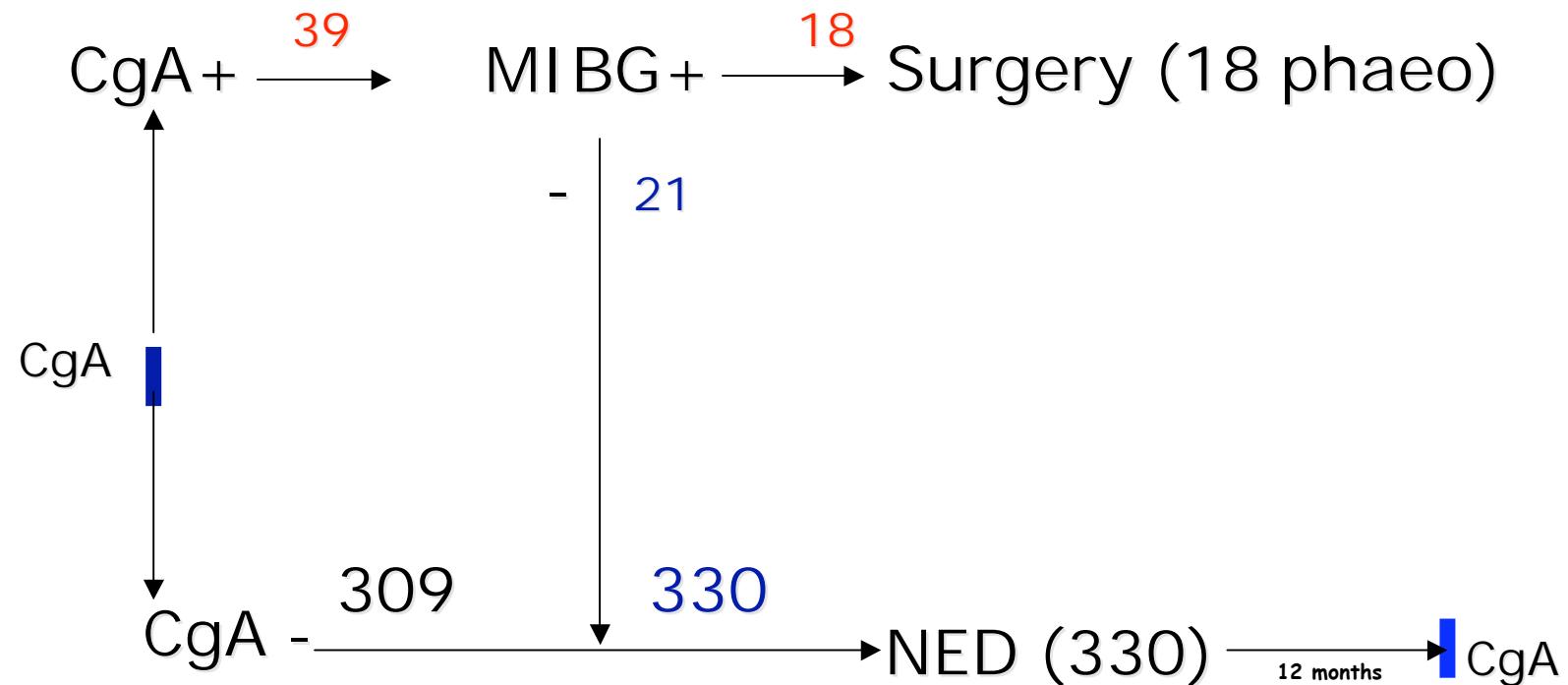
Giovanella L. et al. Int J Biol Markers 2002

| | Area under the ROC curve (\pm SE) | 95% confidence interval | P-value* |
|-----------------|--------------------------------------|-------------------------|----------|
| Chromogranin A | 0.966 (\pm 0.029) | 0.858–0.996 | < 0.0001 |
| Epinephrine | 0.915 (\pm 0.046) | 0.787–0.978 | < 0.0001 |
| Norepinephrine | 0.930 (\pm 0.041) | 0.806–0.985 | < 0.0001 |
| Metanephrine | 0.950 (\pm 0.037) | 0.824–0.993 | < 0.0001 |
| Normetanephrine | 0.977 (\pm 0.026) | 0.864–0.995 | < 0.0001 |

E. Grossrubatscher et al. Clin Endocrinol 2006



348 pts with CT- or MR-detected AI ($\varnothing > 20$ mm)



Diagnostic value of serum chromogranin-A combined with MIBG scintigraphy in patients with adrenal incidentalomas. *Giovanella et al. Q J Nucl Med Mol Imaging 2008*

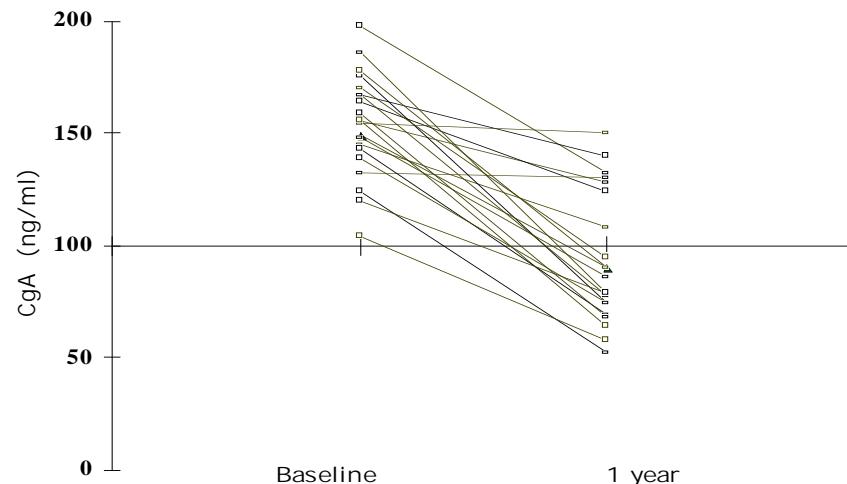


| | number | CgA (ng/mL) |
|--------------------------|--------|--------------------|
| Incidentaloma | 330 | 62 (32-198) (*) |
| CgA - | 309 | 56 (32-96) (°) |
| CgA+/MIBG- | 21 | 149 (104-198) (†) |
| Phaeochromocytoma | | |
| CgA+/MIBG+ | 18 | 320 (186-3500) (§) |

Distribution of serum CgA

[Mann-Whitney U-test].

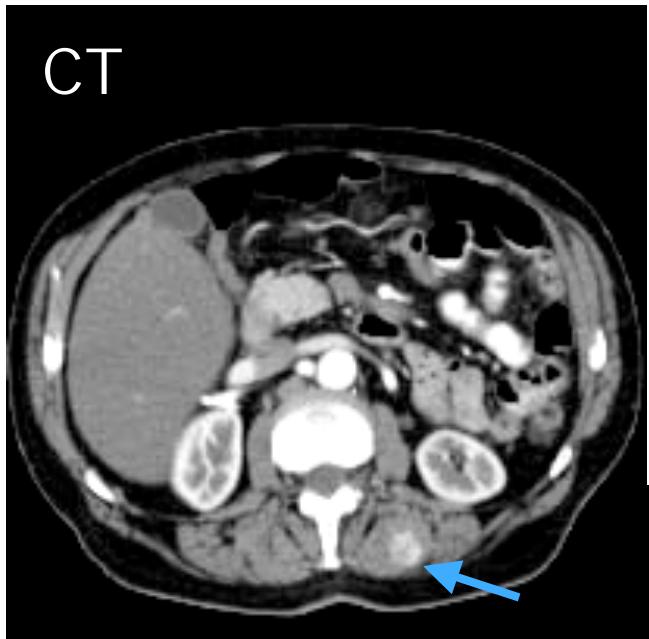
- Phaeo^(§) vs AI^(*) p<0.001
- AI CgA+/MIBG-^(†) vs AI CgA-^(°) p<0.001



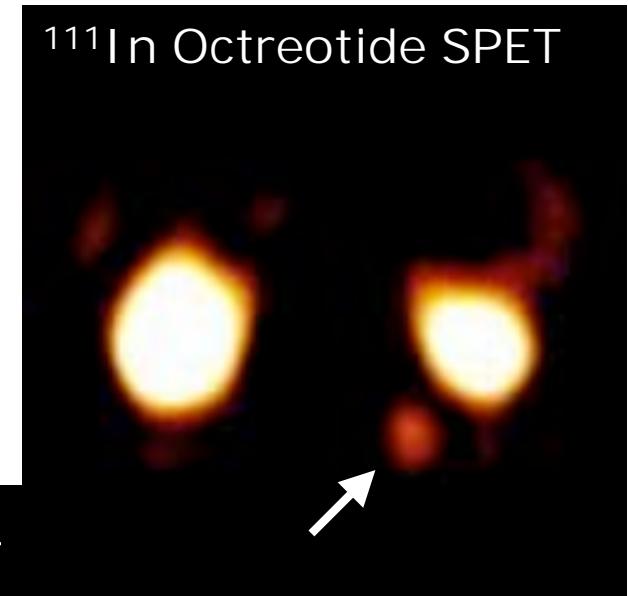
Diagnostic value of serum chromogranin-A combined with MIBG scintigraphy in patients with adrenal incidentalomas. *Giovanella et al. Q J Nucl Med Mol Imaging 2008*



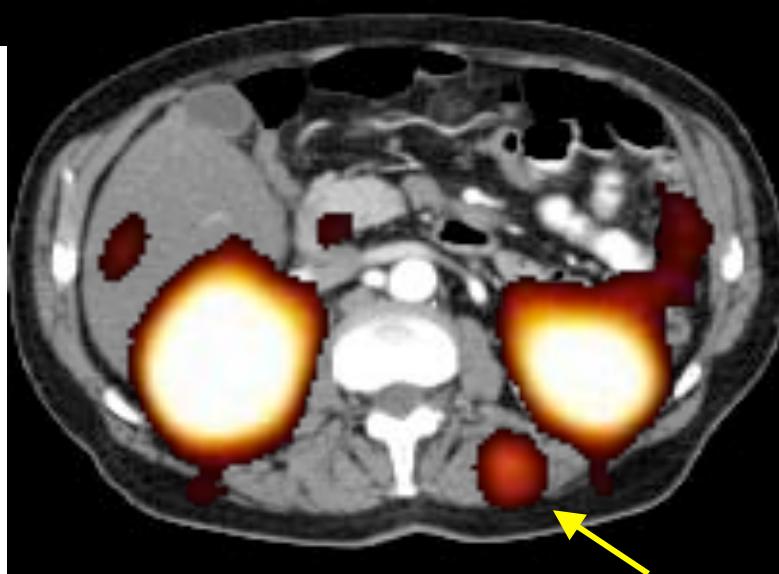
Elevazione *u*-norepinefrina



CgA 43 ng/mL



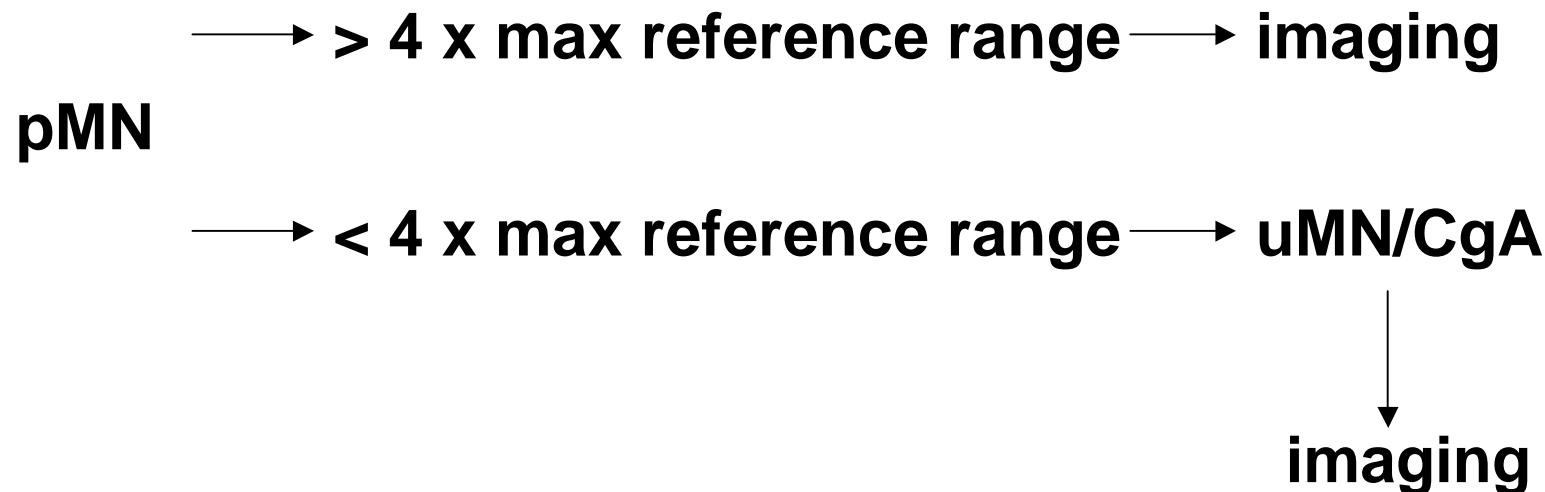
Fused SPET/CT



Algeciras-Schimich A et al. Plasma Chromogranin A or Urine Fractionated Metanephrides Follow-Up Testing Improves the Diagnostic Accuracy of Plasma Fractionated Metanephrides for Pheochromocytoma
J Clin Endocrinol Metab 2008; 1: 91-95

Conclusions

Unless plasma fractionated metanephrides levels are elevated more than 4-fold above the upper limit of normal, patients with a positive plasma fractionated MN test should be evaluated with urine fractionated metanephrides and serum/plasma CgA assays before being subjected to imaging or invasive diagnostic tests.



Conclusioni

1. Fattori interferenti multipli (screening)
2. Problemi metodologici e statistici (range, cut-off e livelli decisionali)
3. Limitazione dei marcatori nei NET-GEP e bronchiali in stadio LD e non-secernenti: integrazione imaging (SRS)
4. Elevata accuratezza di CgA e u/p-MN nella patologia cromaffine.
Altri marcatori non adeguati.
5. Work-up e follow-up: selezione accurata del minor numero di marcatori (idealmente 1).

