Caso clinico

Renato Cozzi
Endocrinologia
Ospedale Niguarda
Milano

Outline

- quadro clinico
- laboratorio
- diagnostica per immagini
- terapia primaria
- anatomia patologica
- terapia adiuvante
- genetica

Domenico, 45 anni (1)

- Marzo 2006: ricovero in Medicina per **Sincope**
- In PS: alterazioni ECG della ripolarizzazione di dubbio significato ischemico

Anamnesi Patologica Remota

- dal 1994 follow-up c/o Amb. M. Infettive per infezione da HIV (in terapia antiretrovirale con buona risposta)
- Epatopatia cronica HCV-correlata
- Ipertensione polmonare primitiva
- Recente riscontro di **ipertensione arteriosa S/D**

Domenico (2)

Decorso clinico

- Indici di necrosi miocardica negativi
- ECG: invariato
- Rx torace, Ecocardiogramma, ECG Holter: normali
- Scintigrafia miocardica con dipiridamolo: difetto di perfusione inferiore (al limite della significatività)
- Dimesso con: ramipril 5 mg, amlodipina 10 mg, carvedilolo 12.5 mg, ASA 100 mg
- Previsto monitoraggio Holter PA 24 ore

Domenico (3)

- 2006-2007: numerosi accessi in DH M. Infettive per patologia di base
- Persistenza di **ipertensione arteriosa non controllata**, con puntate ipertensive
- Variazioni ripetute terapia anti-ipertensiva (cardiologo ed internista)
- Retinopatia ipertensiva
- Diagnosi: **ipertensione essenziale maligna**
- Ultima terapia: carvedilolo 50 mg, amlodipina 20 mg, losartan 50 mg, trinitrina TTS

Domenico (4)

Settembre 2007 Consulenza endocrinologica

- **Contesto clinico**: ipertensione arteriosa non controllata, sudorazione, cardiopalmo, cefalea.
- Richiesti:
  - Catecolamine urine e metaboliti
  - Elettroliti
  - Renina & pAldosterone clino/orto
  - Cromogranina

Outline

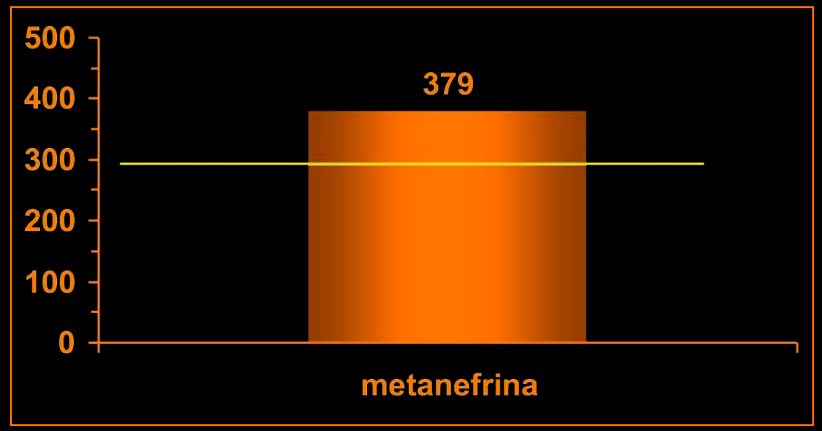
- quadro clinico
- laboratorio
- diagnostica per immagini
- terapia primaria
- anatomia patologica
- terapia adiuvante
- genetica

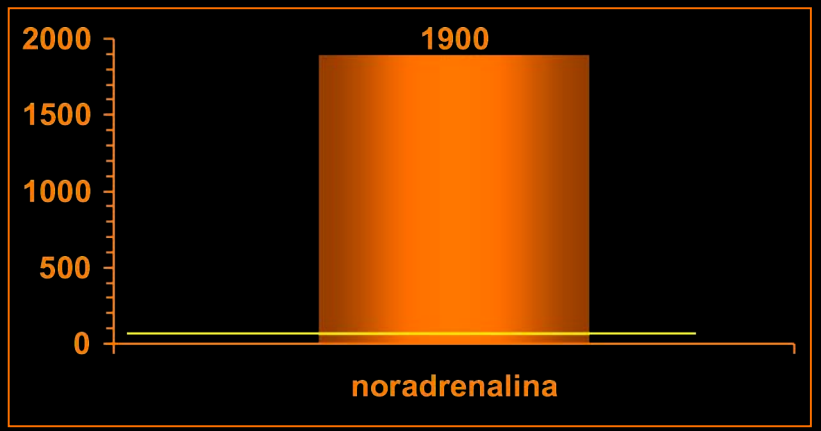
- Glicemia 197 mg/dL, C-Peptide 3.5 ng/mL, Glicosuria 24h (QU 6 L) presente
- Creatininemia 1.33 mg/dL
- Calcemia 10.3 mg/dL
- Na^+-K^+ 137-3.2 mEq/L
- GB 12.300, Hb 16.7 g/dL, Ht 48.2%, VGM 118 fl
- PRA in clino 19.5 (vn 0.2-2 ng/mL/h), in orto 23
- pAldo in clino 94 (vn 2-15 ng/dl), in orto 188
- Cromogranina A 218 U/L (vn < 20)

Quale sospetto diagnostico ?

1. Ipertensione essenziale maligna con iniziale IRC
2. Ipertensione endocrina

Catecolamine urinarie





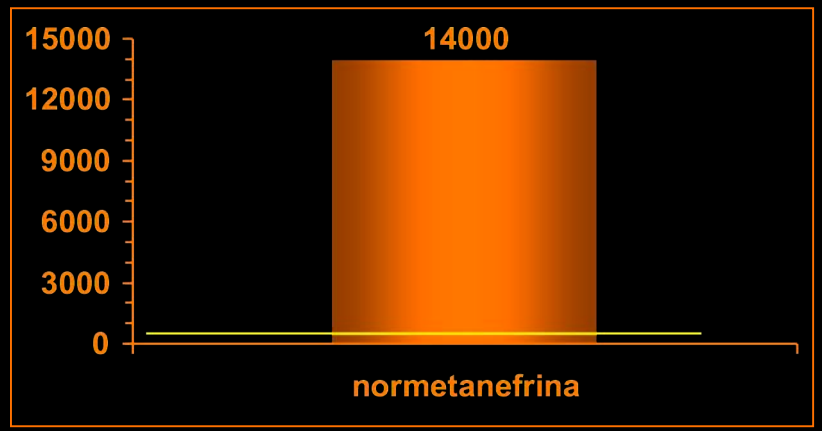


Table I. Signs and symptoms of phaeochromocytoma

Sign/symptoms	Frequency[a]
Signs	
Hypertension	++++
sustained hypertension	++
paroxysmal hypertension	++
Postural hypotension	++
Tachycardia or reflex bradycardia	+++
Pallor	++
Flushing (rare)	+
Weight loss	+
Fasting hyperglycaemia	++
Decreased gastrointestinal motility	+
Increased respiratory rate	+
Psychosis	+
Symptoms	
Headaches	++++
Palpitations	++++
Excessive sweating	++++
Anxiety/nervousness	+++
Tremulousness	++
Pain in chest/abdomen	++
Weakness, fatigue	++
Nausea/vomiting	++
Dizziness or faintness	+
Paraesthesias	+
Constipation (rarely diarrhoea)	+
Visual disturbances	+

a Highest (++++) to lowest (+) frequency.

Feocromocitoma: test diagnostici

- uCatecolamine/uMetanefrine frazionate
- Cromogranina A
- pMetanefrine frazionate libere
- pCatecolamine
- VMA
- Test con Clonidina
- Test provocativi

il test migliore

Sensibilità

- uMetanefrine fraz 98%
- uCatecolamine

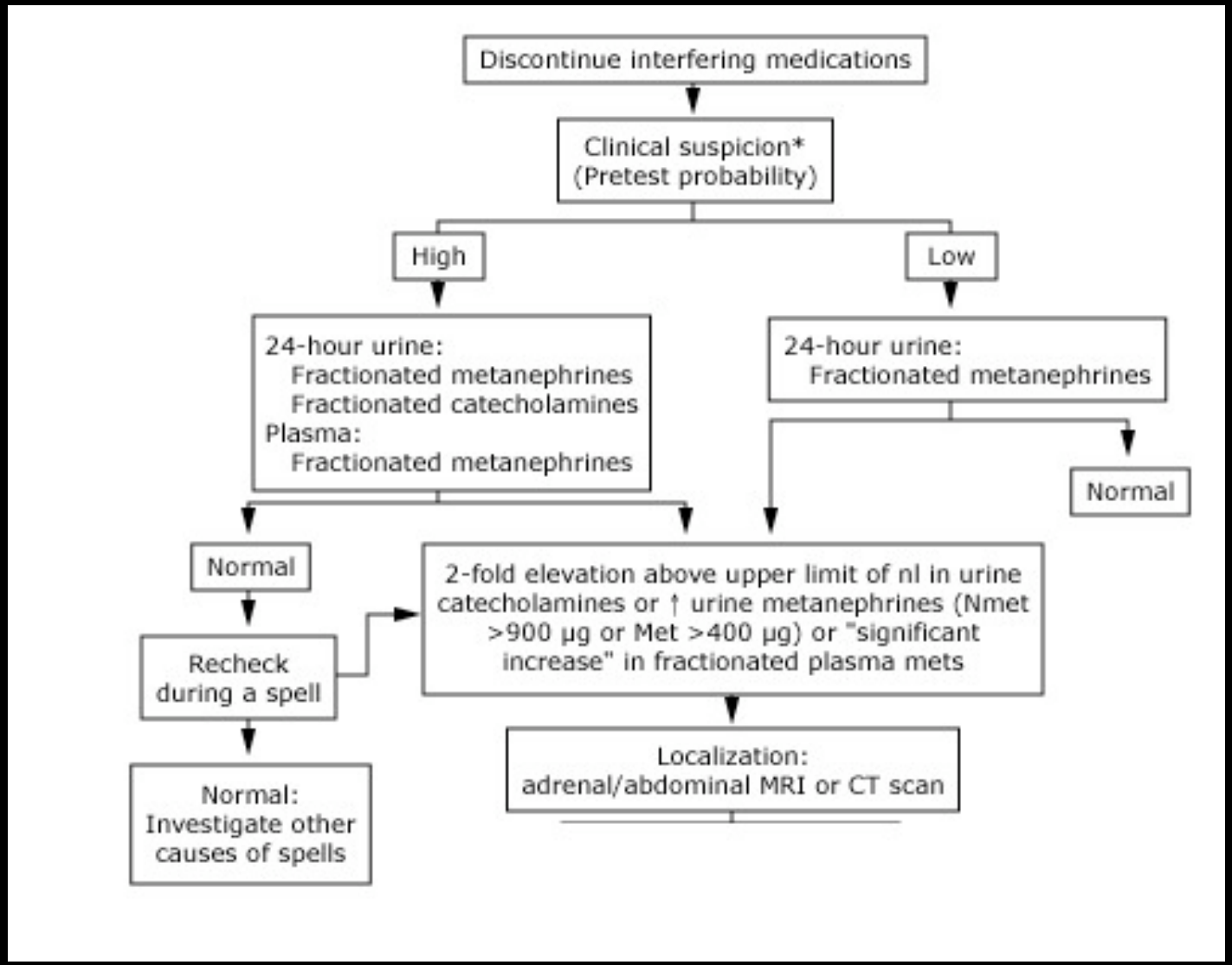
Specificità

- uMetanefrine fraz 98%
- uCatecolamine

NB: in pazienti testati per FEO che non hanno il FEO, i livelli di Normeta sono + alti del 71% e quelli della Meta del 51% del valore massimo di riferimento

Sanka et al 2003
Kudva et al 2003
Perry et al 2003


Associazione Medici Endocrinologi Lombardia
SIMPOSIO
I NETs
A CHE PUNTO
SIAMO?
Milano,
20 giugno 2008
Jolly Hotel Touring


Discontinue interfering medications
Clinical suspicion*
(Pretest probability)
High
Low
24-hour urine:
Fractionated metanephrines
Fractionated catecholamines
Plasma:
Fractionated metanephrines
24-hour urine:
Fractionated metanephrines
Normal
Normal
2-fold elevation above upper limit of nl in urine catecholamines or ↑ urine metanephrines (Nmet >900 µg or Met >400 µg) or "significant increase" in fractionated plasma mets
Recheck during a spell
Localization:
adrenal/abdominal MRI or CT scan
Normal:
Investigate other causes of spells

Adverse Drug Reactions in Patients with Phaeochromocytoma

Incidence, Prevention and Management

Graeme Eisenhofer,[1] *Graham Rivers,*[2] *Alejandro L. Rosas,*[3] *Zena Quezado,*[4] *William M. Manger*[5] and *Karel Pacak*[6]

Drug Safety 2007; 30 (11): 1031-1062
0114-5916/07/0011-1031/$44.95/0

Table III. Main classes of drugs with contraindications in phaeochromocytoma

Drug class	Relevant clinical uses
β-Adrenergic receptor antagonists (β-blockers)[a]	To treat conditions that result from phaeochromocytoma (e.g. hypertension, cardiomyopathy, heart failure, panic attacks, migraine, tachycardia and cardiac dysrhythmias)
Dopamine D_2 receptor antagonists	Control of nausea, vomiting, psychosis, hot flashes and for tranquillising actions
Tricyclic antidepressants	Treatment of insomnia, neuropathic pain, nocturnal enuresis in children, headaches, depression (rarely)
Monoamine oxidase inhibitors	Non-selective agents rarely used as antidepressants (due to 'cheese effect')
Sympathomimetics[a]	Control of low blood pressure during surgical anaesthesia; decongestants; antiobesity agents
Chemotherapeutic agents[a]	Antineoplastic actions; treatment of malignant phaeochromocytoma
Opioid analgesics[a]	Surgical anaesthesia
Neuromuscular blocking agents[a]	Surgical anaesthesia
Peptide and corticosteroid hormones[a]	Diagnostic testing

a Some drugs may have therapeutic or diagnostic use in phaeochromocytoma, but usually only after pretreatment with appropriate antihypertensives (e.g. phenoxybenzamine).

European Journal of Endocrinology (2008) **158** 423–429 ISSN 0804-4643

CASE REPORT

Pheochromocytoma crisis induced by glucocorticoids: a report of four cases and review of the literature

Alejandro L Rosas, Anna A Kasperlik-Zaluska[1], Lucyna Papierska[1], Barbara Lee Bass[2], Karel Pacak[3]

Table 1 Clinical characteristics.

Patient no.	Age (years)	Sex	Steroid, dose/route	Clinical data, complications, outcome	Presenting symptoms	Time to onset (h)
1	26	F	Dexamethasone 2 mg PO QID	PMC: shock; hyperglycemia; pulmonary edema, metabolic acidosis; incidentaloma; *fatal*	HTN, anxiety, shock	36
2	39	M	Betamethasone 6 mg i.m.	PMC: renal, hepatic, CNS dysfunction; shock, labile BP; hyperthermia; hyperglycemia; IABP; *survived*	Chest pain HTN, headache, nausea, and vomiting	12
3	27	M	Solu-Medrol 1.5 g i.v.	Hypertensive crisis; metastatic paraganglioma; norepi. secretor; on chemotherapy protocol; *survived*	Chest, pain, bone pain HTN, nausea, vomiting	8
4	39	F	Dexamethasone 2 mg PO QID	Hypertensive crisis; cardiac ischemia; incidentaloma; *survived*	Chest pain HTN; headache, nausea, vomiting	5
5 (1973)	69	F	Prednisone 45 mg PO[a]	HTN, recurrent episodes when steroid increased; *survived*	HTN	N/A
6 (1968)	39	M	Prednisone, hydrocortisone[a] doses: N/A	PMC: HTN, cardiac ischemia, CHF, pulmonary edema, hyperthermia, elevated SGOT; *survived*	Abdominal pain, palpitation	12
7 (1997)	34	F	Dexamethasone 16 mg route: N/A	Cardiogenic shock; hypotension; cardiac arrest; *survived*	N & V low B/P	12
8 (1997)	43	F	Prednisone 60 mg route: N/A	'Hemodynamic instability'; low EF, cardiac arrest, anecdotal case); *survived*	N/A	N/A
9 (1996)	46	M	'Steroid'	Multisystem illness; (anecdotal case); *fatal*	Chest pain HTN	'Several'
10 (2004)	44	F	Dexamethasone 2 mg PO TID	Cardiac ischemia, infarction; HTN, abdominal pain, retroperitoneal hemorrhage; *survived*	Headache, chest pain palpitation	24
11 (2000)	52	M	Dexamethasone dose: N/A intraarticular	Cardiogenic shock; renal insufficiency; IABP, PCPS, *survived*	Chest pain dyspnea	12

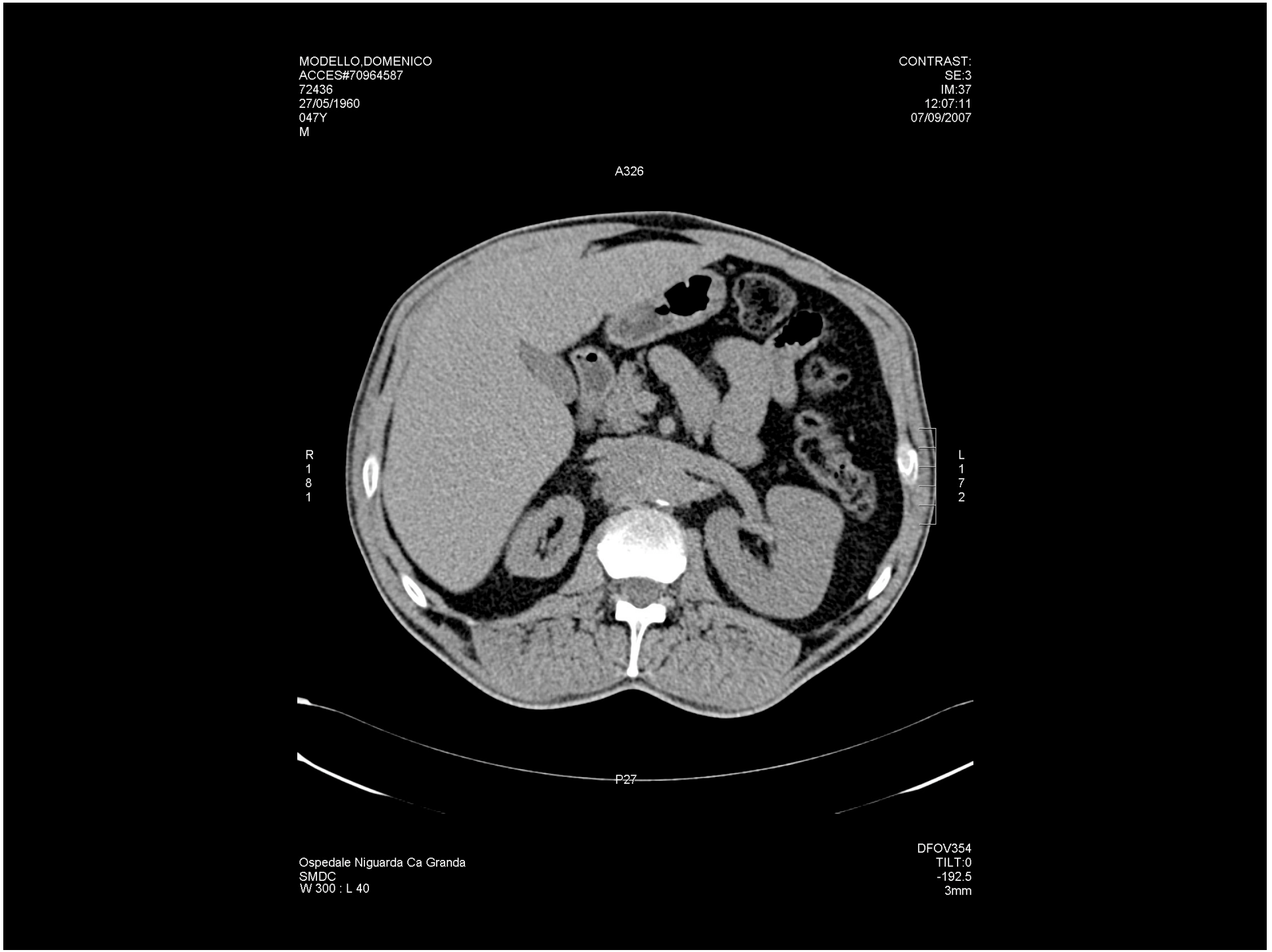
BP, blood pressure; EF, left ventricular ejection fraction; HTN, hypertensive crisis; IABP, intra-aortic balloon pump; i.m., intramuscularly; i.v., intravenously; N/A, information not available; PCPS, percutaneous cardiopulmonary support; PMC, pheochromocytoma multisystem crisis; PO, by mouth; QID, four times daily; TID, three times daily.
[a]Prednisone was administered, then 100 mg i.v. hydrocortisone, both caused HTN.

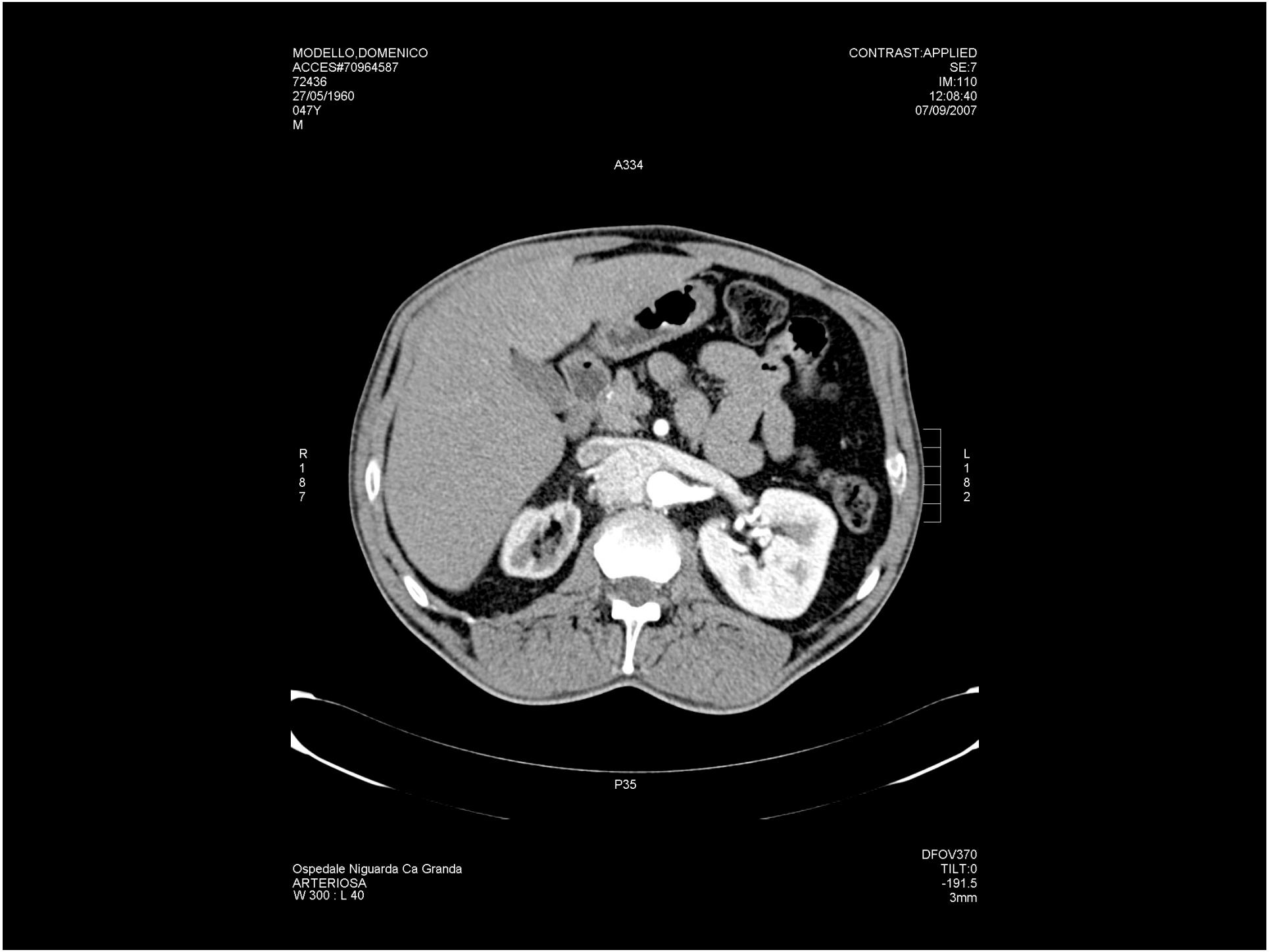
Outline

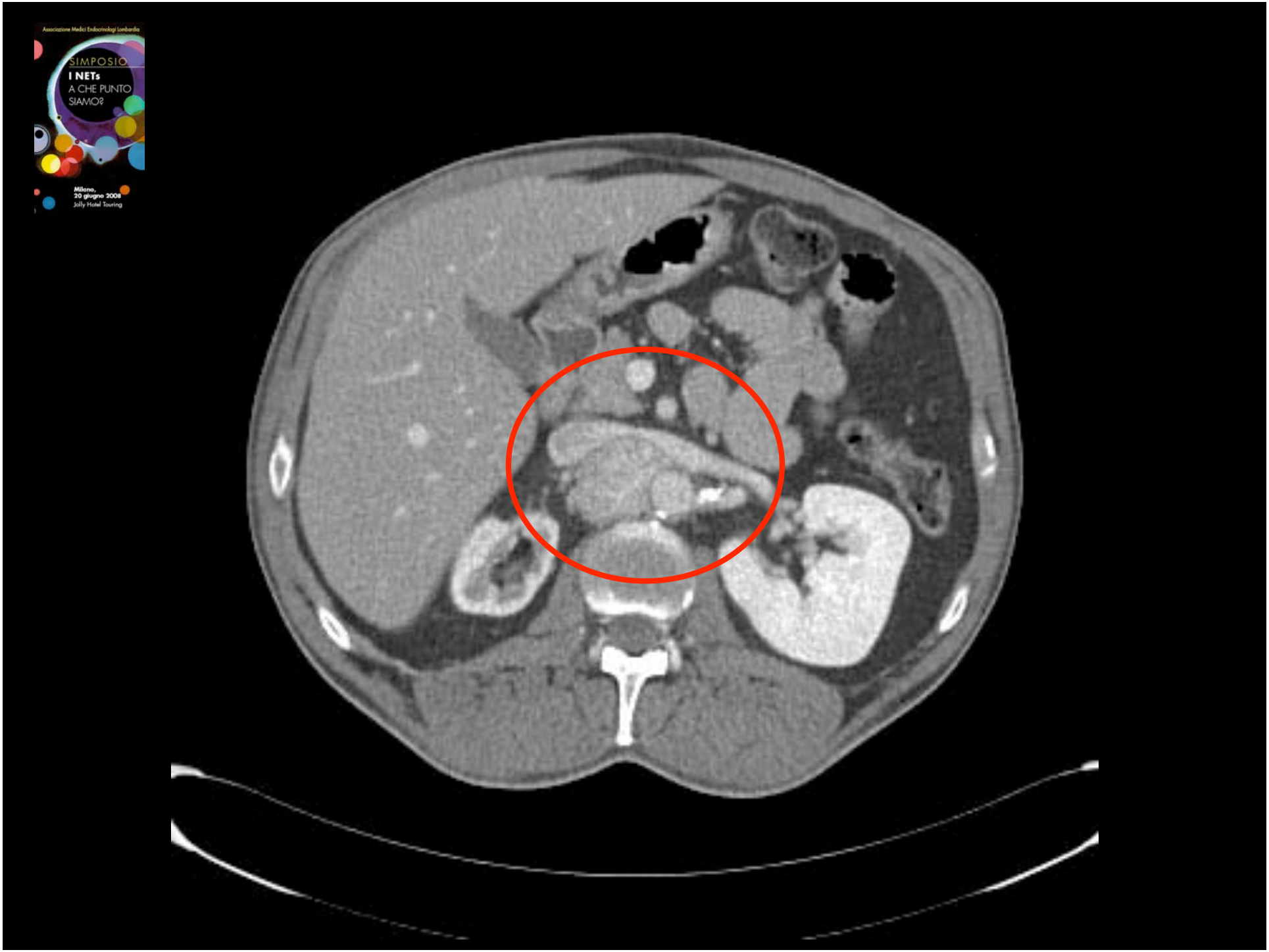
- quadro clinico
- laboratorio
- diagnostica per immagini
- terapia primaria
- anatomia patologica
- genetica
- terapia adiuvante

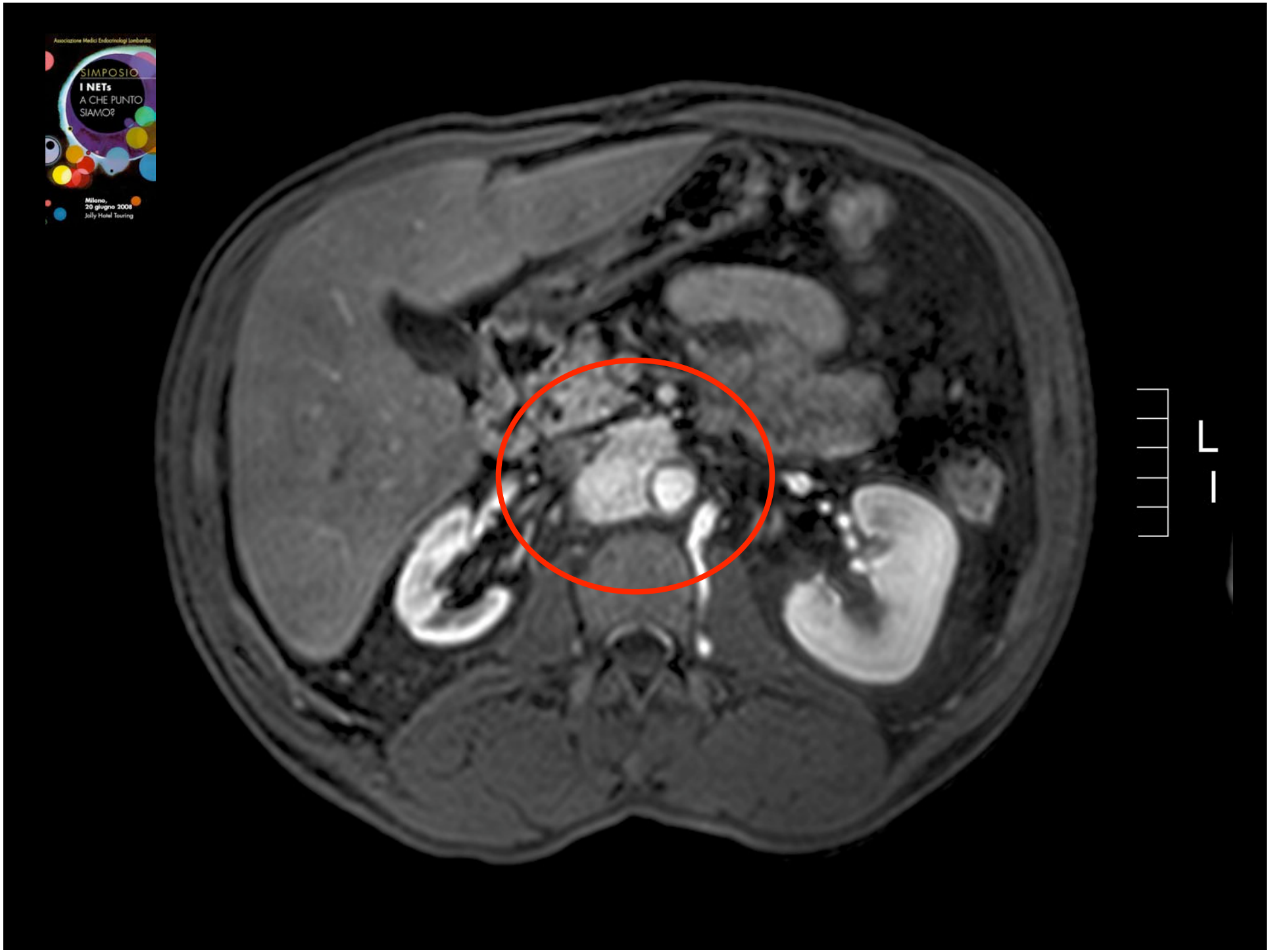
Quali esami strumentali ?
Quale distretto indagare ?

- TC
- RNM
- Scintigrafia


MODELLO,DOMENICO
ACCES#70964587
72436
27/05/1960
047Y
M
CONTRAST:
SE:3
IM:37
12:07:11
07/09/2007
A326
R
1
8
1
L
1
7
2
P27
Ospedale Niguarda Ca Granda
SMDC
W 300 : L 40
DFOV354
TILT:0
-192.5
3mm

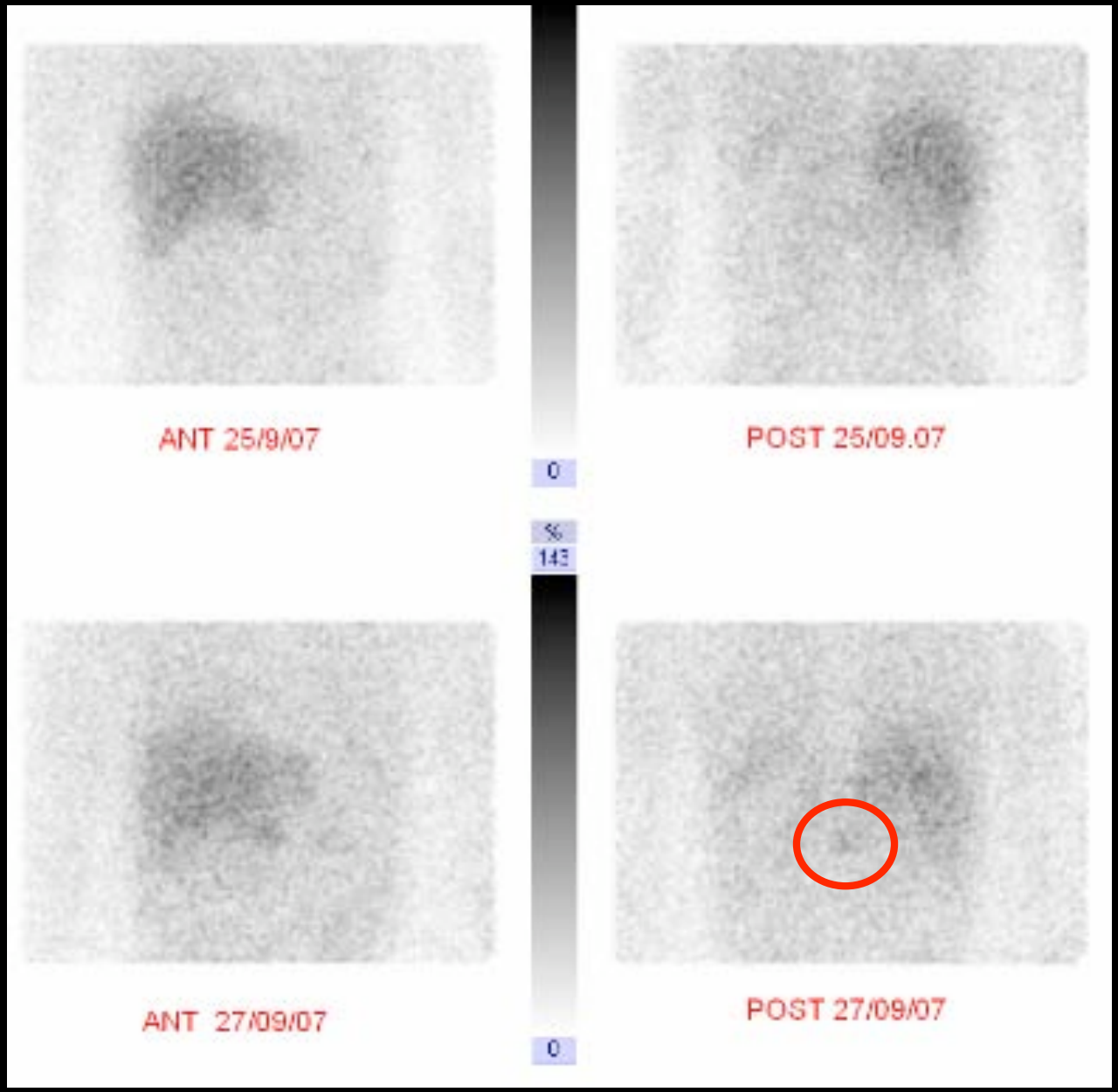

MODELLO,DOMENICO
ACCES#70964587
72436
27/05/1960
047Y
M
CONTRAST:APPLIED
SE:7
IM:110
12:08:40
07/09/2007
A334
R
1
8
7
L
1
8
2
P35
Ospedale Niguarda Ca Granda
ARTERIOSA
W 300 : L 40
DFOV370
TILT:0
-191.5
3mm


Associazione Medici Endocrinologi Lombardia
SIMPOSIO
I NETs
A CHE PUNTO
SIAMO?
Milano,
20 giugno 2008
Jolly Hotel Touring


Associazione Medici Endocrinologi Lombardia
SIMPOSIO
I NETs
A CHE PUNTO
SIAMO?
Milano,
20 giugno 2008
Jolly Hotel Touring
L
I


Associazione Medici Endocrinologi Lombardia
SIMPOSIO
I NETs
A CHE PUNTO
SIAMO?
Milano,
20 giugno 2008
Jolly Hotel Touring

MIBG


ANT 25/9/07
POST 25/09.07
0
%
143
ANT 27/09/07
POST 27/09/07
0

Terapia pre-chirurgica

- Doxazosin 8 mg/die

- Controllo PA

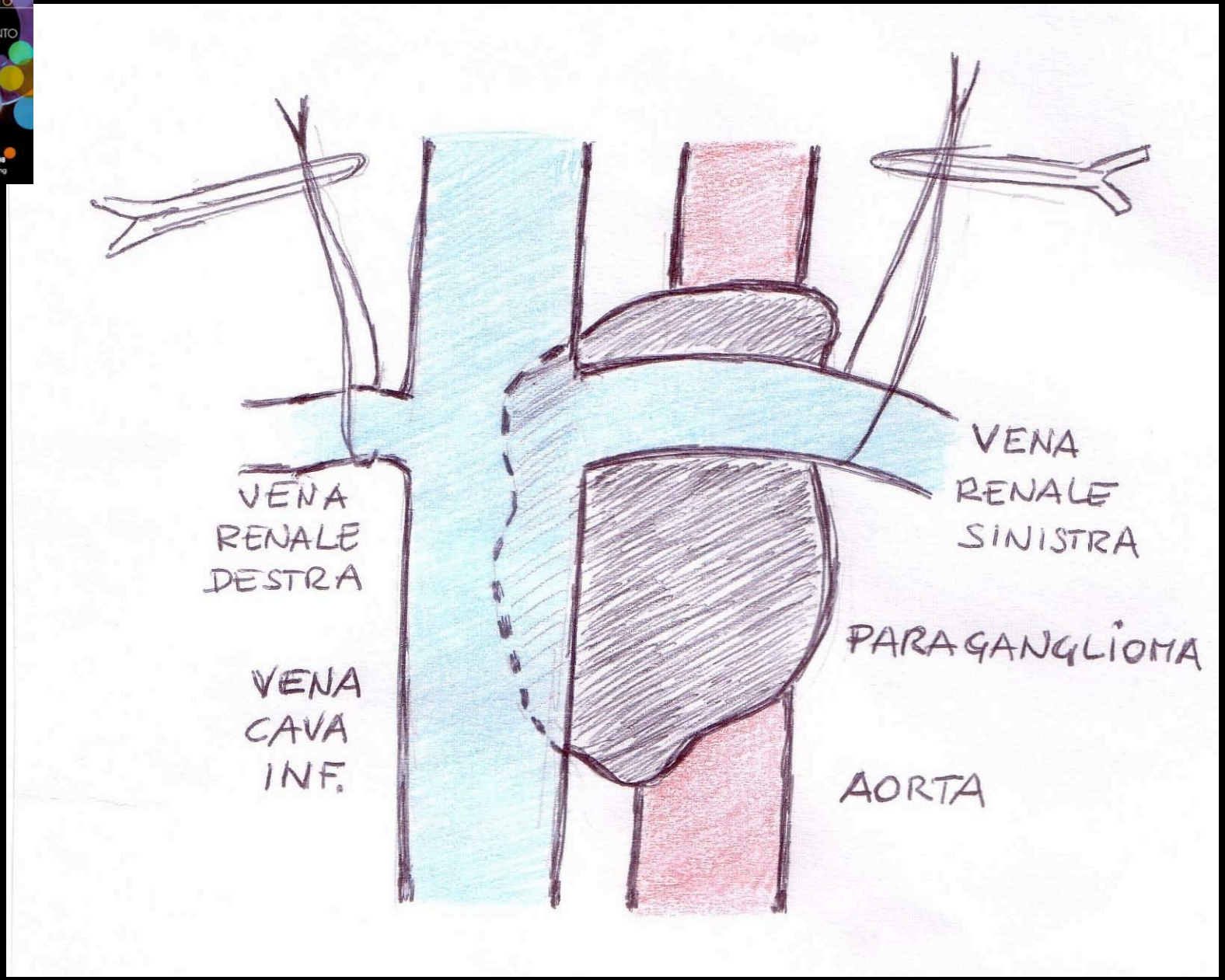
Outline

- quadro clinico
- laboratorio
- diagnostica per immagini
- terapia primaria
- anatomia patologica
- terapia adiuvante
- genetica

Intervento chirurgico

- Massa dura, contorni irregolari, riccamente vascolarizzata tra cava inf, Ao addominale e v. renale sin; v. renale dx circondata dalla lesione.
- Intervento di asportazione della massa
- Arteria renale dx inglobata dalla massa: sezione di necessità dell'a. renale e sua ricostruzione
- Controllo angiografico dopo 48 ore: occlusione completa dell'arteria renale dx, nefrectomia dx
- Decorso post-operatorio: normalizzazione dei valori pressori


Associazione Medici Endocrinologi Lombardia
SIMPOSIO
I NETs
A CHE PUNTO
SIAMO?
Milano,
20 giugno 2008
Jolly Hotel Touring

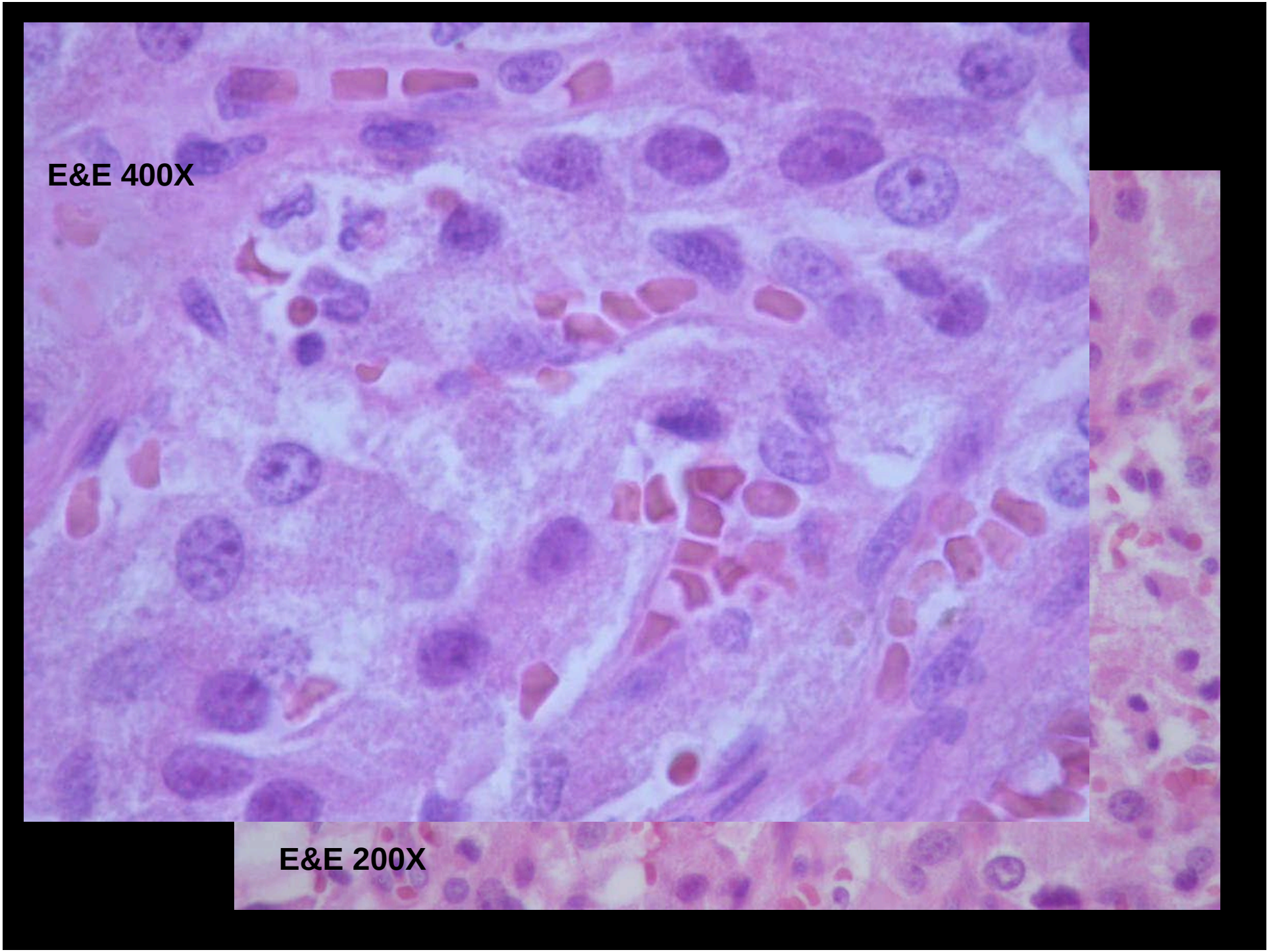

VENA
RENALE
DESTRA
VENA
CAVA
INF.
VENA
RENALE
SINISTRA
PARAGANGLIOMA
AORTA

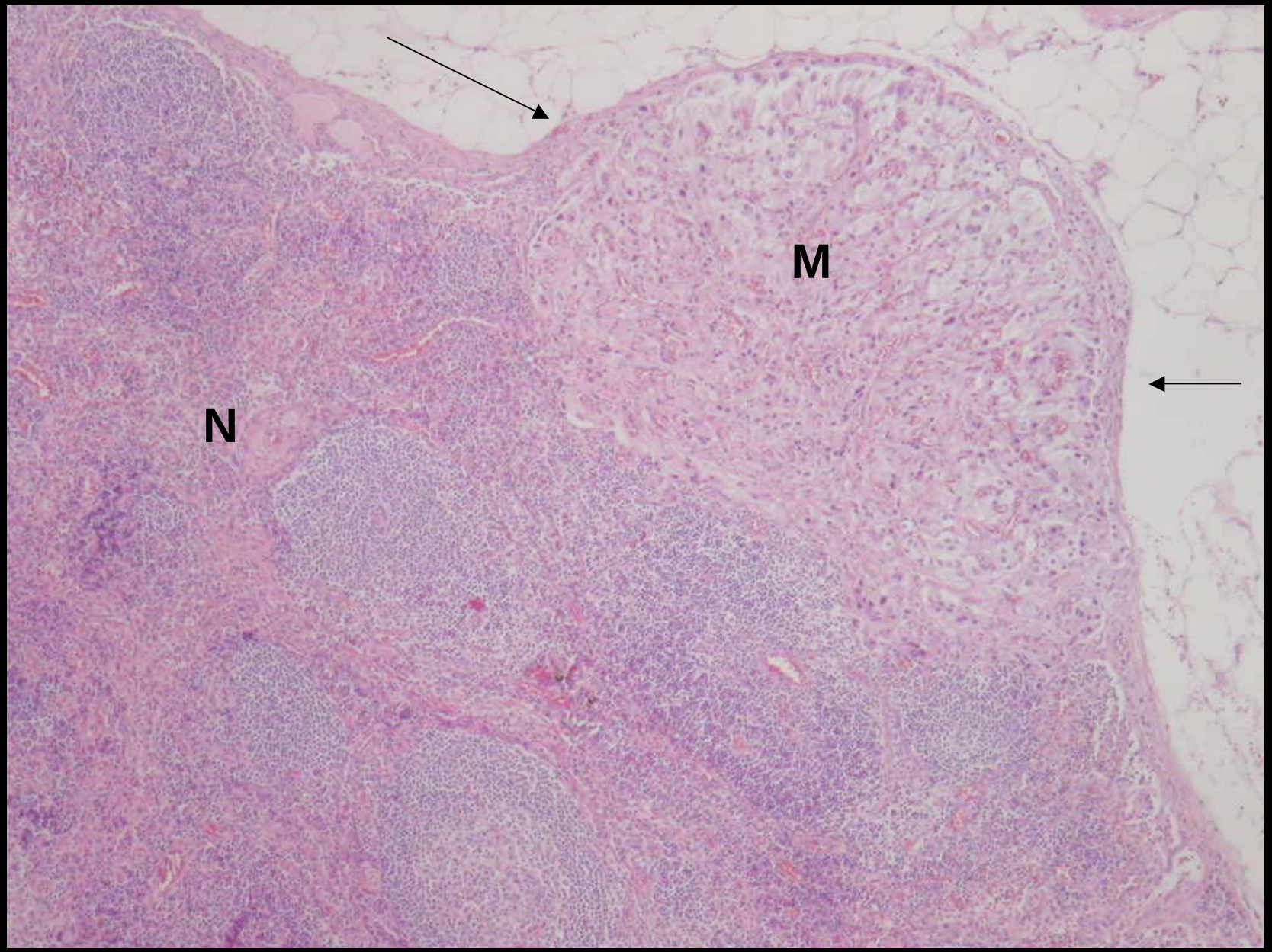
Outline

- quadro clinico
- laboratorio
- diagnostica per immagini
- terapia primaria
- anatomia patologica
- terapia adiuvante
- genetica

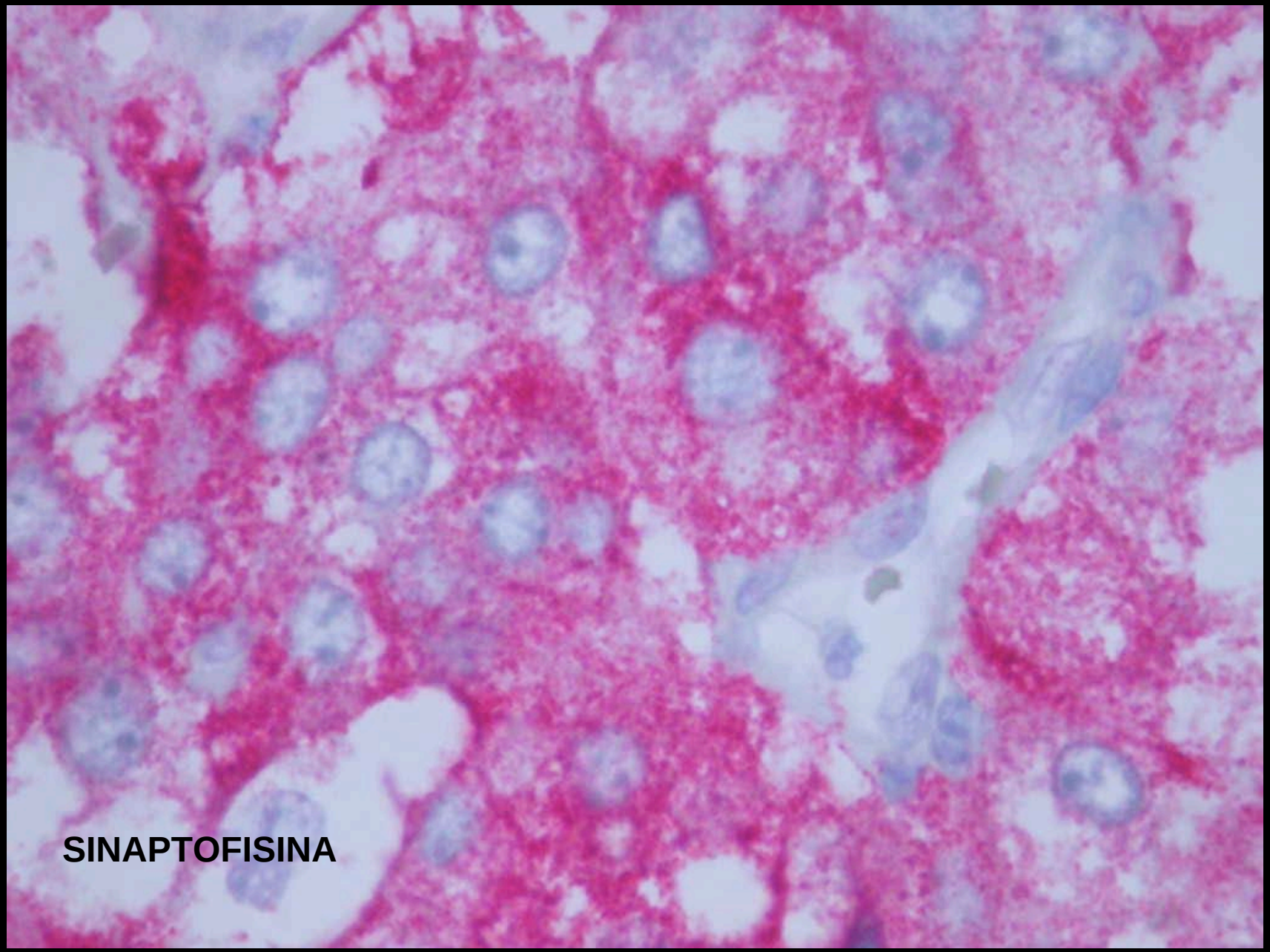
Esame istologico

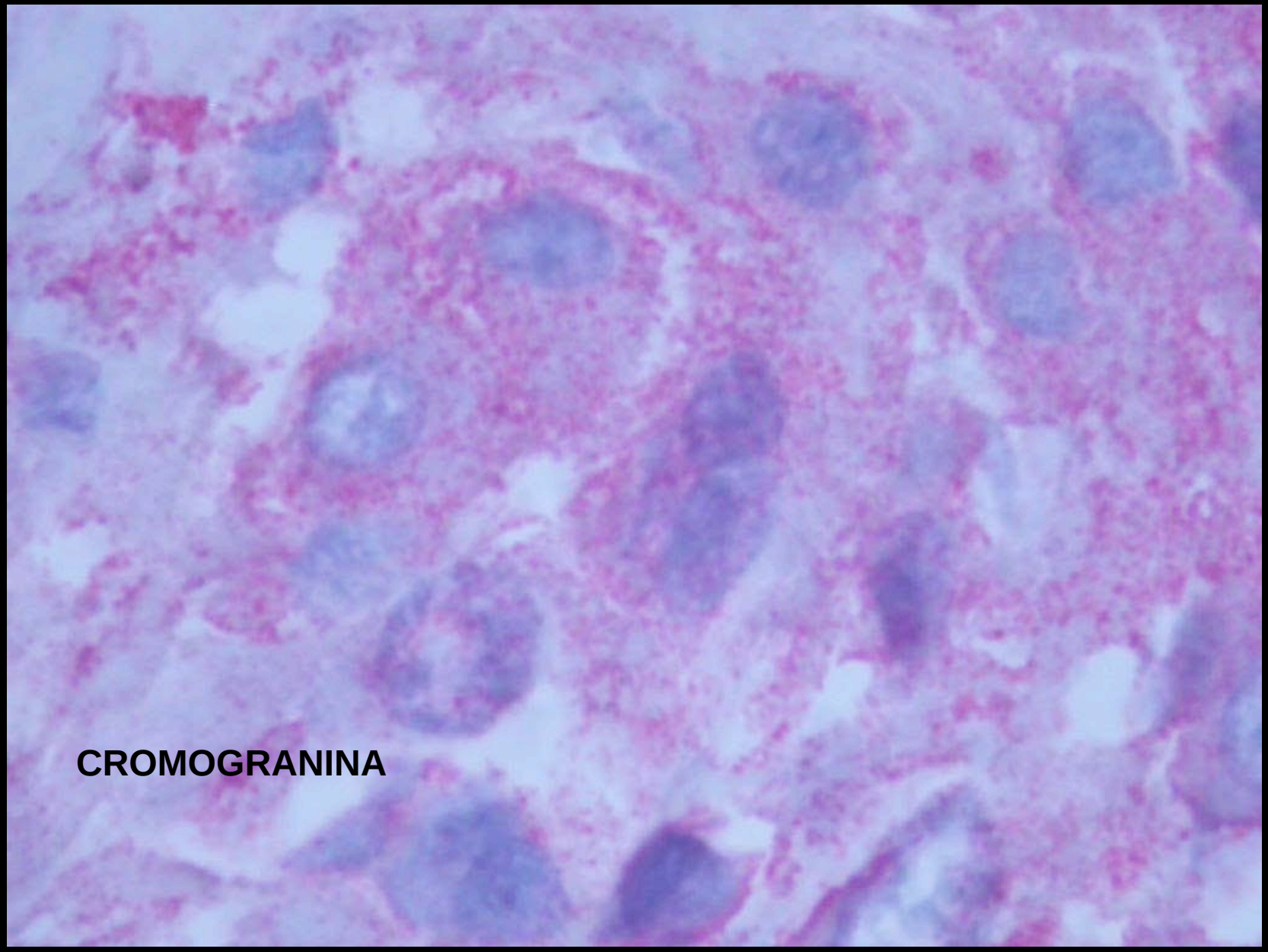
- Focale invasione tessuti molli circostanti; linfonodo indenne da npl
- Regione paracavale: metastasi in 1/2 linfonodi
- **Paraganglioma maligno**
- IIC: CK -, S100 -, Cr +, MIB 1%


E&E 400X
E&E 200X



METASTASI LINFONODALE AL SENO PERIFERICO-MARGINALE


SINAPTOFISINA


CROMOGRANINA

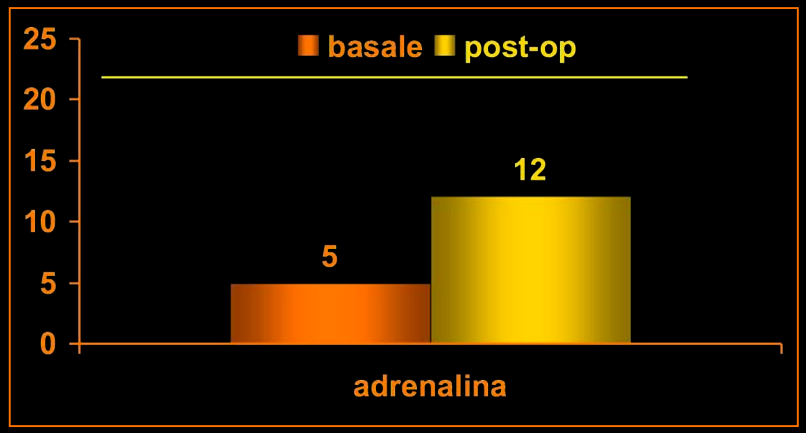
Istologia & sopravvivenza

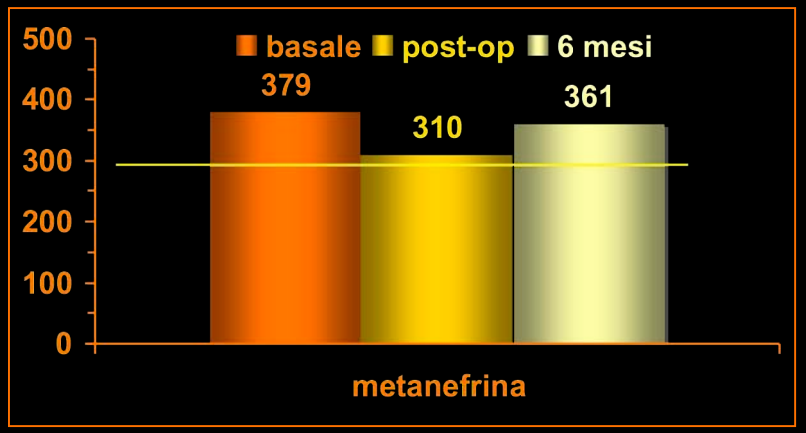
- 146 paragangliomi (36 metastatici)
- Grading istologico in relazione a 6 fattori: istologia, cellularità, necrosi coagulativa, invasine capsulare/vascolare, Ki67, tipo di catecolamina prodotto

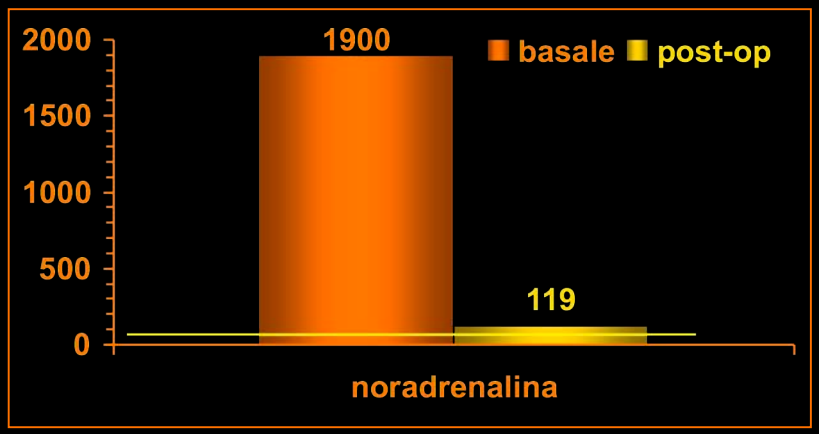
Differenziazione	n	Metastasi	Sopravvivenza a 5 aa
Buona	113	15	92%
Moderata	27	17	69%
Scarsa	6	6	0%

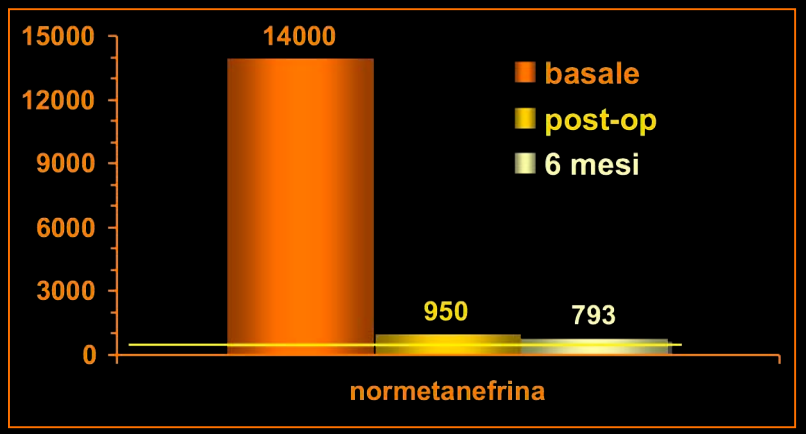
Kimura, Endocr Pathol 2005

Valutazione post-operatoria



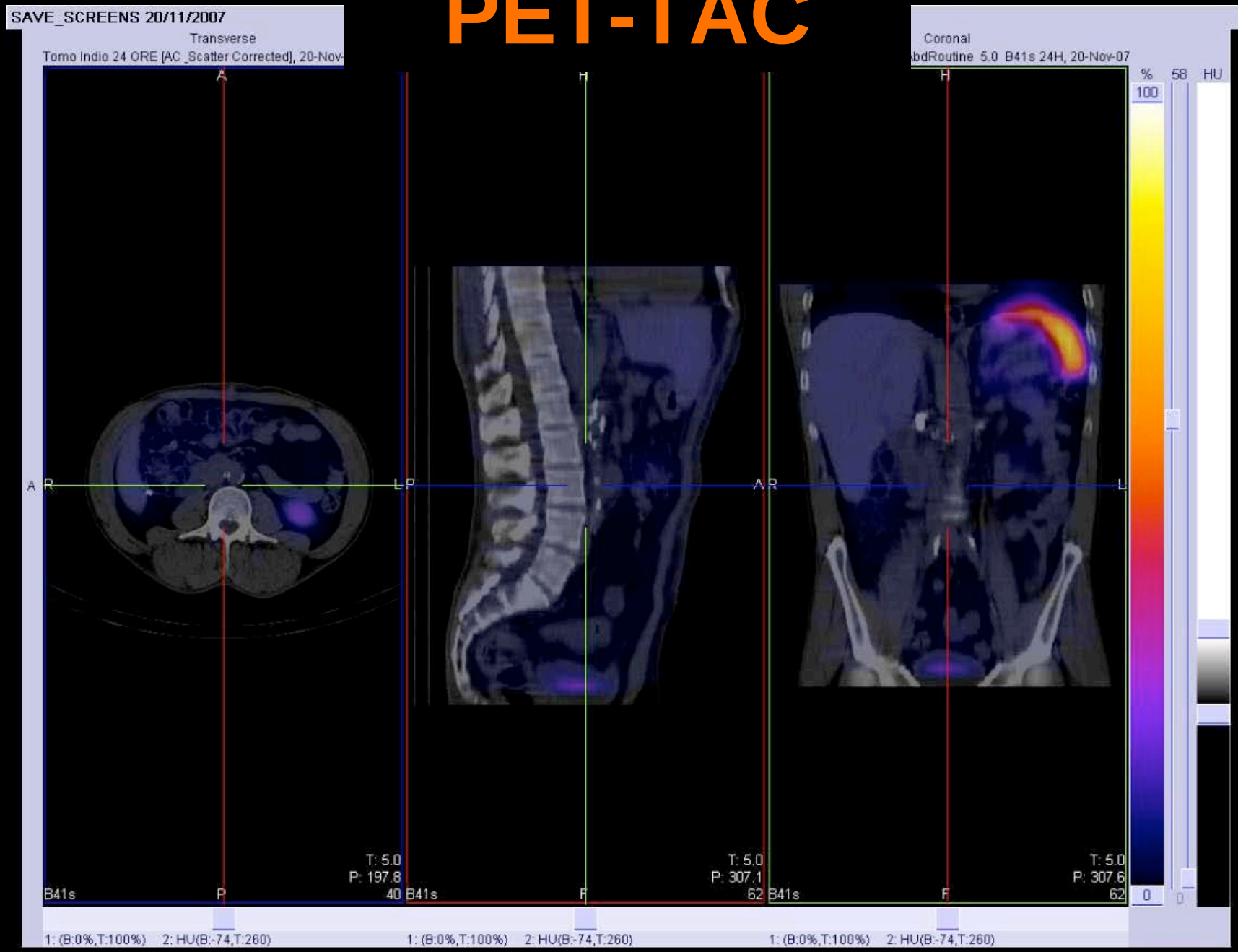






TC: negativa, cromogranina-A 19 U/L, glicemia 102 mg/dL

PET-TAC


SAVE_SCREENS 20/11/2007
Transverse
Tomo Indio 24 ORE [AC _Scatter Corrected], 20-Nov-
Coronal
bdRoutine 5.0 B41s 24H, 20-Nov-07
%
58
HU
100
0
T: 5.0
P: 197.8
40
B41s
T: 5.0
P: 307.1
62
B41s
T: 5.0
P: 307.6
62
B41s
1: (B:0%,T:100%) 2: HU(B:-74,T:260)
1: (B:0%,T:100%) 2: HU(B:-74,T:260)
1: (B:0%,T:100%) 2: HU(B:-74,T:260)

Outline

- quadro clinico
- laboratorio
- diagnostica per immagini
- terapia primaria
- anatomia patologica
- terapia adiuvante
- genetica

Quale follow-up ?

- Wait and see
- Radioterapia
- Chemioterapia
- Terapia radiometabolica

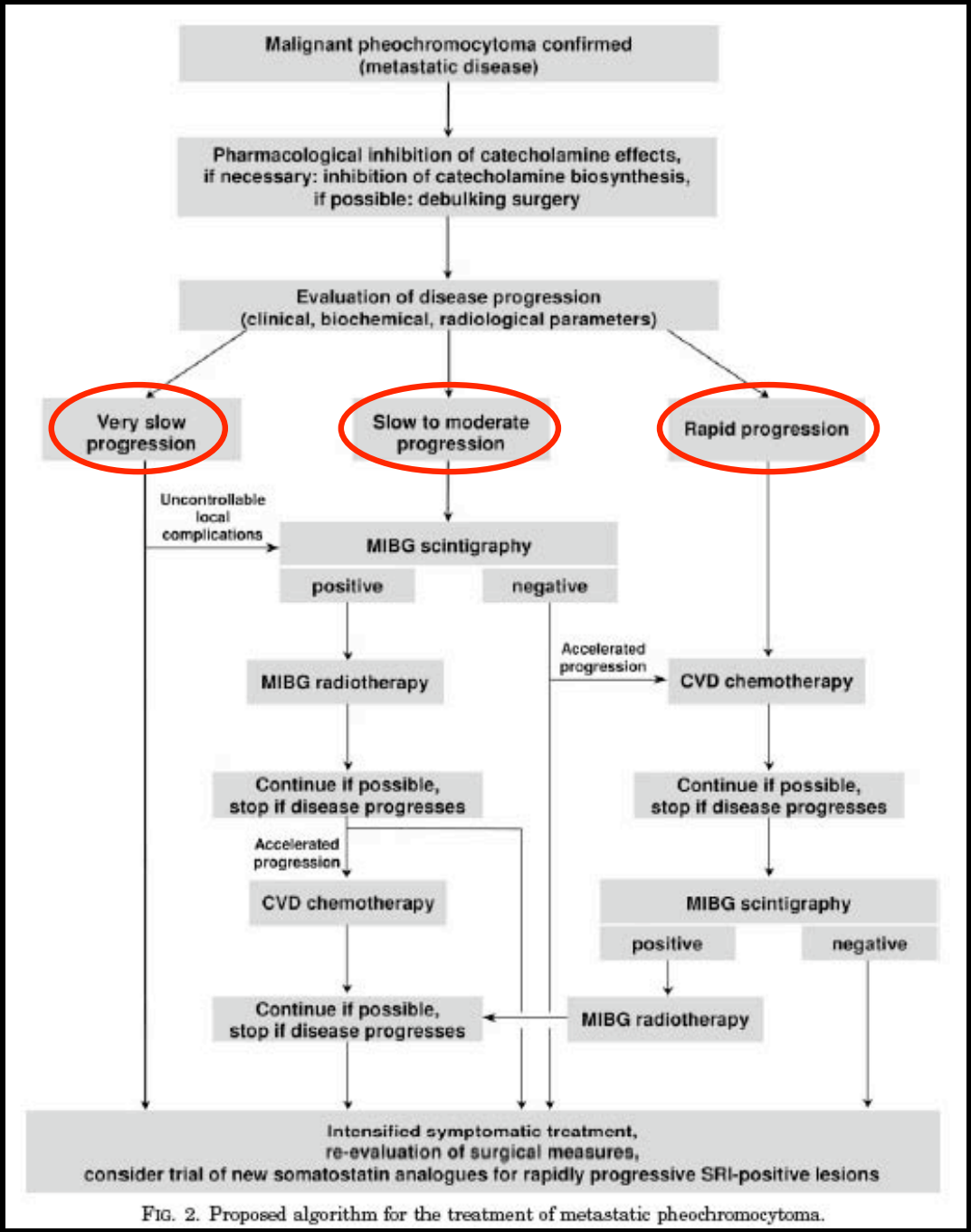


FIG. 2. Proposed algorithm for the treatment of metastatic pheochromocytoma.

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(4):1217–1225

doi: 10.1210/jc.2006-1544

CLINICAL REVIEW: Current Treatment of Malignant Pheochromocytoma

Tim Scholz, Graeme Eisenhofer, Karel Pacak, Henning Dralle, and Hendrik Lehnert

Department of Endocrinology and Metabolism (T.S., H.L.), Otto von Guericke University Medical School, D-39120 Magdeburg, Germany; Warwick Medical School (H.L.), University Hospital of Coventry, Coventry CV4 7AL, United Kingdom; National Institutes of Health (G.E., K.P.), Bethesda, Maryland 20892; and Department of General, Visceral, and Vascular Surgery (H.D.), Martin Luther University, D-06099 Halle/Saale, Germany

TABLE 2. MIBG radiotherapy for malignant PCC (selected reports)

Publication year (ref.)	No. of patients	Biochemical response (%)		Tumor response (%)		Stable disease (%)	Progression (%)
		Complete	Partial	Complete	Partial		
1997 (88)[a]	116[b]	13	32	4	26	57	13
1999 (89)[a]	137[c]	43[d]	43[d]	6	18	55	21
1999 (86)	6	17	17	0	33	33	33
2001 (87)[e]	6[f]	0	20	0	0	67	33
2003 (96)[g]	12[h]	33	50	18	18	45	18
% of evaluable cases[i]		13	32	4	25	56	15

The best response is listed irrespective of later relapse. Stable disease and progression refer to tumor presence only.
[a] Review of publications since 1983, additional report on three own patients in (88).
[b] Biochemical response evaluable in 96 patients.
[c] Includes patients from Ref. 88; biochemical response evaluable in 120 patients.
[d] No differentiation was made concerning complete and partial biochemical responses.
[e] First-line treatment in three patients, the other three receiving chemotherapy first (two CVD, one vincristine/ifosfamide/cisplatin).
[f] Biochemical response evaluable in five patients.
[g] High dose therapy (one to three treatments, cumulative dose 14.3–63.5 GBq).
[h] Includes two patients from Ref. 88; biochemical response evaluable in six, tumor response evaluable in 11 patients.
[i] Patients reported more than once were accounted for.

Outline

- quadro clinico
- laboratorio
- diagnostica per immagini
- terapia primaria
- anatomia patologica
- terapia adiuvante
- genetica

GERM-LINE MUTATIONS IN NONSYNDROMIC PHEOCHROMOCYTOMA

HARTMUT P.H. NEUMANN, M.D., BIRKE BAUSCH, SARAH R. MCWHINNEY, B.A., BERNHARD U. BENDER, M.D., OLIVER GIMM, M.D., GERLIND FRANKE, PH.D., JOERG SCHIPPER, M.D., JOACHIM KLISCH, M.D., CARSTEN ALTEHOEFER, M.D., KLAUS ZERRES, M.D., ANDRZEJ JANUSZEWICZ, M.D., AND CHARIS ENG, M.D., PH.D., FOR THE FREIBURG–WARSAW–COLUMBUS PHEOCHROMOCYTOMA STUDY GROUP*

N Engl J Med, Vol. 346, No. 19 · May 9, 2002 · www.nejm.org · 1459

Genetics	0-10	11-20	21-30	31-40	42-50	51-60	61-80	tot
VHL	6	17	2	3	2	0	0	30
RET	0	0	4	4	5	0	0	13
SDHD	1	2	3	3	1	1	0	11
SDHB	0	5	3	2	2	0	0	12
No mutations	3	23	19	32	46	50	32	205
% mutations	70	51	39	27	18	2	0	24.4

A germ-line mutation is present in 24.4% (66/271) of patients affected by an apparently sporadic pheochromocytoma

GERM-LINE MUTATIONS IN NONSYNDROMIC PHEOCHROMOCYTOMA

HARTMUT P.H. NEUMANN, M.D., BIRKE BAUSCH, SARAH R. MCWHINNEY, B.A., BERNHARD U. BENDER, M.D., OLIVER GIMM, M.D., GERLIND FRANKE, PH.D., JOERG SCHIPPER, M.D., JOACHIM KLISCH, M.D., CARSTEN ALTEHOEFER, M.D., KLAUS ZERRES, M.D., ANDRZEJ JANUSZEWICZ, M.D., AND CHARIS ENG, M.D., PH.D., FOR THE FREIBURG–WARSAW–COLUMBUS PHEOCHROMOCYTOMA STUDY GROUP*

N Engl J Med, Vol. 346, No. 19 · May 9, 2002 · www.nejm.org · 1459

- RET+: 12/13 → CMT
- VHL+: 5/30 → altri segni di VHL
- SHD+: 4/23 → paragangliomi

Sviluppo di storia familiare

- RET+: → 6/13
- VHL+: → 12/30
- SHD+: → 4/23

Famiglia del gene succinico deidrogenasi (SDH)

- SDHD
- SDHA
- SDHB
- SDHC

0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(3):827–836

doi: 10.1210/jc.2005-1862

Clinical Presentation and Penetrance of Pheochromocytoma/Paraganglioma Syndromes

Diana E. Benn,* Anne-Paule Gimenez-Roqueplo,* Jennifer R. Reilly,* Jérôme Bertherat, John Burgess, Karen Byth, Michael Croxson, Patricia L. M. Dahia, Marianne Elston, Oliver Gimm, David Henley, Philippe Herman, Victoria Murday, Patricia Niccoli-Sire, Janice L. Pasieka, Vincent Rohmer, Kathy Tucker, Xavier Jeunemaitre, Deborah J. Marsh, Pierre-François Plouin, and Bruce G. Robinson, for the International SDH Consortium

Results: *SDHB* mutation carriers were more likely than *SDHD* mutation carriers to develop extraadrenal pheochromocytomas and malignant disease, whereas *SDHD* mutation carriers had a greater propensity to develop head and neck paragangliomas and multiple tumors. For the index cases,

Conclusions: For clinical follow-up, features of *SDHB* mutation-associated disease include a later age of onset, extraadrenal (abdominal or thoracic) tumors, and a higher rate of malignancy. In contrast, *SDHD* mutation carriers, in addition to head and neck paragangliomas, should be observed for multifocal tumors, infrequent malignancy, and the possibility of extraadrenal pheochromocytoma. (***J Clin Endocrinol Metab* 91: 827–836, 2006**)

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(10):3822–3828

doi: 10.1210/jc.2007-0709

Succinate Dehydrogenase B Gene Mutations Predict Survival in Patients with Malignant Pheochromocytomas or Paragangliomas

Laurence Amar, Eric Baudin, Nelly Burnichon, Séverine Peyrard, Stéphane Silvera, Jérôme Bertherat, Xavier Bertagna, Martin Schlum
Pierre-François Plouin*

*Hypertension Unit (L.A., P.-F.P.), De
9201 (S.P.), Hôpital Européen Georg
Radiology (S.S., J.B., X.B.), Hôpital
de la Recherche Médicale U-567 (J.B
France; Institut National de la Santé
France, 75231 Paris, France; and De
Roussy, 94805 Villejuif, France*

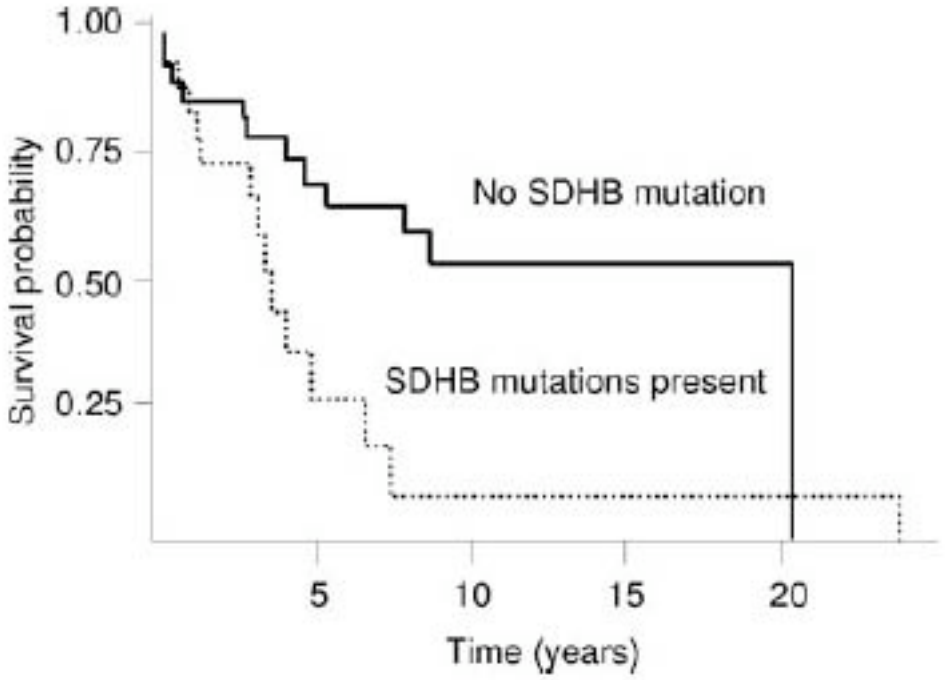


FIG. 2. Probability of survival according to mutation status.

www.associazionemediciendocrinologi.it

ame flash
marzo 2007

Responsabile Editoriale AME:
Vincenzo Toscano

IMPIEGO CLINICO DEI TEST GENETICI NEL FEOCROMOCITOMA

Anna Pia
UOC di Endocrinologia
Ospedale di Cuneo

Tabella 2. Elementi clinici orientativi nella scelta dei test genetici da effettuare nei pazienti con Feo sporadico di età < 50 anni.

SINDROME	Età media alla diagnosi	FEO surrene	FEO bilaterale	FEO extra-surrenalico	Maligno	Profilo biochimico
VHL	20-30 anni	++	++	+	-	NE
MEN 2	35-40 anni	++	++	-	-	E > NE
SDHB	20-30 anni	+	-	++	++	NE > E
SDHD	20-30 anni	+	+	++	+	NE > E

NE= Norepinefrina E=Epinefrina

Sorveglianza genetica

- **A chi**: parenti di primo grado di pz con mutazioni SDH
- **Quando**: 10 anni prima dell'epoca diagnostica più precoce
- **Come**
  - controllo clinico e biochimico (uMetanefrine fraz e uCatecolamine) annuale
  - TC/RM ogni 2 anni della sede interessata dalla mutazione
  - F-DOPA PET/ MIBG ogni 3-5 anni

Grazie a

- Cristina Moioli, SC Malattie Infettive
- Marco Boniardi, SC Chirurgia DEA
- Cristina Patrosso, SC Biochimica
- Massimo Milella, SC Medicina Nucleare
- Angelo Vanzulli, SC Radiodiagnostica
- Edgardo Bonacina & Pierluigi Oreste, SC Anatomia Patologica

Grazie dell'attenzione

e arrivederci al

9° Congresso Nazionale AME

Milano 20-22 novembre 2009