Malattie rare in Endocrinologia

Dalla teoria alla pratica

Dott.ssa Daniela Agrimi

Casi Clinici/Oncogenetica

Bari,
7-10 novembre 2013

- **Malattie rare** (prevalenza nella popolazione generale < 0.05 %, UE)
- **Malattie genetiche ed eredo-familiari**

- Test genetico **presintomatico** e **prognostico** sul probando

Comitato Nazionale per la Bioetica-Orientamenti Bioetici per i Test Genetici, 19 Novembre 1999

Fabiana

S.F. 15 aa
Visita endocrinologica: amenorrea primaria

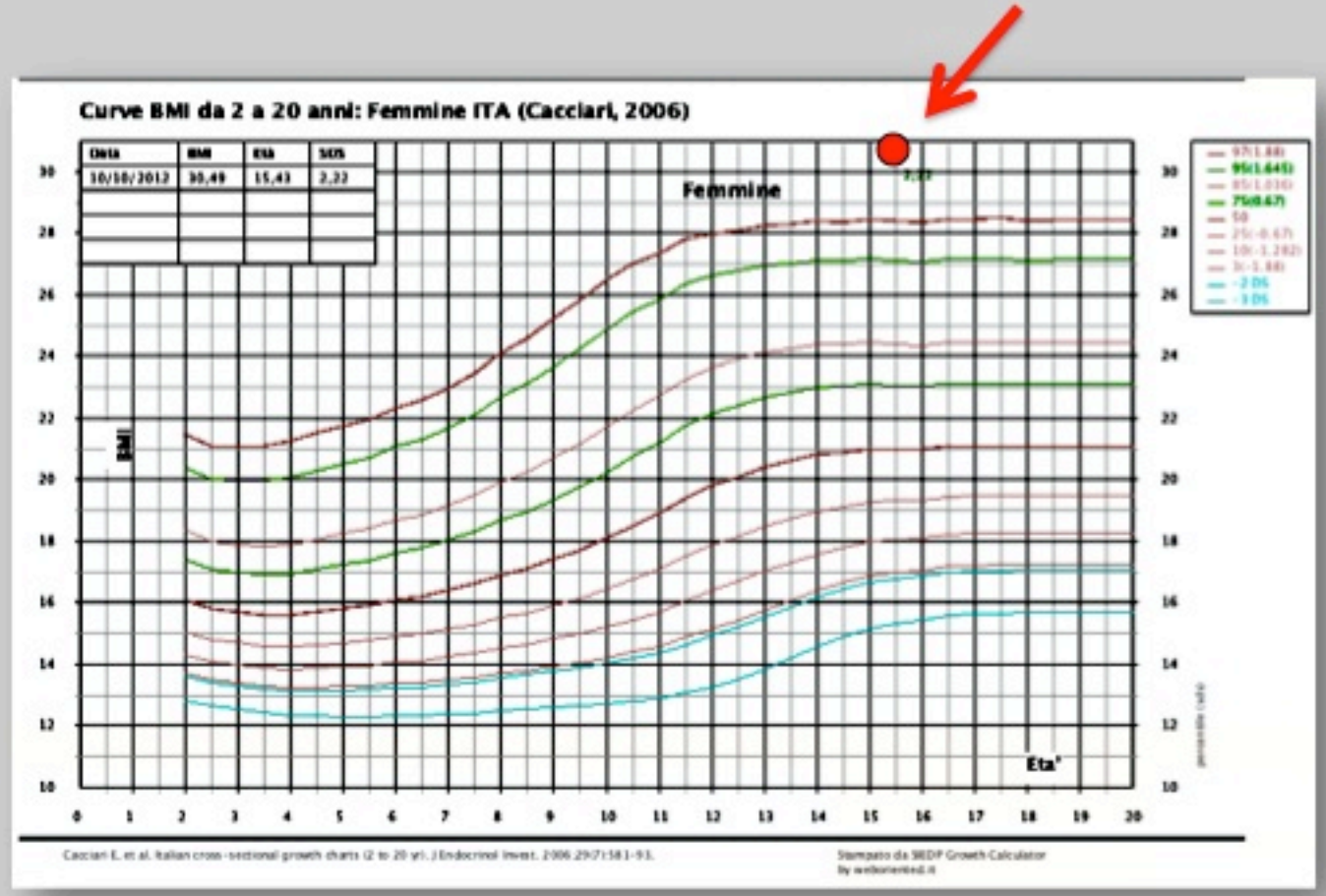
Anamnesi fisiologica: primogenita, nata a termine, II° liceo scientifico, rendimento scolastico buono; pratica sport saltuariamente

Anamnesi patologica remota: a 10 aa tonsillectomia, sin dall'infanzia eccesso ponderale

Dati clinici:
165 cm 83 Kg BMI 30.49 B3 P4
Adiposità ginoide, lieve iperisutismo (mento ++)

Fabiana

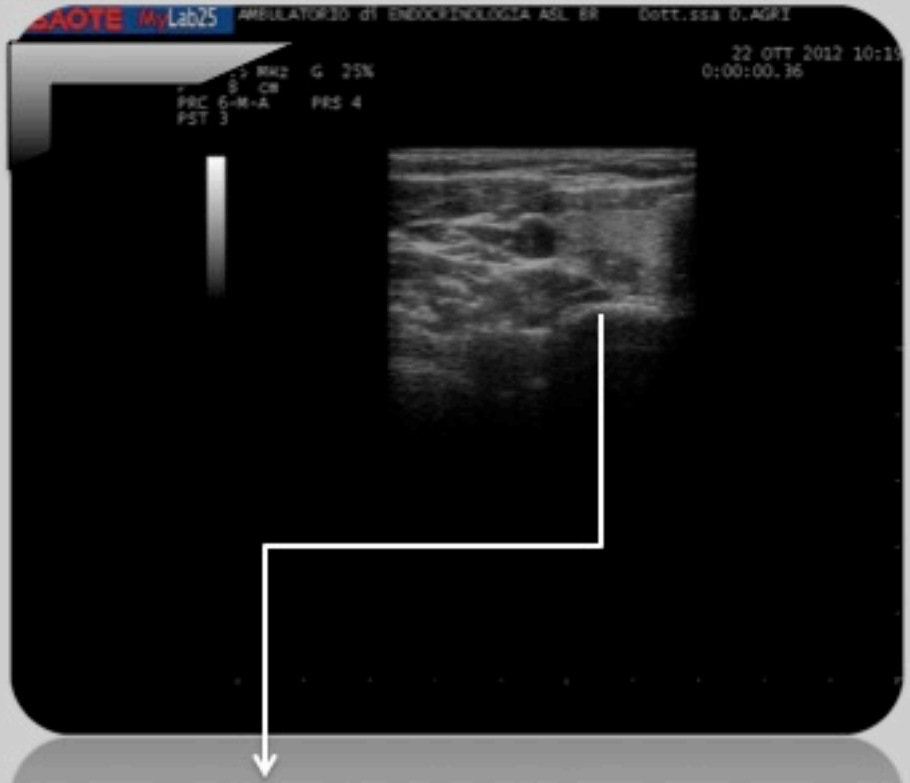
Bari,
7-10 novembre 2013



Fabiana

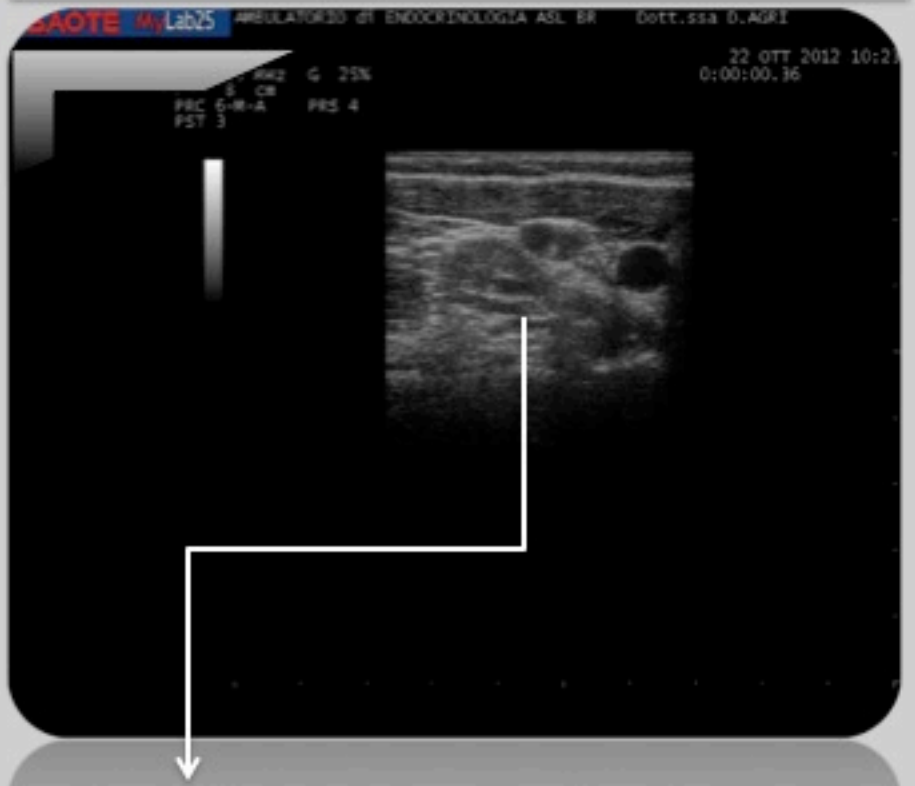
Bari,
7-10 novembre 2013

3° inferiore lobo dx:
nodulo ipoecogeno, 8 x 6.6 x 11 mm



CT (eluato): 2000 pg/ml

III livello latero-cervicale dx:
linfonodo oblungo, 9 x 5 x 15 mm



CT (eluato): 9.92 pg/ml

Fabiana

Bari,
7-10 novembre 2013

ESAMI di LABORATORIO	
CEA	
Ca	
Ca++	
Calciuria (24 h)	
PTH-intatto	
Metanefrine plasmatiche	
Metanefrine urinarie (24 h)	
Catecolamine plasmatiche	
Catecolamine urinarie (24 h)	

ESAMI STRUMENTALI
Ecografia addome superiore
Ecografia addome inferiore
Rx torace
Visita cardiologica, ECG
RMN regione sellare e parasellare

CALCITONINA (CT): 38 pg/ml (v.n. 0.1-9.9)

Carcinoma Midollare

Bari,
7-10 novembre 2013

- Tiroidectomia, Linfonadenectomia VI livello (26.11.12)

Diagnosi istologica:

"Tiroide sede, a carico del lobo destro, di ***carcinoma midollare*** *(1 cm) e di* ***duplice microcarcinoma midollare*** *(cm 0.3 e cm 0.1) e a carico del lobo sinistro di* ***microcarcinoma midollare*** *(cm 0.3). Lieve iperplasia bilaterale delle cellule C. Linfonodi, in numero di 5, esenti da neoplasia"*

IRCCS-Casa Sollievo della Sofferenza-Opera S. Pio da Pietrelcina
U.O.C. di Anatomia Patologica

MEN2a

Bari,
7-10 novembre 2013

- Analisi Genetica Molecolare

Mutazione germinale nel gene RET

c.1901G>T (p.Cys**634**Tyr)

Metodica: sequenziamento del DNA, PCR

U.O.C. Laboratorio di Genetica Medica
Università degli Studi di Bari "A. Moro"

Multiple Endocrine Neoplasia Type 2

Bari,
7-10 novembre 2013

La **MEN 2** (prevalenza 1/35.000) è classificata in 3 sottotipi:

- ✓ **MEN 2A** (70-80 %)
- ✓ **FMTC** (10-20 %)
- ✓ **MEN 2B** (5 %)

Il MTC compare tipicamente nella **infanzia** nella MEN 2B, nei **giovani adulti** (5-25 aa) nella MEN 2A e in **età media** nella FMTC

Table 2. Percent of Clinical Features by MEN 2 Subtype

Subtype	Medullary Thyroid Carcinoma	Pheochromocytoma	Parathyroid Disease
MEN 2A	95%	50%	20%-30%
FMTC	100%	0%	0%
MEN 2B	100%	50%	Uncommon

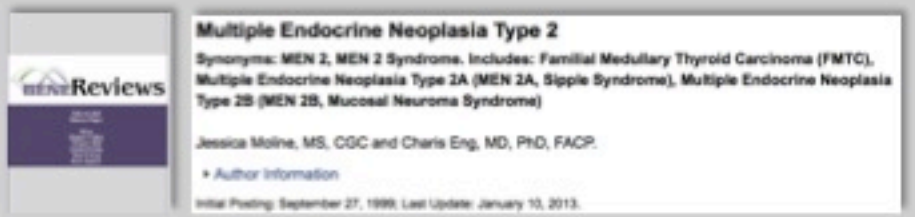
CHIRURGIA PROFILATTICA

Bari,
7-10 novembre 2013

Prevention of Primary Manifestations

Prophylactic thyroidectomy is the primary preventive measure for individuals with an identified germline *RET* mutation [Cohen & Moley 2003, American Thyroid Association Guidelines Task Force 2009].

Prophylactic thyroidectomy is safe for all age groups; however, the timing of the surgery is controversial [Moley et al 1998]. According to the consensus statement from the American Thyroid Association Guidelines Task Force, the age at which prophylactic thyroidectomy is performed can be guided by the codon position of the *RET* mutation (Table 4, Genotype-Phenotype Correlations) [American Thyroid Association Guidelines Task Force 2009]. However, these guidelines continue to be modified as more data become available.



GeneReviews

Multiple Endocrine Neoplasia Type 2

Synonyms: MEN 2, MEN 2 Syndrome. Includes: Familial Medullary Thyroid Carcinoma (FMTC), Multiple Endocrine Neoplasia Type 2A (MEN 2A, Sipple Syndrome), Multiple Endocrine Neoplasia Type 2B (MEN 2B, Mucosal Neuroma Syndrome)

Jessica Moline, MS, CGC and Charis Eng, MD, PhD, FACP.

+ Author Information

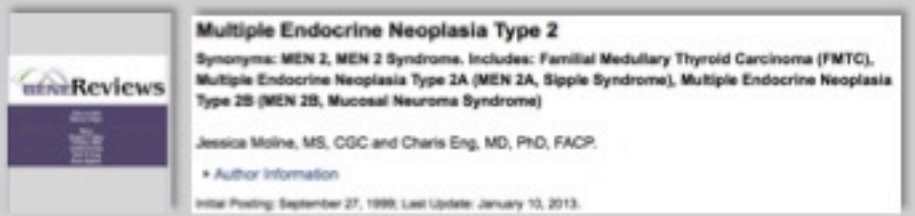
Initial Posting: September 27, 1999; Last Update: January 10, 2013.

CLASSE di RISCHIO D

Bari,
7-10 novembre 2013

Table 4. Risk for Aggressive MTC Based on Genotype and Recommended Interventions

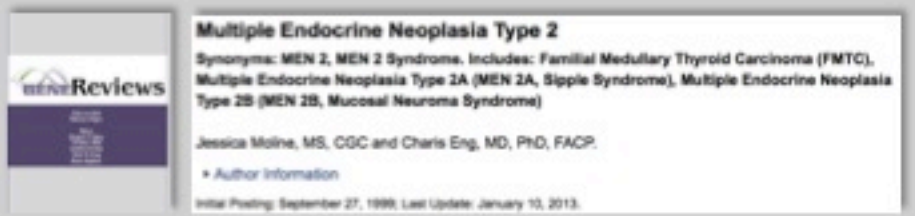
ATA [1] Risk Level	Mutations [2, 3]	Age of Prophylactic Surgery	Age to Begin Screening	
			For PHEO	For HPT
Level D (highest risk)	p.Ala883Phe p.Met918Thr p.Val804Met+p.Glu805Lys [4] p.Val804Met+p.Tyr806Cys [4] p.Val804Met+p.Ser904Cys [4]	As soon as possible in 1st year of life	8 yrs	NA



CLASSE di RISCHIO C

Bari,
7-10 novembre 2013

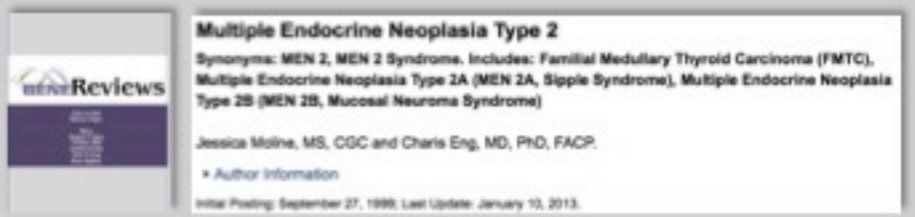
ATA [1] Risk Level	Mutations [2, 3]	Age of Prophylactic Surgery	Age to Begin Screening	
			For PHEO	For HPT
Level C	p.Cys634Arg/Gly/Phe/Ser /Trp/Tyr	<5 yrs	8 yrs	8 yrs



CLASSE di RISCHIO B

Bari,
7-10 novembre 2013

ATA [1] Risk Level	Mutations [2, 3]	Age of Prophylactic Surgery	Age to Begin Screening	
			For PHEO	For HPT
Level B	p.Cys609Phe/Arg/Gly/Ser/Tyr p.Cys611Arg/Gly/Phe/Ser/Trp/Tyr p.Cys618Arg/Gly/Phe/Ser/Tyr p.Cys620Arg/Gly/Phe/Ser/Trp/Tyr p.Cys630Arg/Phe/Ser/Tyr p.Asp631Tyr p.633/9 bp dup p.634/12 bp dup p.Val804Met+p.Val778Ile [4]	Consider <5 yrs; may delay if criteria met [4]	Codon 630 mutation: 8 yrs All others: 20 yrs	Codon 630 mutation: 8 yrs All others: 20 yrs



CLASSE di RISCHIO A

Bari,
7-10 novembre 2013

ATA [1] Risk Level	Mutations [2, 3]	Age of Prophylactic Surgery	Age to Begin Screening	
			For PHEO	For HPT
Level A	p.Arg321Gly p.531/9 bp dup p.532 dup p.Cys515Ser p.Gly533Cys p.Arg600Gln p.Lys603Glu p.Tyr606Cys p.635/insert ELCR;p.Thr636Pro p.Lys666Glu p.Glu768Asp p.Asn777Ser p.Leu790Phe p.Val804Leu/Met p.Gly819Lys p.Arg833Cys p.Arg844Gln p.Arg866Trp p.Ser891Ala p.Arg912Pro	May delay beyond age 5 yrs if criteria met [5]	20 yrs	20 yrs

5. Criteria: normal annual basal and or stimulated serum calcitonin; normal annual neck ultrasound examination; family history of less aggressive MTC

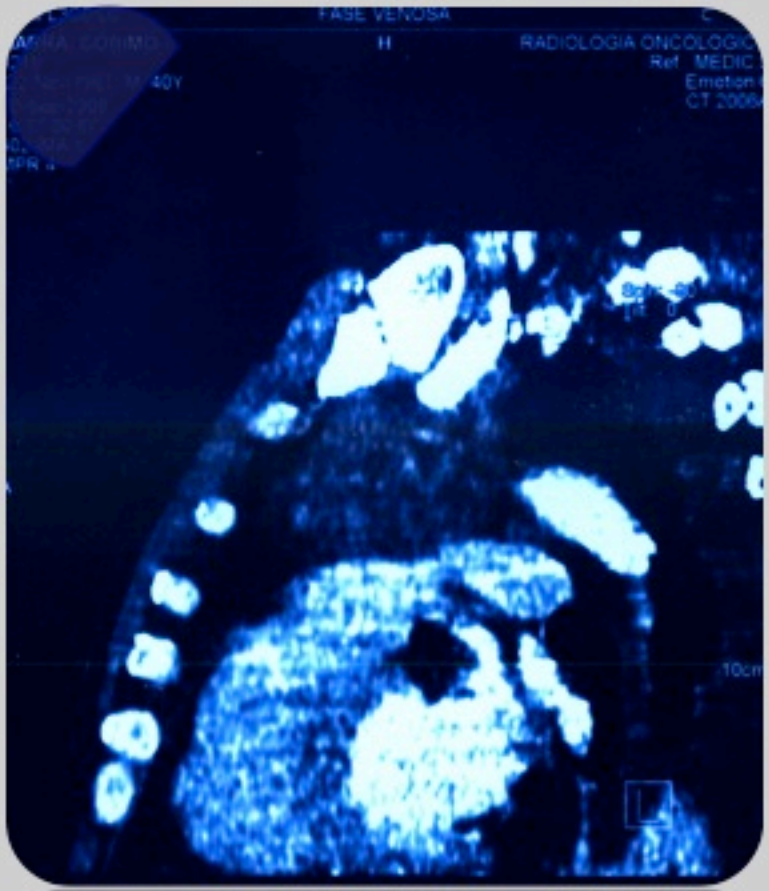
Cosimo

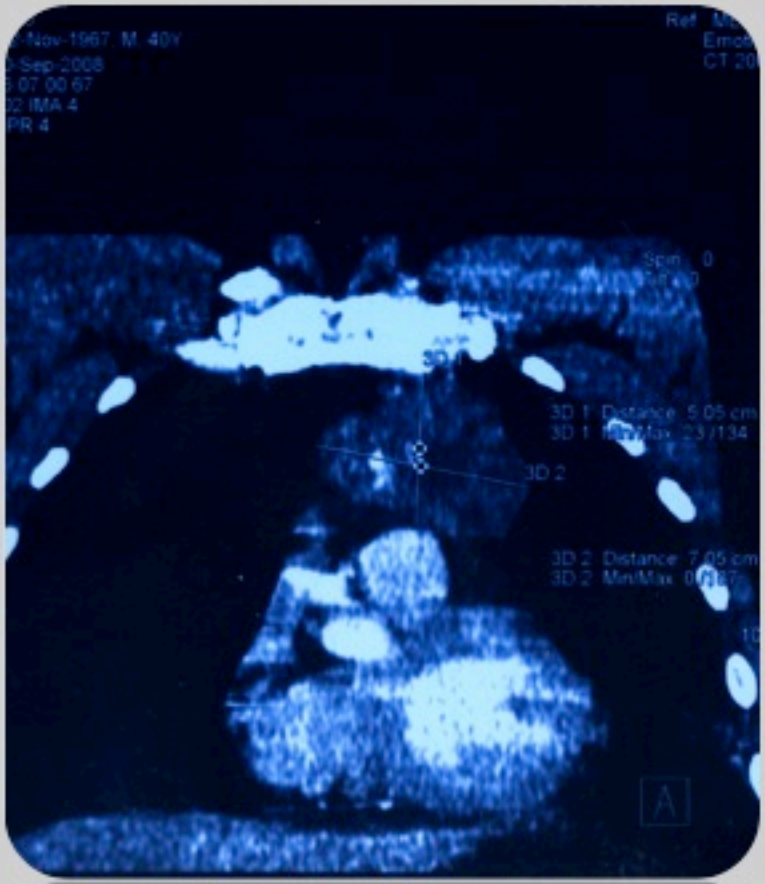
Bari,
7-10 novembre 2013

M.C. 41 aa
Coniugato, 1 figlio; infermiere

09/2008

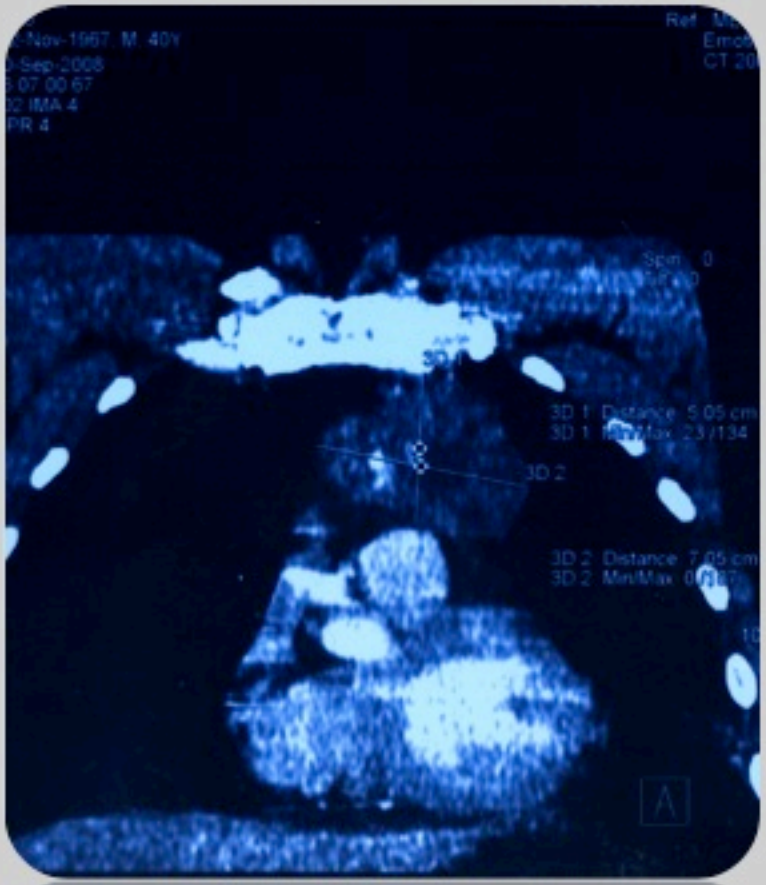
Per comparsa di febbre, dolore toracico e dispnea viene ricovero in Medicina Interna, con diagnosi di "**Pleurite acuta sinistra con polmonite e pericardite satellite**"


FASE VENOSA
RADIOLOGIA ONCOLOGICO
10cm


3D 1 Distance 5.05 cm
3D 2
3D 2 Distance 7.05 cm

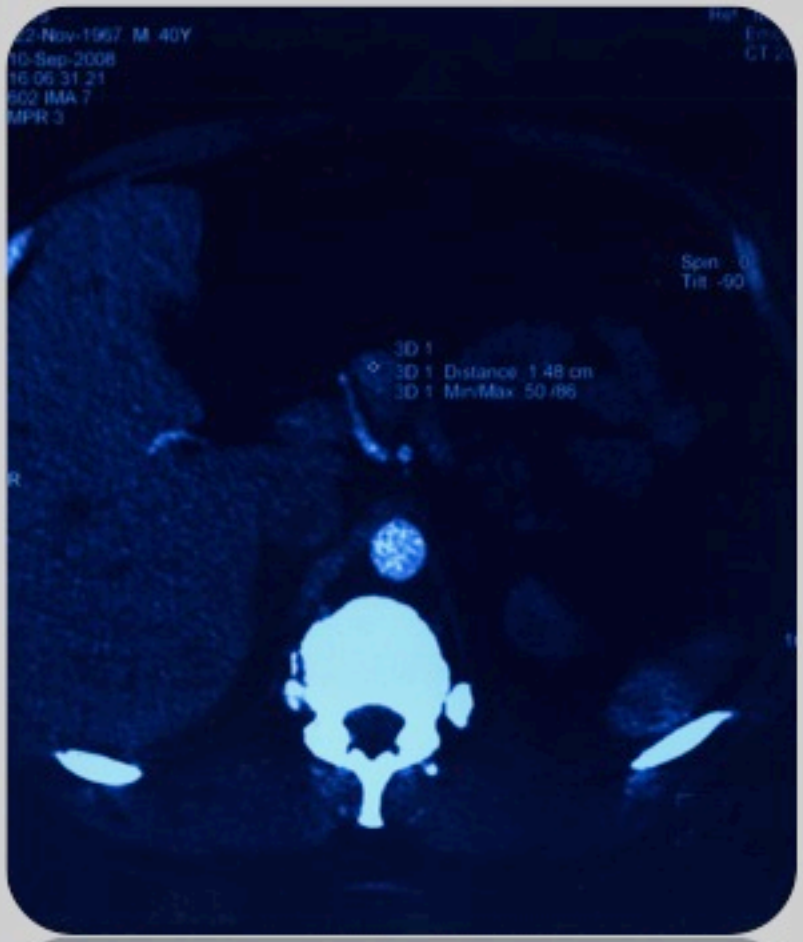
Neoformazione mediasitnica

- In corrispondenza del mediastino antero-superiore si evidenzia **neoformazione di 6 x 7 cm**, disomogenea per la presenza di calcificazioni intra-lesionali, riferibile a **timoma**



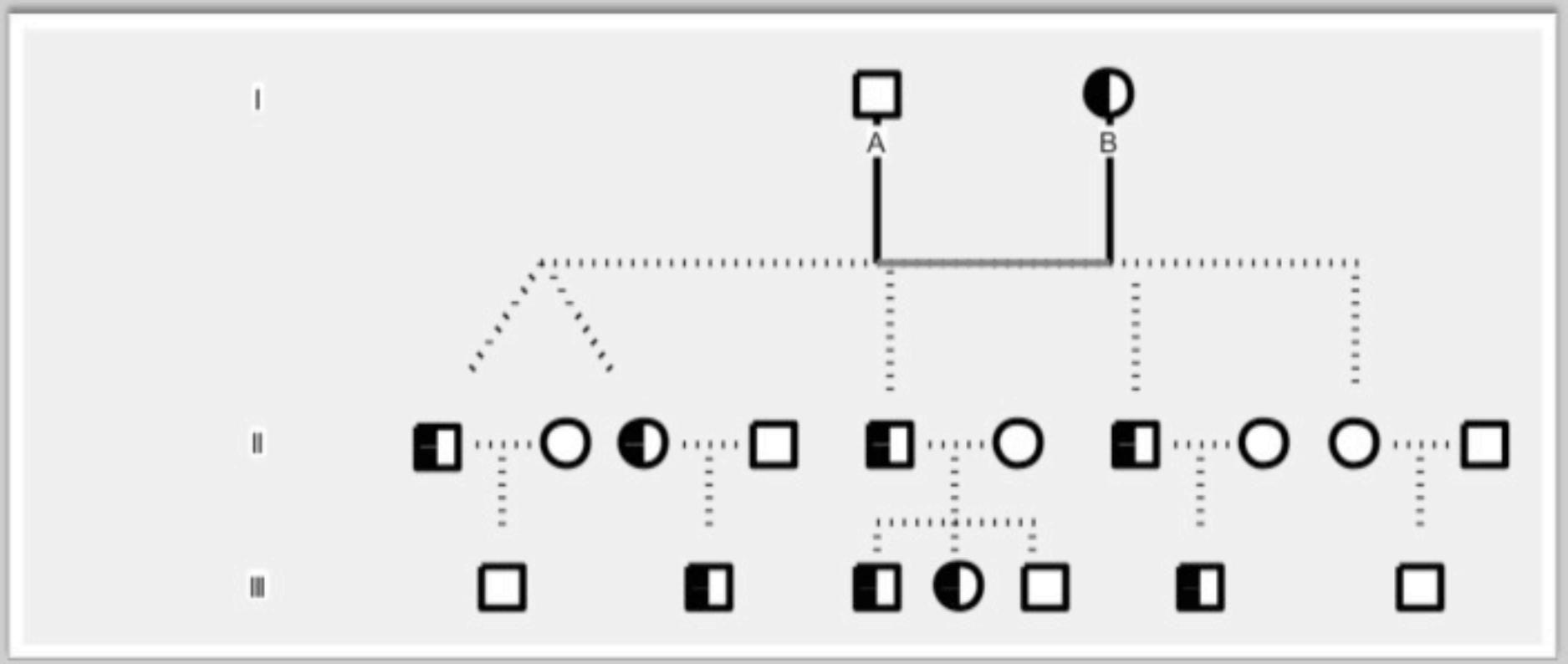
Neoformazione pancreatica

- In corrispondenza del corpo del pancreas, sul versante anteriore, area **focale nodulare** di tenue iperenhancement in fase arteriosa di 15 mm circa, compatibile con possibile **tumore neuroendocrino**



La FAMIGLIA MEN1

Bari,
7-10 novembre 2013



MEN 1-Portatore asintomatico

Bari,
7-10 novembre 2013

4/1995

MEN 1

Ca: **11.7** ↑ mg/dl (8.5-10.5 mg/dl)

Ecografia tiroidea: struttura ecografica del parenchima omogenea se si accettua la presenza di un **nodulo isoecogeno** al 3° superiore del lobo destro 1 x 1 cm, non processi occupanti spazio in sede paratiroidea

MEN 1-Portatore asintomatico

Bari,
7-10 novembre 2013

4/1995

Scintigrafia tiroidea: **areola ipercaptante** al polo inferiore del lobo tiroideo dx, **sospetta per paratiroide iperfunzionante**; probabile presenza di un' altra areola al polo superiore dello lobo stesso.

Ecografia addome: nella norma, pancreas non visualizzabile.

MEN 1-Portatore sintomatico

Bari,
7-10 novembre 2013

07/2004

Ca ↑ P ↓ PTH ↑

Ecografia tiroidea: al 3° superiore **nodulo** del **lobo destro** di 21 x 17 mm, solido ed ipoecogeno, al 3° inferiore è presente una formazione ipoecogena di 22 x 11 mm (paratiroide?)

Scintigrafia paratiroidi: **adenoma paratiroideo** al di sotto del lobo tiroidea di destra

Ecografia addome: **neoformazione pancreatica**

MEN-1 Portatore sintomatico

Bari,
7-10 novembre 2013

07/2004

TAC addome: presenza di **nodulo a livello della testa pancreatica di 1.5 cm** con patologica impregnazione.
RMN regione sellare e para sellare:nella norma

Diagnosi: **Neoplasia endocrina multipla MEN1** (**adenoma della paratiroide dx, neoformazione pancreatica e del lobo destro della tiroide**).
Opportuna emitiroidecotmia destra e paratiroidectomia dx.

Multiple Endocrine Neoplasia tipo 1

Bari,
7-10 novembre 2013

Abstract

Multiple Endocrine Neoplasia type I (MEN1) is a rare autosomal dominant hereditary cancer syndrome presented mostly by tumours of the parathyroids, endocrine pancreas and anterior pituitary, and characterised by a very high penetrance and an equal sex distribution. It occurs in approximately one in 30,000 individuals. Two different forms, sporadic and familial, have been described. The sporadic form presents with two of the three principal MEN1-related endocrine tumours (parathyroid adenomas, entero-pancreatic tumours and pituitary tumours) within a single patient, while the familial form consists of a MEN1 case with at least one first degree relative showing one of the endocrine characterising tumours. Other endocrine and non-endocrine lesions, such as adrenal cortical tumours, carcinoids of the bronchi, gastrointestinal tract and thymus, lipomas, angiofibromas, collagenomas have been described. The responsible gene, *MEN1*, maps on chromosome 11q13 and encodes a 610 aminoacid nuclear protein, menin, with no sequence homology to other known human proteins. MEN1 syndrome is caused by inactivating mutations of the *MEN1* tumour suppressor gene. This gene is probably involved in the regulation of several cell functions such as DNA replication and repair and transcriptional machinery. The combination of clinical and genetic investigations, together with the improving of molecular genetics knowledge of the syndrome, helps in the clinical management of patients. Treatment consists of surgery and/or drug therapy, often in association with radiotherapy or chemotherapy. Currently, DNA testing allows the early identification of germline mutations in asymptomatic gene carriers, to whom routine surveillance (regular biochemical and/or radiological screenings to detect the development of MEN1-associated tumours and lesions) is recommended.

Multiple endocrine neoplasia type 1

Francesca Marini, Alberto Falchetti, Francesca Del Monte, Silvia Carbonell Sala, Alessia Gozzini, Ettore Luzi and Maria Luisa Brandi

Terapia chirurgica

Bari,
7-10 novembre 2013

11/2008

Intervento di **Cervicotomia e Sternotomia** presso reparto di Chirurgia Toracica

- **Carcinoma neuroendocrino moderatamente differenziato** (Ki 67 25 %) in **sede timica con coinvolgimento dei margini, invasione vascolare e localizzazioni linfonodali**.
- Lesioni neuroendocrina del pancreas non tipizzata
- Iperparatiroidismo primitivo in paziente affetto da MEN 1

NETs Timico-Tumore raro*

*epidemiologia

Bari,
7-10 novembre 2013

orphanet

Lingue: FR | EN | ES | DE | IT | PT | NL

Il portale delle malattie rare e dei farmaci orfani

Inserm

*Le malattie rare sono **rare**, **ma** le persone affette sono **tante***

Homepage
Aiuto
Contatti

Malattie rare | Farmaci orfani | Centri specializzati | Laboratori di diagnosi | Ricerca e sperimentazioni | Associazioni dei pazienti | Professionisti e Istituti | Altre informazioni

Cerca | Ricerca per segno | Classificazioni | Geni | Enciclopedia dedicata ai pazienti | Enciclopedia dedicata ai professionisti | Linee guida di Emergenza

Homepage » Malattie rare » Classificazioni

CERCARE UNA MALATTIA

Nome della malattia: timo * → OK

(*) campo obbligatorio

Indietro all'elenco delle classificazioni

: : Classificazione di Orphanet dei tumori rari

Termine generico [↗]

- Malattia oncologica rara
  - Tumore raro
    - Tumore timico
      - Neoplasia epiteliale del timo
        - Carcinoma neuroendocrino del timo
          - Carcinoma neuroendocrino timico ben differenziato
          - Carcinoma neuroendocrino timico moderatamente differenziato
          - Carcinoma neuroendocrino timico scarsamente differenziato

Informazioni supplementari

Quaderni di Orphanet

- Prevalenza delle malattie rare
- Farmaci orfani in Europa

Partecipare/informare

- Leggere la newsletter
- Leggere il OJRD [↗]
- Registrare la propria attività

Tutte le informazioni presenti nel sito non sostituiscono in alcun modo il giudizio di un medico specialista, l'unico autorizzato ad

The prevalence of thymic NET is ~3% of the total number of NETs at all sites. In the last SEER database, a reported incidence of thymic NETs is 0.02/100 000 population per year [4]. They constitute ~5% of all thymic tumors. Both bronchial and thymic NETs may be part of multiple endocrine neoplasia type 1 syndrome (MEN-1, 5%–15%). The median age at diagnosis for bronchial NETs is 64 years and for thymic NETs 59 years. This review is restricted to typical/atypical NETs and thymic NETs.

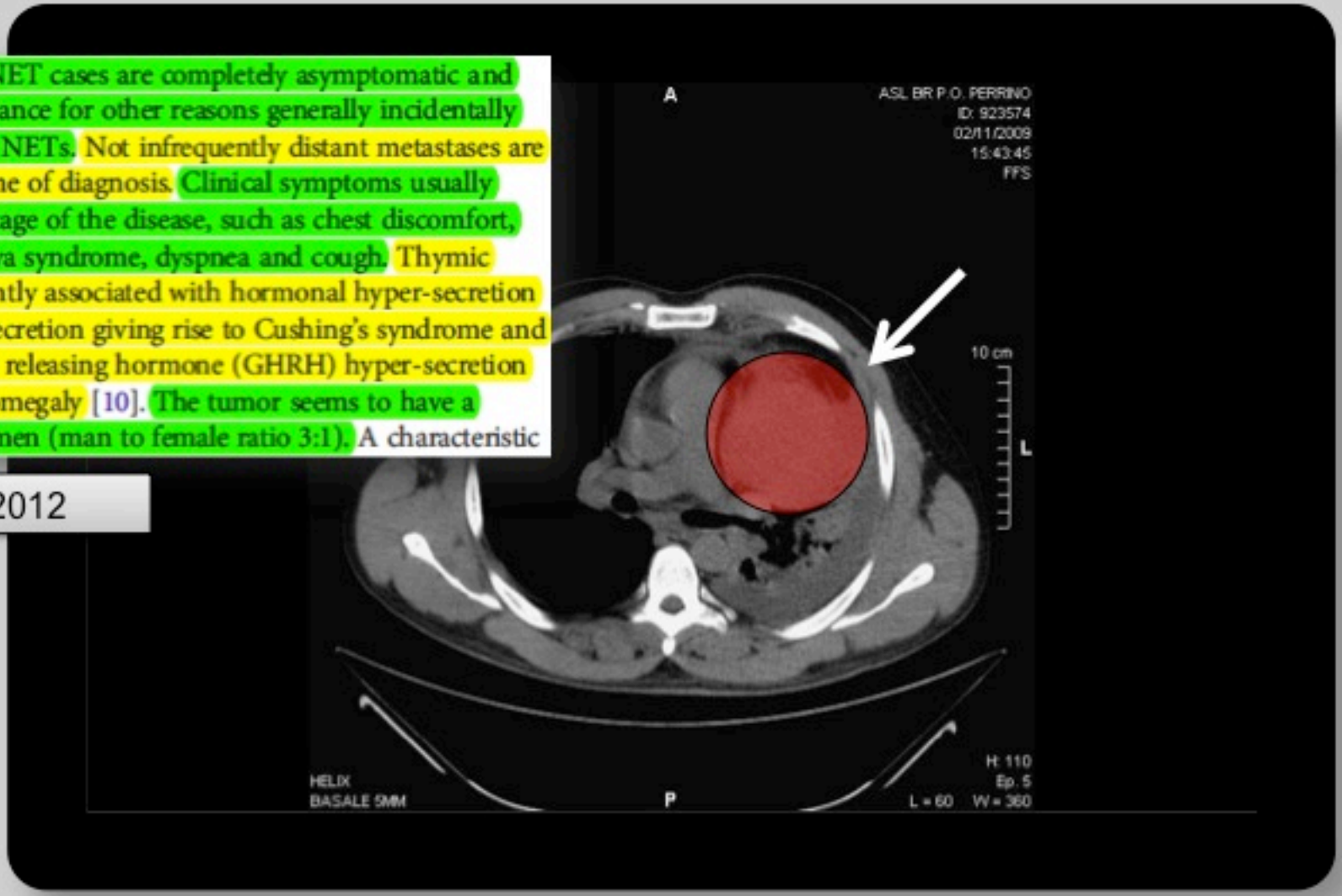
ESMO,2012

NETs Timico-DIAGNOSI

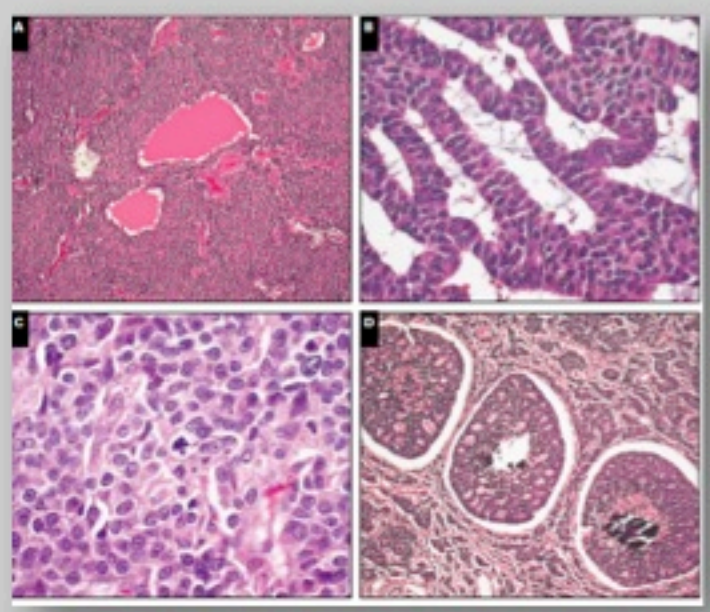
Bari,
7-10 novembre 2013

Most thymic NET cases are completely asymptomatic and imaging performance for other reasons generally incidentally discovers thymic NETs. Not infrequently distant metastases are present at the time of diagnosis. Clinical symptoms usually occur at a later stage of the disease, such as chest discomfort, superior vena cava syndrome, dyspnea and cough. Thymic NETs are frequently associated with hormonal hyper-secretion such as ACTH secretion giving rise to Cushing's syndrome and growth hormone releasing hormone (GHRH) hyper-secretion with ectopic acromegaly [10]. The tumor seems to have a predilection for men (man to female ratio 3:1). A characteristic

ESMO,2012



NETs Timico-Comportamento biologico



predilection for men (man to female ratio 3:1). A characteristic feature of these tumors is the presence of nests of tumor cells that are detached from the surrounding stroma and contain areas of necrosis. The tumors often show architectural features of neuroendocrine differentiation with positive immunohistochemistry for chromogranin A, synaptophysin and CD56. They can be divided into low, intermediate and high-grade tumors. Low-grade tumors present <10 mitoses/10 high power field (HPF), intermediate tumors 10-20 mitoses/HPF and high grade tumors > 20 mitoses/10 HPF. The tumors may be

Tabella 2—*Comparazione dei vari termini proposti per i tumori neuroendocrini timici**

Rosai e Sobin[13]	Klemm e Moran[10]
CT	Carcinoma neuroendocrino ben differenziato (basso grado)
CA	Carcinoma neuroendocrino moderatamente differenziato (grado intermedio)
Carcinoma neuroendocrino a grandi cellule	Carcinoma neuroendocrino scarsamente differenziato (alto grado)
Carcinoma a piccole cellule	Carcinoma neuroendocrino scarsamente differenziato (alto grado)

*Adattato da Klemm e Moran[10] e Rosai e Sobin.[13]

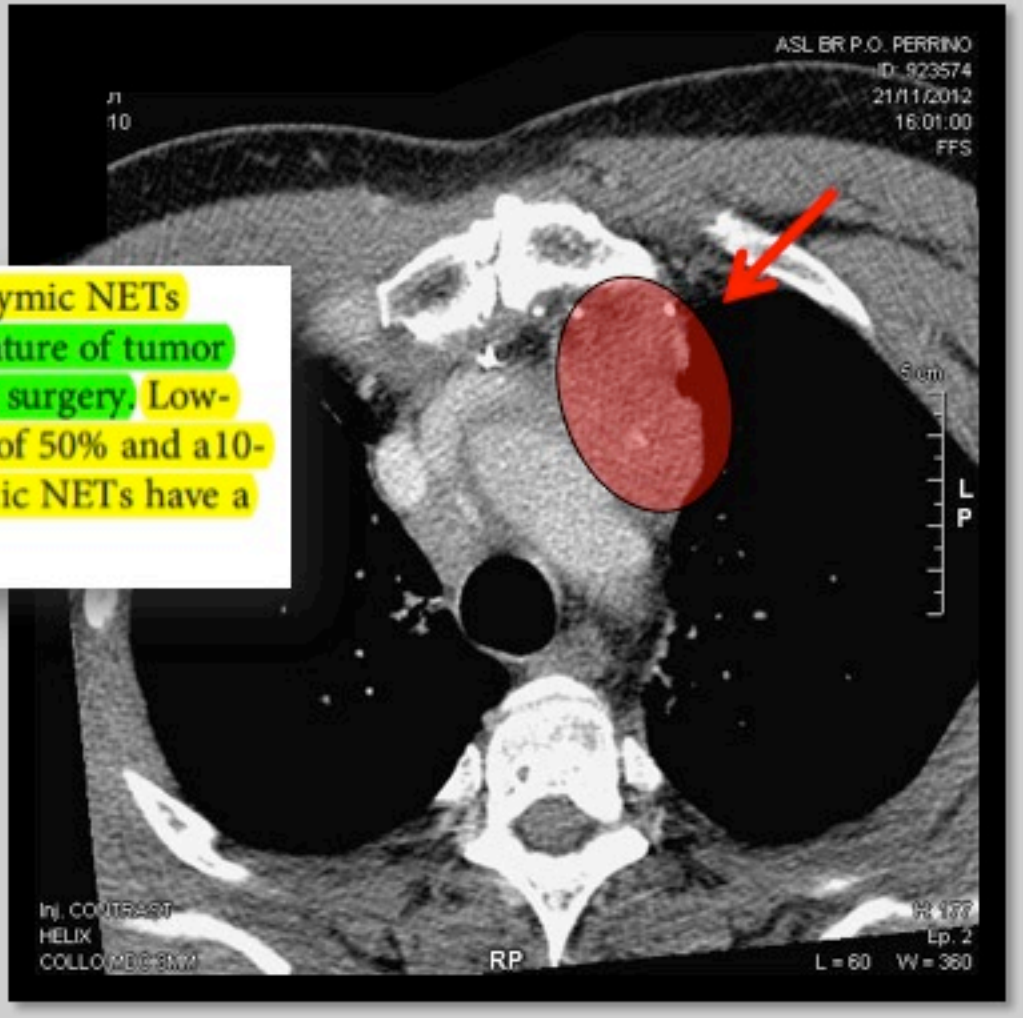
ESMO,2012

NETs Timico-PROGNOSI

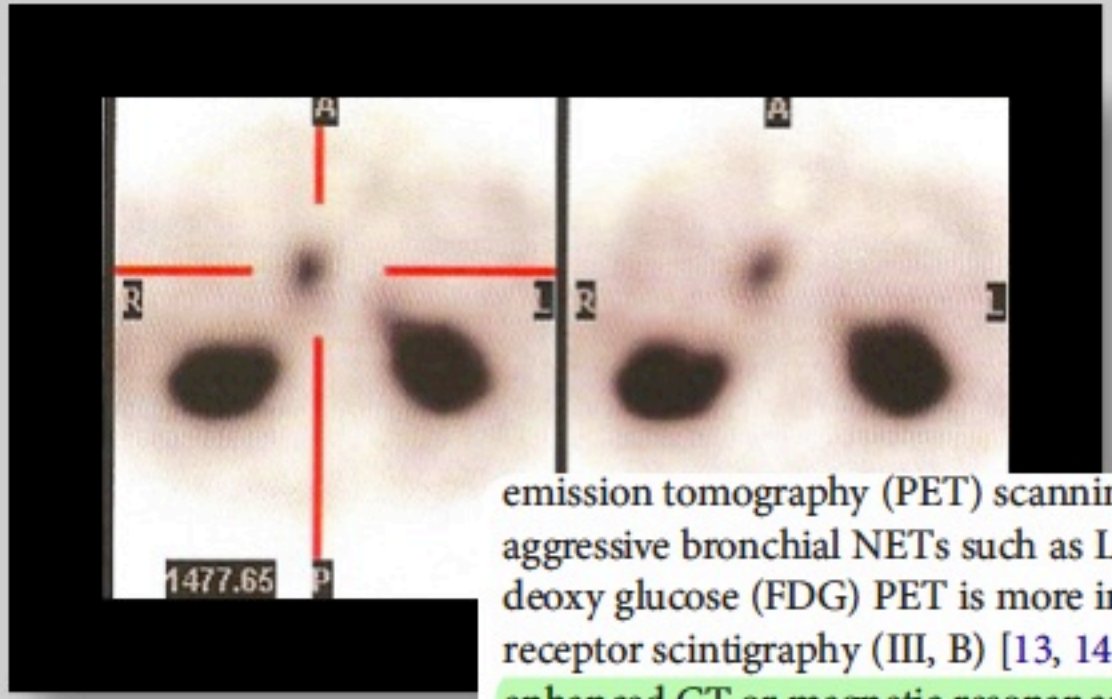
Bari,
7-10 novembre 2013

The prognosis for patients with primary thymic NETs remains poor. This is due to the aggressive nature of tumor with a high incidence of recurrence following surgery. Low-grade thymic NETs present a 5-year survival of 50% and a10-year survival of 9%, whereas high-grade thymic NETs have a 5-year survival of nearly 0% [10].

ESMO,2012



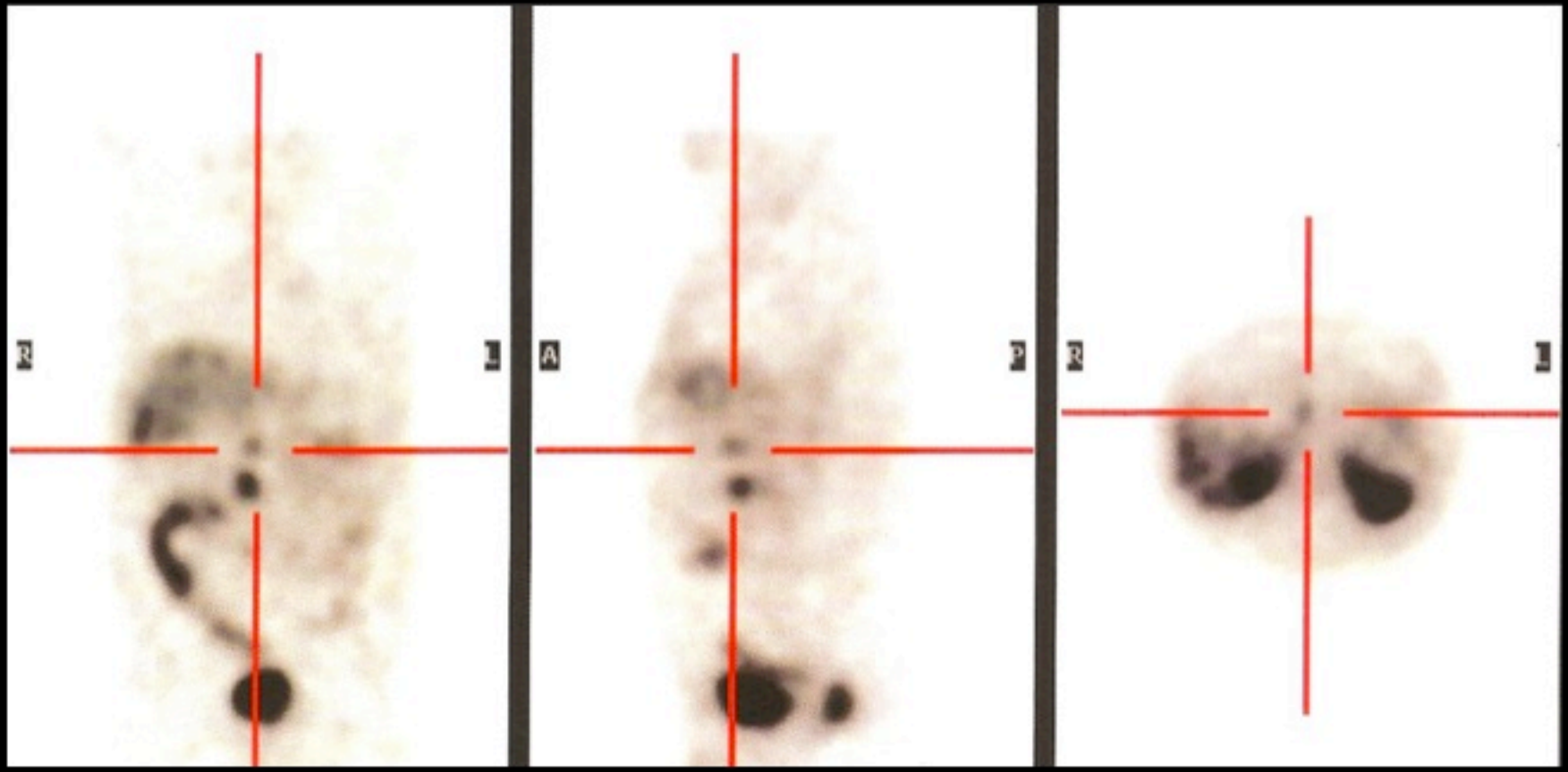
NETs Timico-STAGING



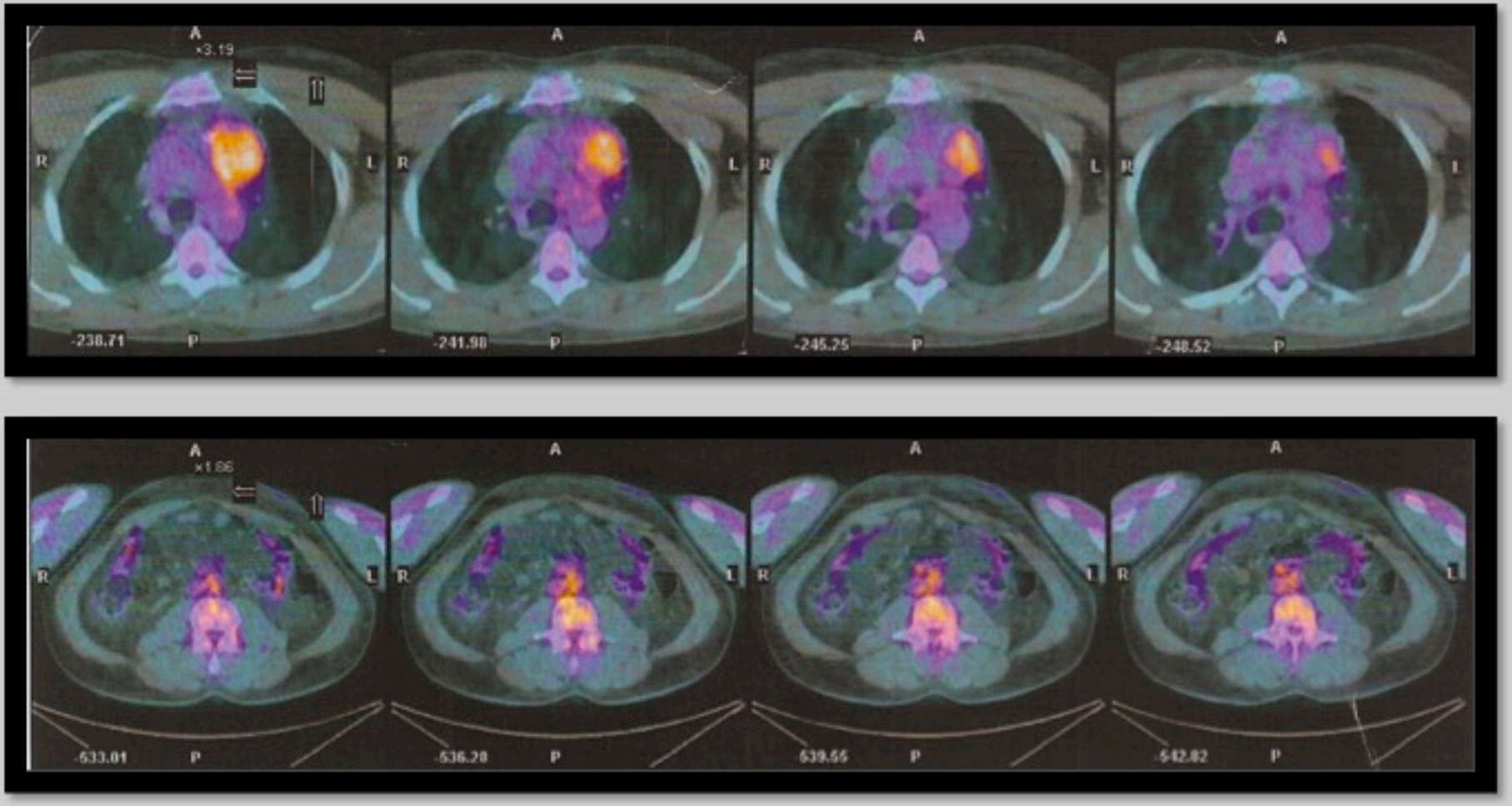
emission tomography (PET) scanning (III, B) [11, 12]. For more aggressive bronchial NETs such as LCNEC and SCLC, fluoro deoxy glucose (FDG) PET is more informative than somatostatin receptor scintigraphy (III, B) [13, 14]. For thymic NETs contrast enhanced CT or magnetic resonance imaging (MRI) is recommended to detect tumor metastases. Somatostatin receptor scintigraphy may be used for these tumors as well as PET scanning with ^{68}Gallium-DOTATATE (III, B). Bronchial NETs sometimes present with AC syndrome related to the secretion of

ESMO,2012

Scintigrafia OCTREOSCAN



PET-TC


A
×3.19
R
L
-238.71
P
A
R
L
-241.98
P
A
R
L
-245.25
P
A
R
L
-248.52
P
A
×1.86
R
L
-633.01
P
A
R
L
-636.28
P
A
R
L
639.55
P
A
R
L
-642.82
P

12/2010

- **Sternotomia esplorativa**, biopsia del pericardio e della pleura parietale sinistra
- Timo di 44 g e di 12 x 7 x 2 cm con un addensamento di 4.5 cm di asse maggiore
- **Focolai di carcinoma neuroendocrino, con modificazioni architetturali e citocariologiche riferibili a terapia, in timo parzialmente fibrotico e minime localizzazioni pleuriche e pericardiche**.

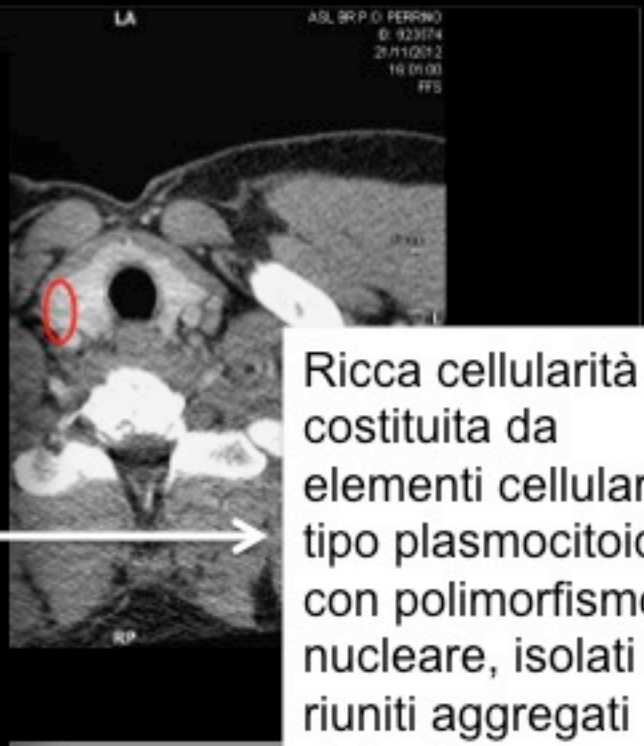
12/2010

- **Immunofenotipo della popolazione neoplastica**: positivo per cromogranina, sinaptofisina e CD56. La frazione di proliferazione (Ki-67) è pari al 5%.

NETs Timico/Tiroide

Bari,
7-10 novembre 2013

09/2012



Ricca cellularità costituita da elementi cellulari di tipo plasmocitoide con polimorfismo nucleare, isolati o riuniti aggregati abbastanza coesi a struttura cordonale. (THY4)

01/2013

- Tiroide comprendente **multipli nodi di carcinoma neuroendocrino** .
  Immunoistochimica con anticorpi anti TTF1 e calcitonina, negativa. Confronto con esame istologico relativo alla lesione mediastinica si propende per una **localizzazione in sede tiroidea del carcinoma neuroendocrino precedentemente diagnosticato in sede mediastinica**.

TERAPIA

COUNSELING GENETICO

Bari,
7-10 novembre 2013

Nelle neoplasie eredo-familiari qual la finalità del counseling genetico nella **definizione di rischio di malattia** nei componenti il nucleo familiare e/o nella valutazione prenatale?