X Seminario I.T.M.O.
NEOPLASIE A BASSA INCIDENZA
Monza, 7 maggio 2012

I Sessione: Oncologia endocrina

Caso clinico paradigmatico

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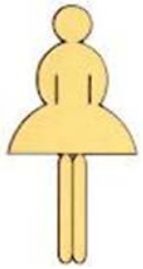


Scenario Clinico

Agosto 2003

S. T., 37 anni

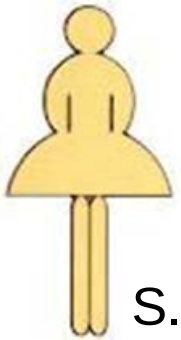
Vomito
Dolore addominale di tipo crampiforme associato a distensione

Rx Diretta addome: livelli idro-aerei tenuali
Leucocitosi neutrofila

Resezione di una delle ultime anse ileale stenotica

… segmento di piccolo intestino di cm 20 ripiegato su se stesso con pareti ispessite. A 2 cm dal margine di resezione è presente zona stenotica causata da formazione polipoide con asse principale di 25 mm …

“Carcinoide del piccolo intestino che interessa la mucosa, la sottomucosa e la tonaca muscolare a tutto spessore, nonché il grasso periviscerale…. presente nella sierosa in forma di nidi ben circoscritti ed è metastatico ad un linfonodo regionale (1/4). Margini chirurgici indenni ”



ANAMNESI

S. T., 37 anni

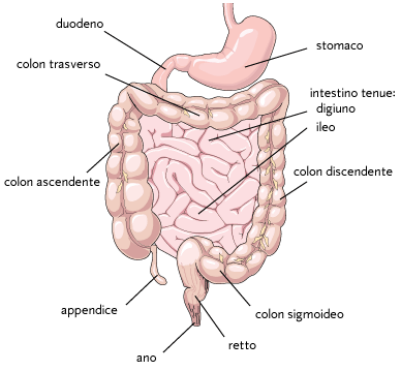
Impiegata amministrativa presso Pubblica Amministrazione

<u>Anamnesi Fisiologica:</u>
Due gravidanze a termine
Menarca a 13 anni, cicli regolari
Non allergie

<u>Anamnesi Patologica Remota:</u>
Asportazione polipo endometriale
Colecistectomia per litiasi

Nessuna familiarità oncologica

NETs Ileo



Tumori del *midgut* (digiuno-ileo-cieco-appendice)
Tumori endocrini differenziati a cellule EC
Carcinoide classico

Incidenza NETs piccolo intestino: 21-17.7% (dati SEER)[1]

- 40% dei casi sono multicentrici
- 60% metastatizzano ai linfonodi
- 5-20% dei casi è presente sindrome
- Reazione desmoplastica / fibroblastica

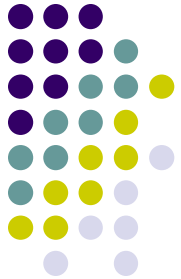
Table 1 Sites and overall frequencies of primary NETs in the USA (from the SEER Programme) and Norway (from the NRC)[12–14]

	Percentage of cases		
	SEER (n = 17 321)		
Primary NET	Black patients	White patients	NRC (n = 2013)
Lung	18.3	31.9	21.0
Stomach	5.7	5.7	5.7
Small intestine	21.0	17.7	25.5
Pancreas	3.7	4.1	6.9
Meckel	0.1	0.4	0.5
Appendix	2.0	3.2	4.8
Colon	7.9	7.4	8.0
Rectum	27.0	12.3	7.2
Breast	0.4	0.4	1.6
Prostate	0.3	0.4	1.5
Ovary	1.2	1.6	2.4

NET, neuroendocrine tumour; NRC, Norwegian Registry of Cancer; SEER, Surveillance, Epidemiology and End Results.

[1]Guidelines for management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut, Jan 2012; vol 61: 6-32.

Scenario Clinico



TAC torace-addome con m.d.c.: onc. neg.
CgA, CEA, NSE, 5-HIAA: nei limiti
Colonscopia: onc. neg.
Octreoscan: non captazioni patologiche

- Carcinoide del piccolo intestino
- KI67: *non noto*
- pT4 N+
- NED

TERAPIA ADIUVANTE?

… nessun dato …

Scenario Clinico

Giugno 2006

Alvo diarroico (3-4 scariche/die)
Episodi di flushing

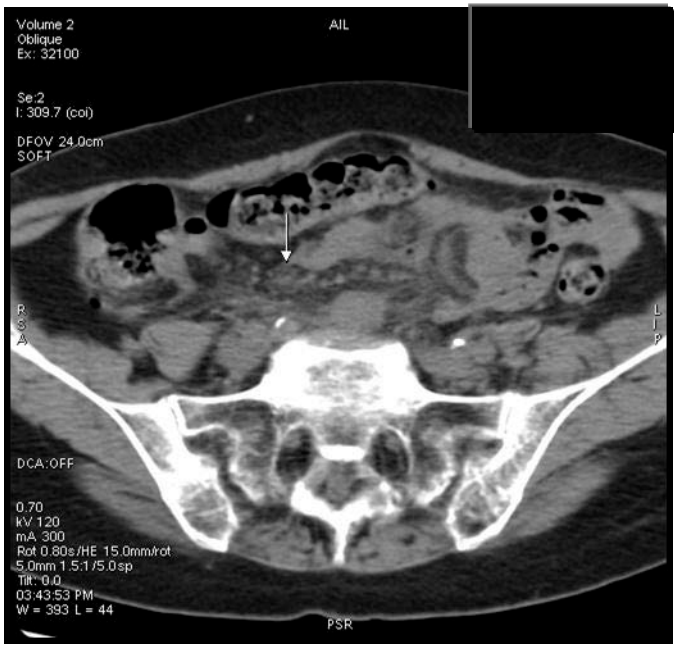
Modesto aumento della CgA sierica (157 ng/ml) e del 5-HIAA (23 mg/24h)

TAC torace-addome con m.d.c.: ispessimento di un'ansa del piccolo intestino in regione ipogastrica destra; ingrandimento con disomogeneità densitometrica dell'utero e dell'annesso di sinistra.

Octreoscan: patologico accumulo in regione meso-ipogastrica mediana-paramediana (sospetta recidiva). Tale area, già evidente nelle immagini SPET precoci, presenta maggiore accumulo nelle immagini tardive.

EcoCG: norma.

Sindrome tipica (5% in assenza di metastasi epatiche)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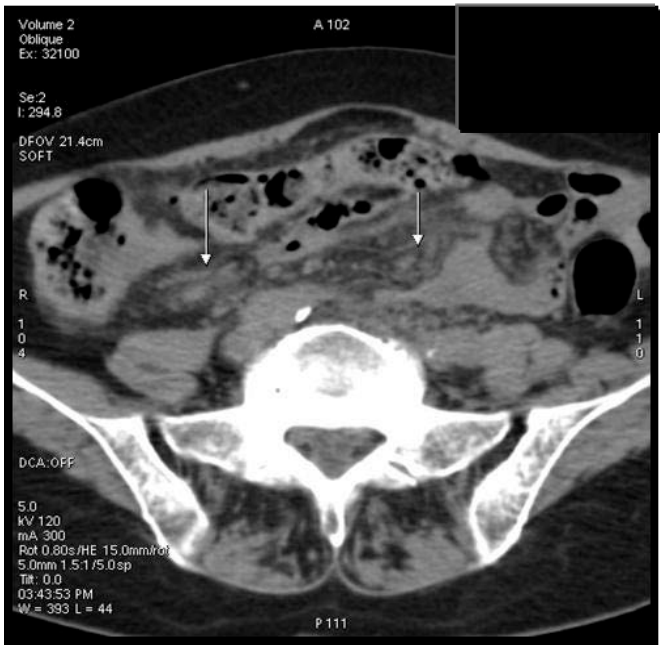
Oblique
Ex: 32100
AIL
Se:2
I: 309.7 (coi)
DFOV 24.0cm
SOFT
R
S
A
L
I
P
DCA:OFF
0.70
kV 120
mA 300
Rot 0.80s/HE 15.0mm/rot
5.0mm 1.5:1/5.0sp
Tilt: 0.0
03:43:53 PM
W = 393 L = 44
PSR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A 102
Se:2
I: 294.8
DFOV 21.4cm
SOFT
R
1
0
4
L
1
1
0
DCA:OFF
5.0
kV 120
mA 300
Rot 0.80s/HE 15.0mm/rot
5.0mm 1.5:1/5.0sp
Tilt: 0.0
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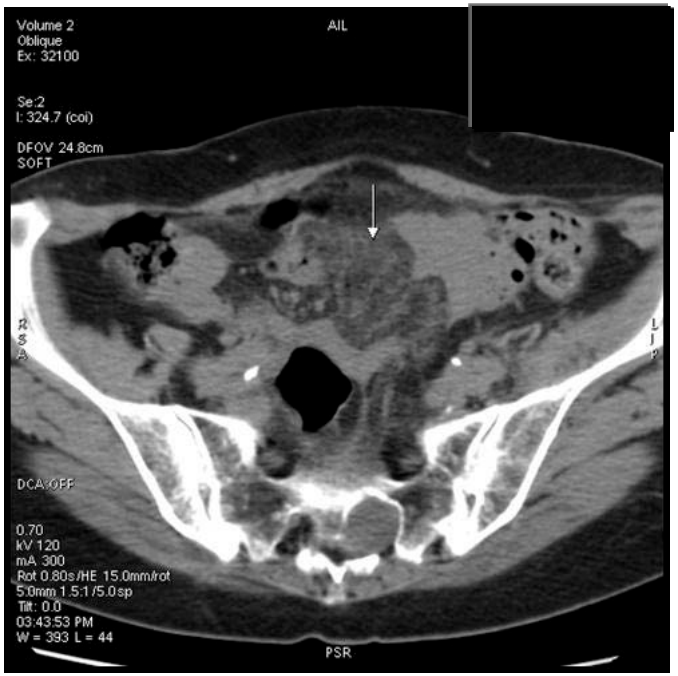
P 111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Oblique
Ex: 32100
AIL
Se:2
I: 324.7 (coi)
DFOV 24.8cm
SOFT
R
S
A
L
I
P
DCA:OFF
0.70
kV 120
mA 300
Rot 0.80s/HE 15.0mm/rot
5.0mm 1.5:1/5.0sp
Tilt: 0.0
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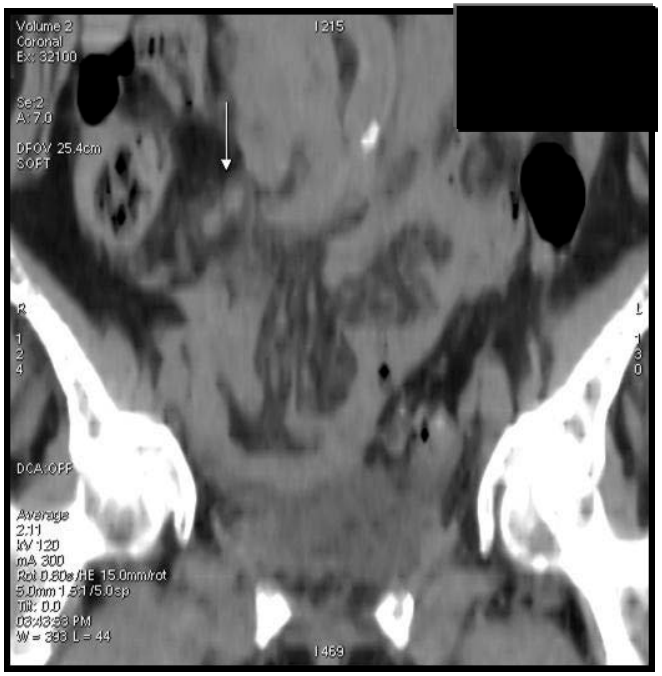
W = 393 L = 44
PSR


Volume 2
Coronal
Ex: 32100
I 215
Se:2
A: 7.0
DFOV 25.4cm
SOFT
R
1
2
4
L
1
3
0
DCA:OFF
Average
2:11
kV 120
mA 300
Rot 0.80s/HE 15.0mm/rot
5.0mm 1.5:1/5.0sp
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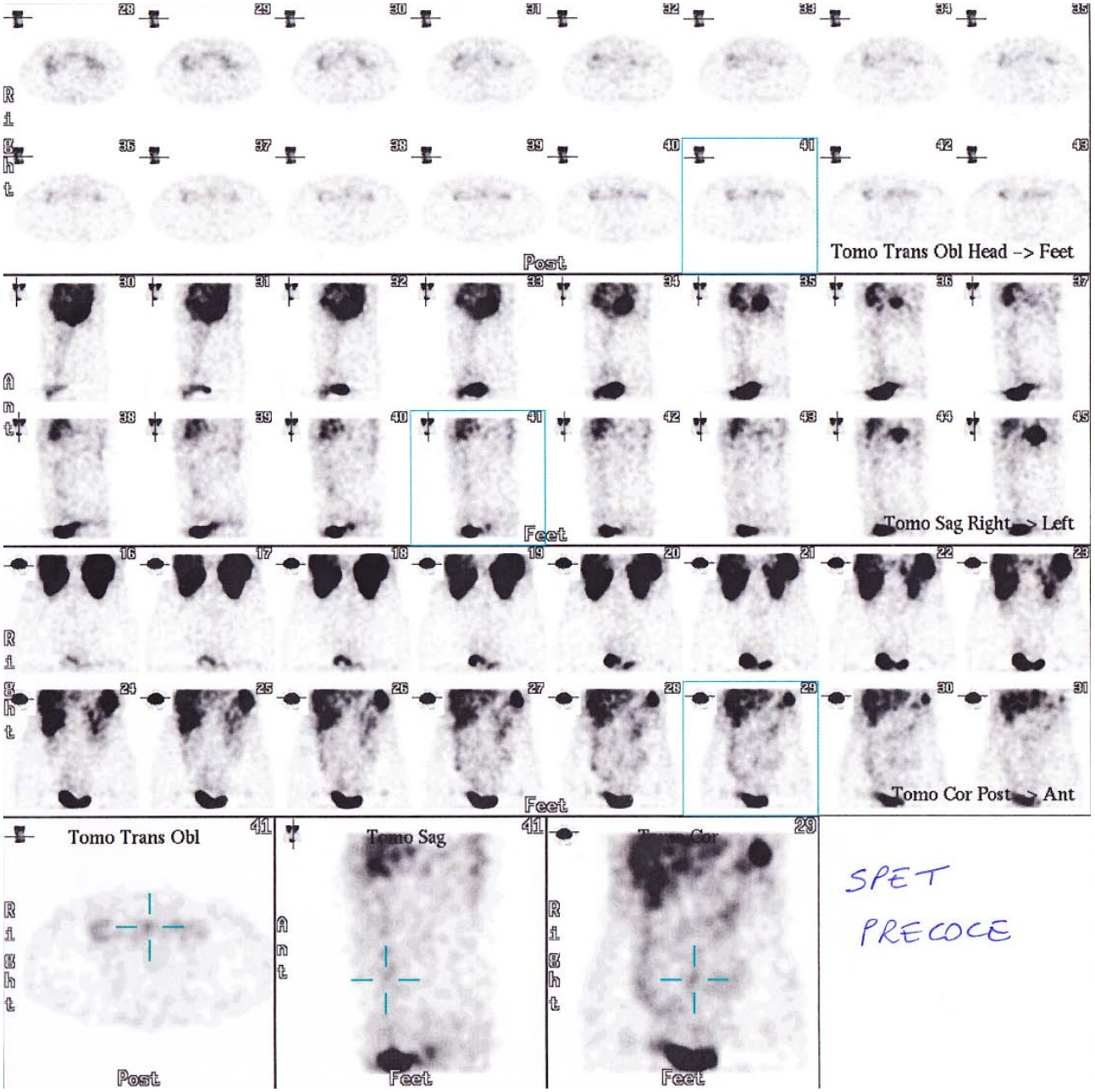
03:43:53 PM
W = 393 L = 44
I 469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Tomo Trans Obl Head -> Feet
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Tomo Sag Right -> Left
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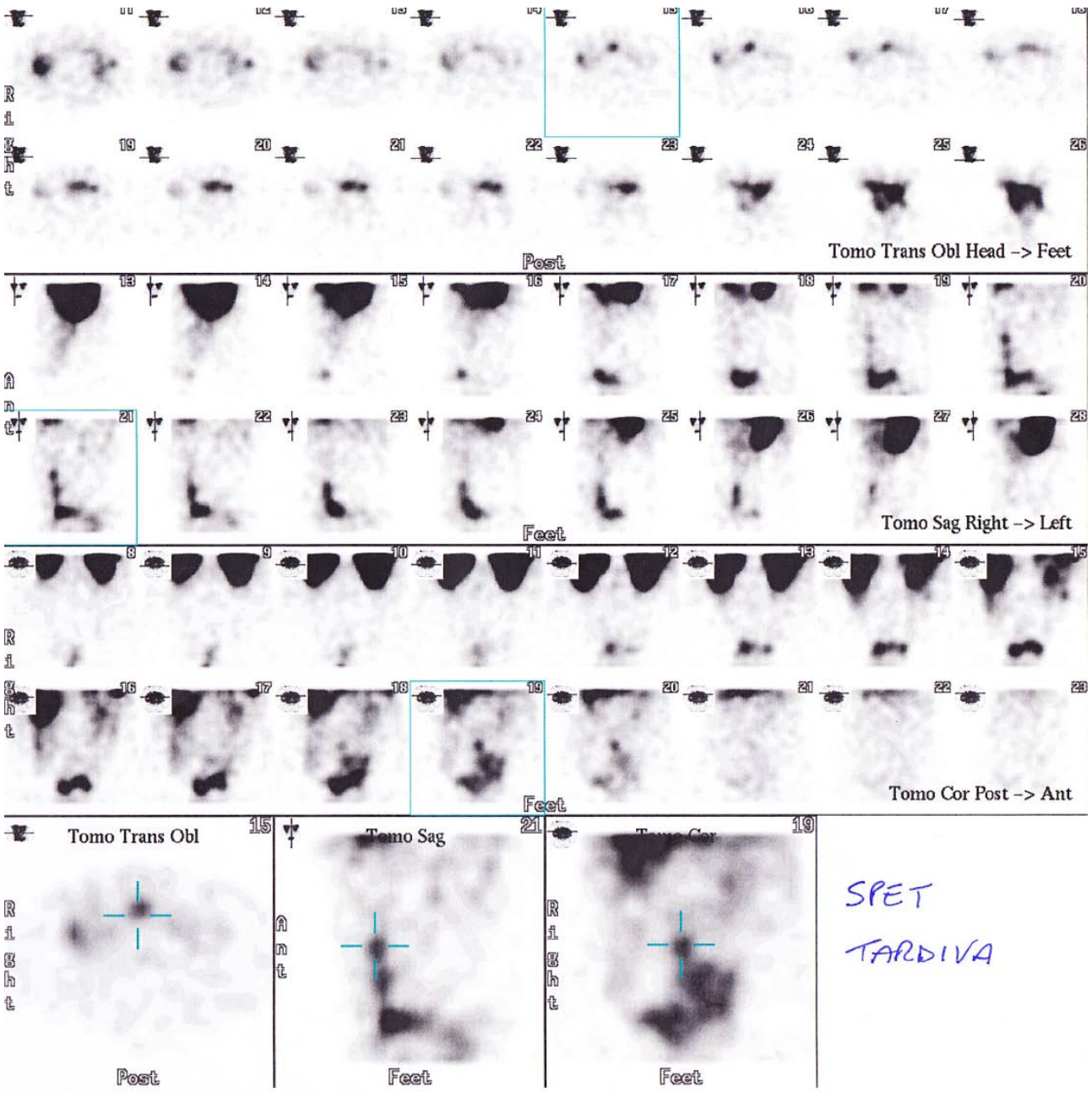
Tomo Cor Post -> Ant
Tomo Trans Obl
Post
Tomo Sag
Feet
Feet
SPET
PRECOCE


Tomo Trans Obl Head -> Feet
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Tomo Trans Obl
Post
Tomo Sag
Feet
Feet
SPET
TARDIVA

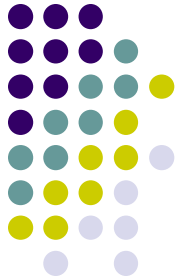
Scenario Clinico

Settembre 2006

Laparotomia esplorativa con omentectomia + biopsie plurime peritoneali e annessiali

Secondarismi peritoneali da carcinoma neuroendocrino ben differenziato a carico dell'omento, peritoneo sovra-vescicale, parametrio destro, peritoneo para-duodenale. Cisti follicolari ovariche bilaterali. MIB1 < 2%.

Scenario Clinico



09/2006	Inizia terapia con Lanreotide LAR 60-90 mg q28
	Miglioramento della diarrea e scomparsa del flushing
	Normalizzazione CgA e dell'5-HIAA
	SD per circa 2 aa (TAC/RMN onc. neg)
11/2008	Ripresa della diarrea (4-5 scariche/die) ed episodi di flushing
	Modesto rialzo della CgA
	PD linfonodale addominale (RMN/Octreoscan)
	Inizia terapia con Octreotide LAR 30 mg q28

CROSSOVER Analoghi SSA

non resistenza crociata

Annals of Oncology 11: 1127–1130, 2000.

Original article

Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumors pretreated with lanreotide

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Summary

Background: In the present study we investigated the efficacy and tolerability of i.m. octreotide acetate (octreotide LAR) in patients with metastatic neuroendocrine tumors (NETs) previously treated and failed on i.m. lanreotide.

Patients and methods: Fifteen patients (8 females, 7 males, median age 67 years, range 28–81 years) with metastatic NETs (8 endocrine pancreatic tumors, 7 midgut carcinoids) were enrolled in the study. All patients were in progressive disease (objective: 11 patients, symptomatic: 10 patients, biochemical: 11 patients) after treatment with slow release lanreotide, 30 mg every 14 days for a median time of 8 months (range 3–19 months). All patients had measurable disease; 12 patients had elevated serum and/or urine markers and 11 were symptomatic. Octreotide scintigraphy was positive in 13 of 15 patients. Octreotide LAR was administered as i.m. injection at the dose of 20 mg every four weeks until disease progression.

Results: An objective partial response (PR) was documented in one patient (7%), no change (NC) in six (40%), and progressive disease (PD) in eight patients (53%). The PR was observed in one patient with non-functioning endocrine pancreatic tumor with progressive liver and lymph node metastases after 16 months of i.m. lanreotide therapy. The median duration of disease stabilization was 7.5 months (range 6–12+ months). The overall biochemical response rate was 41%, including CRs (33%) and PRs (8%); biochemical responses were observed in carcinoids as well as in endocrine pancreatic tumors; the median duration of response was 5 months for CRs and 7.5 months for PRs. The overall symptomatic response rate was 82%. The median duration of response for diarrhoea, abdominal pain, or both was 6.5 months (range 3–12+ months). Improvement in performance status (PS) was obtained in 5 of 11 patients with PS of 1 at study entry.

Median duration of octreotide LAR treatment was seven months (range 3–12+ months). No serious adverse events were reported; mild side effects were reported in 26% of patients.

Conclusions: Octreotide LAR 20 mg shows significant efficacy in terms of objective response rate (PR + SD), biochemical and symptomatic control in patients with metastatic NETs of the GEP system pretreated and progressing on slow release lanreotide.

Key words: depot lanreotide, neuroendocrine tumors, octreotide LAR

Treatment of Carcinoid Syndrome

A Prospective Crossover Evaluation of Lanreotide versus Octreotide in Terms of Efficacy, Patient Acceptability, and Tolerance

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Olivier Bouché, M.D.[5]
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The authors thank Drs. M. Amouretti (Bordeaux), D. Cattan (Villeneuve Saint Georges), S. Chaussade (Paris), J. L. Dupas (Amiens), J. Frexinos (Toulouse), H. Gouérou (Brest), E. Lerebours (Rouen), H. Michel (Montpellier), R. Modigliani (Paris), and M. J. Tréffot (Hyères) for their participation in this study.

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Received September 13, 1999; accepted November 1, 1999.

BACKGROUND. The somatostatin analogues lanreotide and octreotide have previously been shown to be effective in controlling flushing and diarrhea in patients with carcinoid syndrome. As lanreotide requires injection only every 10 days, compared with twice-daily injections of octreotide, a direct comparison between these two treatments in terms of patient acceptability, patient preference, and efficacy in controlling symptoms was performed in patients with carcinoid syndrome.

METHODS. Thirty-three patients with carcinoid syndrome were included in an open, multicenter, crossover study. Half of the patients received octreotide 200 μg subcutaneously twice or thrice daily for 1 month followed by lanreotide 30 mg intramuscularly every 10 days for 1 month, while the other half commenced with lanreotide followed by octreotide in a similar fashion. Quality-of-life assessments were performed at each visit and patient preference for one of the two treatments evaluated. The number and intensity of flushing episodes and bowel movements, urinary 5-hydroxyindoleacetic acid (5HIAA) levels, and plasma serotonin levels were recorded.

RESULTS. No significant differences were found between lanreotide and octreotide in terms of quality of life. The majority of patients (68%) preferred lanreotide ($P = 0.03$), largely due to its simplified mode of administration. Disappearance or improvement in flushes occurred in 53.8% of patients (14 of 26) while on lanreotide and in 68% (17 of 25) on octreotide. A disappearance or improvement of diarrhea in 45.4% (10 of 22) on lanreotide, compared with 50% (11 of 22) on octreotide, was also observed. Lanreotide and octreotide were equally effective in reducing urinary 5HIAA levels and plasma serotonin levels. Both treatments were well tolerated, with mild symptoms of abdominal pain and nausea observed in 29% and 14% receiving octreotide and lanreotide, respectively.

CONCLUSIONS. Lanreotide and octreotide are equally efficacious in terms of symptom control and reduction in tumor cell markers for patients with carcinoid syndrome. Due to its simplified mode of administration, most patients prefer treatment with lanreotide. ***Cancer*** **2000;88:770–6.**

© 2000 American Cancer Society.

KEYWORDS: somatostatin analogues, lanreotide, octreotide, carcinoid syndrome, patient preference.

Carcinoid tumors are rare, slowly progressive tumors principally of the lower gastrointestinal tract. The cell of origin is the chromaffin cell, which is part of the amine precursor uptake and decarboxylation system. Thus, these tumors have the ability to secrete vasoactive peptides, mainly serotonin, which is responsible for cutaneous flushing, diarrhea, and bronchospasm, features referred to as the carcinoid syndrome. The occurrence and severity of the syndrome are related

Scenario Clinico

Dicembre 2010

Diarrea (5-6 scariche/die)
Flushing

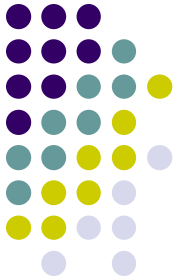
CgA: 320 ng/ml
5HIAA: 42 mg/24h

RMN addome-pelvi con m.d.c.: multiple metastasi epatiche; alcune anse digiunali risultano aderenti al profilo anteriore dell'addome come per fibrosi; linfoadenopatie addomino-pelviche (in sede iliaca destra).

Octreoscan: comparsa di multiple aree di accumulo patologico del radiofarmaco localizzate ad entrambi i lobi epatici, in regione centro addominale ed iliaca destra (riferibili ad adenopatie).

Scenario Clinico

Gennaio 2011



Agobiopsia epatica ecoguidata: metastasi epatiche da tumore neuroendocrino; MIB1: 3,6%. G2 (sec. WHO 2010).

Quale strategia terapeutica?

- ✓Trattamenti locali
- ✓Analogo SSA
- ✓Chemioterapia
- ✓PRRT
- ✓Terapia biologica

Cosa avevamo a disposizione nel 2010-2011?

Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study

Marianne E Pavel, John D Hainsworth, Eric Baudin, Marc Peeters, Dieter Hörsch, Robert E Winkler, Judith Klimovsky, David Lebwohl, Valentine Jehl, Edward M Wolin, Kjell Öberg, Eric Van Cutsem, James C Yao, for the RADIANT-2 Study Group

THE LANCET Published online November 25, 2011

Trial RAD-ITMO: An open label, single arm, phase II study of combination RAD001 and octreotide LAR in patients with advanced neuroendocrine tumors as first line treatment

Uso terapeutico del medicinale RAD001 (everolimus), sottoposto a sperimentazione clinica, in pazienti con tumore neuroendocrino (NET)

Scenario Clinico

Febbraio 2011

RAD001 10 mg/die + Octreotide LAR 30 q28

<u>Rivalutazione clinico-strumentale a 3 mesi</u>:

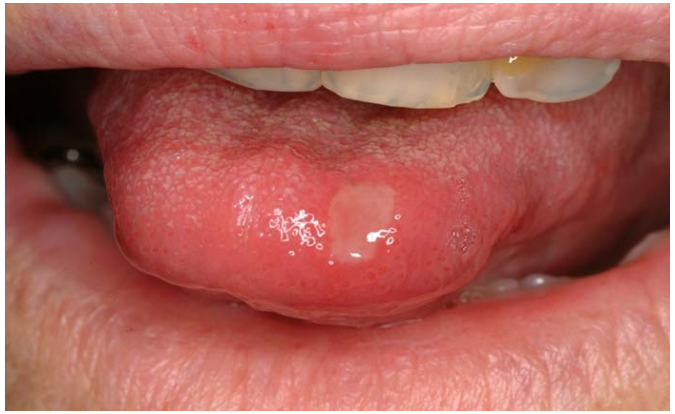
TAC torace/RMN addome-pelvi con m.d.c.: SD

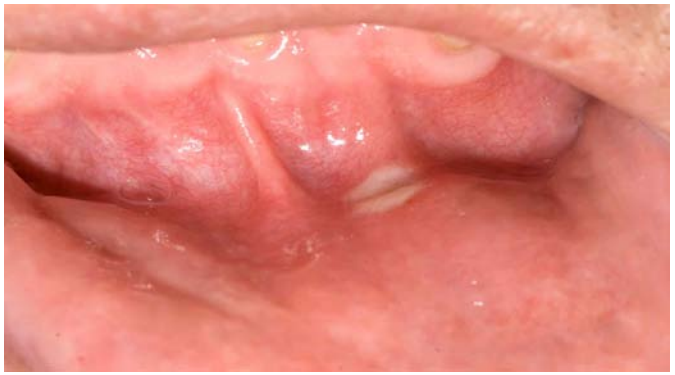
CgA: 46 ng/ml

5-HIAA: 19 mg/24h

Occasionali episodi di diarrea

…… dopo circa 4 mesi …..





TOSSICITA' GASTROINTESTINALE

Stomatite, stomatite aftosa, ulcerazioni della bocca e/o lingua

Grade	Symptoms	Management	Everolimus Dose Modification
1	Minimal (normal diet)	• Rinse several times daily with nonalcoholic mouthwash or 0.9% salt water	• No change
2	Symptomatic but can eat and swallow modified diet	• Topical analgesic mouth treatments (eg, "magic mouthwash," viscous lidocaine 2%, benzocaine, phenol) • Topical corticosteroids	• Maintain dose if patient is able to tolerate • If patient unable to tolerate, hold dose until recovery to grade ≤1, then restart
3	adequately eat or hydrate orally		ade ≤1 then restart at reduced dose
4	Severe (symptoms are life threatening)	• Avoid antifungal agents unless a fungal infection is diagnosed. If fungal infection diagnosed, avoid all systemic imidazole fungal agents* and apply topical antifungal agents	• Discontinue everolimus

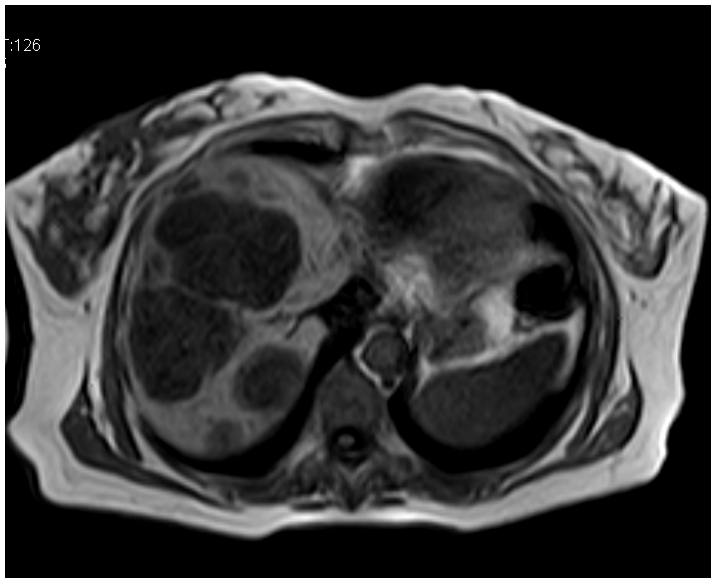
RAD001 5 mg/die + Octreotide LAR 30 q28

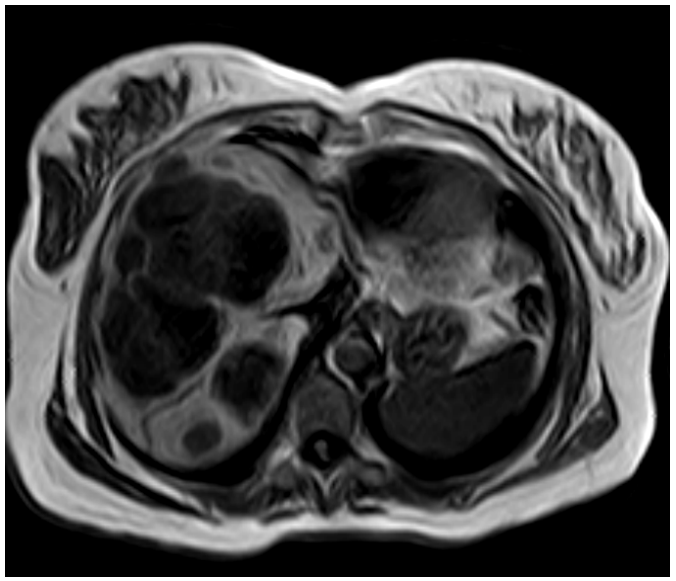
*Ketocanazole, flucanazole, itracanazole, etc.

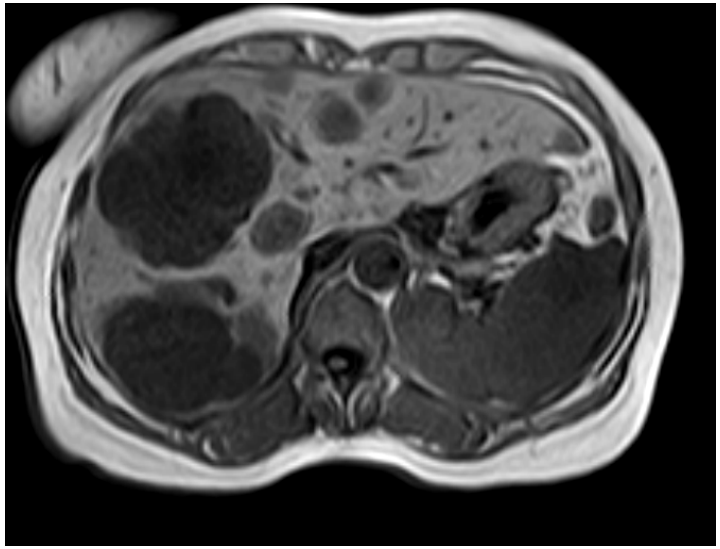
Porta C et al. *Eur J Cancer.* 2011;47:1287-1298. Pilotte AP et al. *Clin J Oncol Nurs.* 2011;15(5):E83-E89. Moldawer NP, Wood LS. *Kidney Cancer J.* 2010;8(2):51-59. de Oliveira F, et al.*Oral Oncol.* 2011;47(10):998-1003. Eisen T et al. *J Natl Cancer Inst.* 2012;104:93-113.

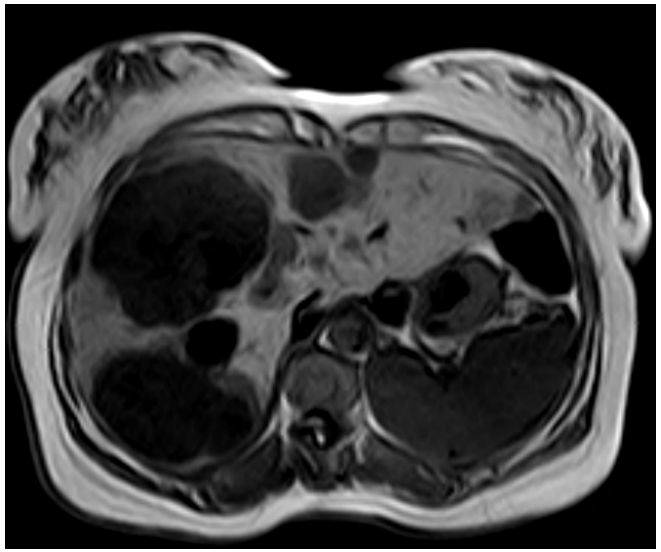
Scenario Clinico

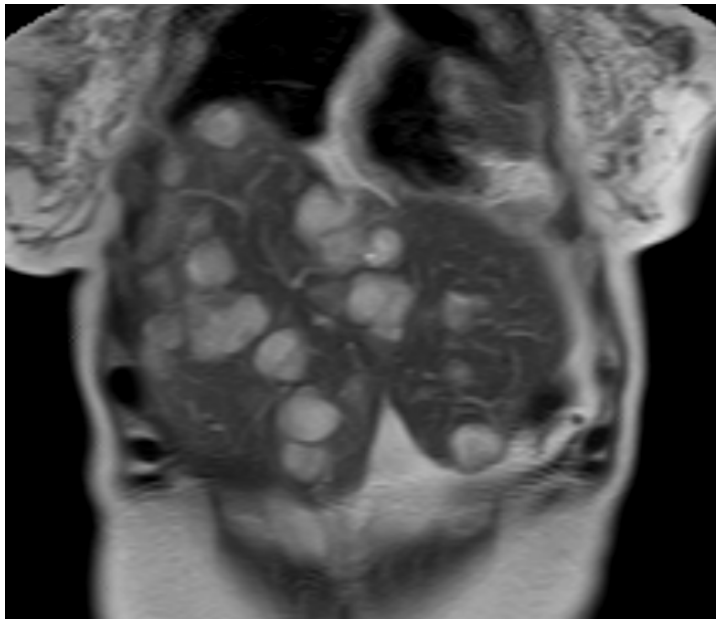
Novembre 2011: PD?

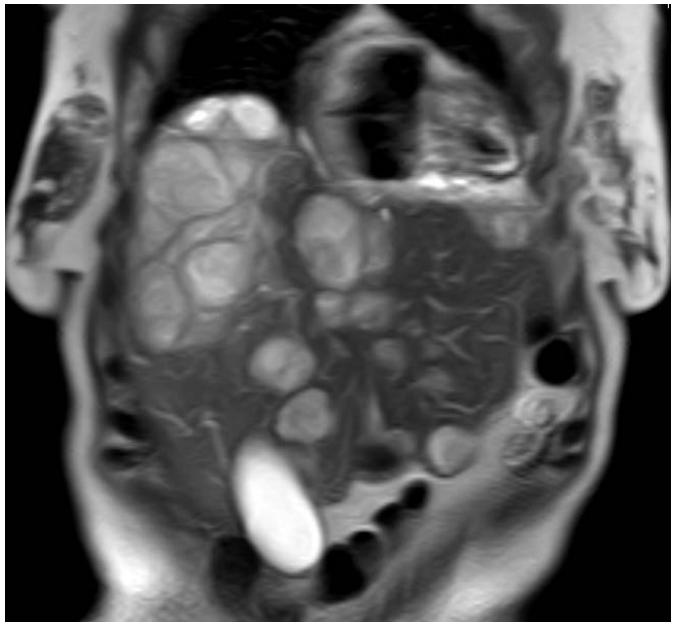


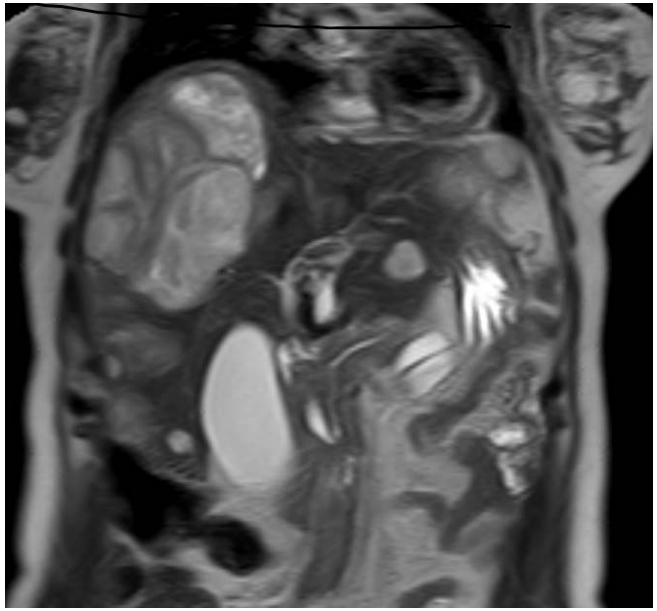


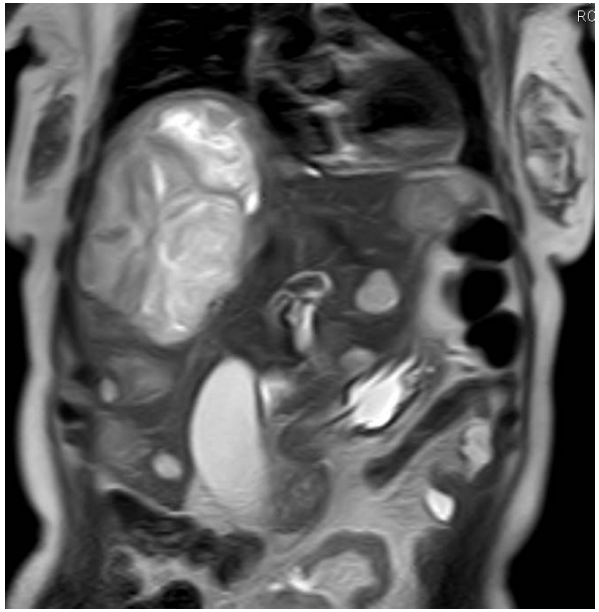












Valutazione delle risposte

Criteri RECIST *vs* CHOI

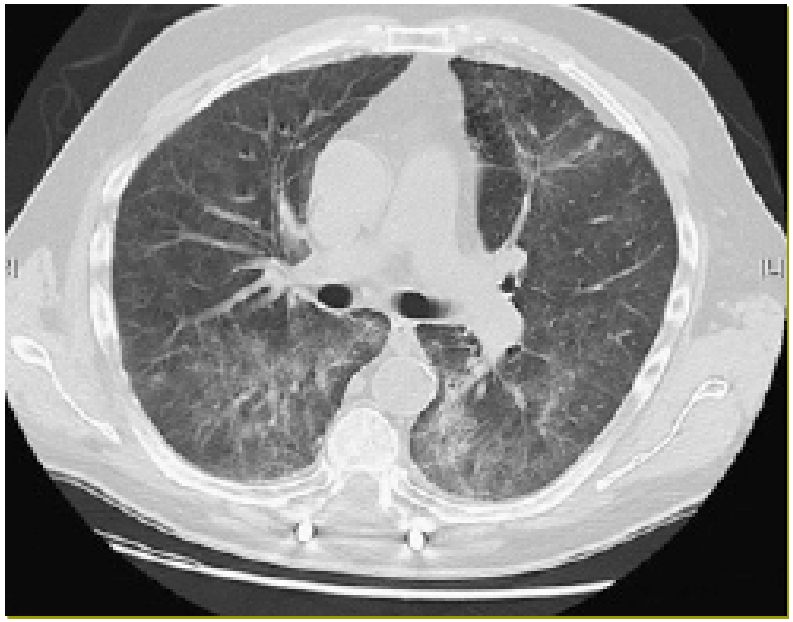
Choi Criteria

Response	Definition
Complete response	Disappearance of all lesions No new lesions
Partial response	A decrease in size of 10% or more or a decrease in tumor density (HU) of 15% or more on CT No new lesions No obvious progression of non-measurable disease
Stable disease	Does not meet criteria for complete response, partial response, or progression No symptomatic deterioration attributed to tumor progression
Progression of disease	An increase in tumor size of 10% or more and does not meet criteria of partial response by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of existing intratumoral tumor nodules

Choi H, et al. *AJR Am J Roentgenol.* 2004;183:1619-1628.

Scenario Clinico

Gennaio 2012



… strie distelettasiche di tipo fibroso a carico del terzo inferiore di entrambi i campi polmonari, nei piani posteriori …

TOSSICITA' POLMONARE
Polmonite non infettiva
Malattia polmonare interstiziale

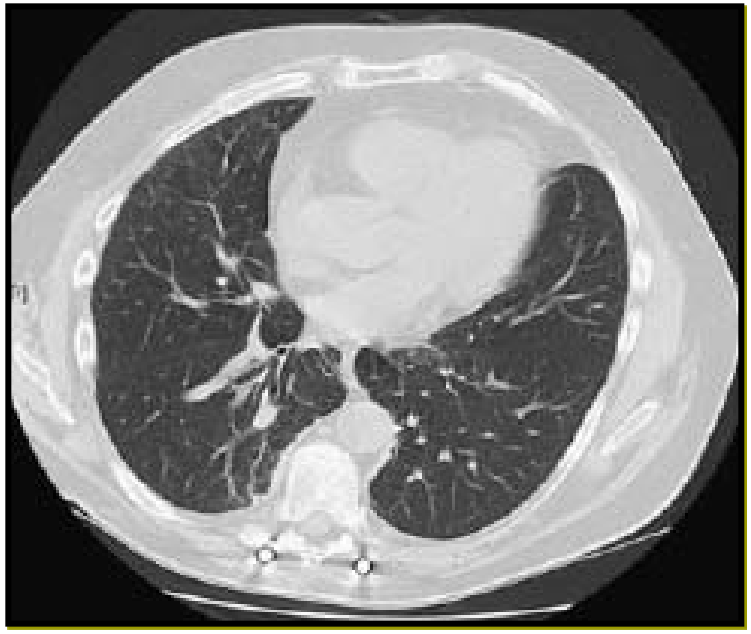
Grade	Symptoms	Management	Everolimus Dose Modification
1	Asymptomatic	• No specific therapy	• No change
2	Symptomatic, not interfering with ADL	Depending on severity of symptoms: • Consider consulting a pulmonologist • Consider diagnostics to exclude infectious causes • Consider corticosteroids	• Consider dose interruptions/reduction • Decrease dose until grade ≤1 and consider re-escalation of dose • If no recovery to grade ≤1, discontinue treatment
3	Symptomatic, interfering with ADL, O_2 required	• Consult a pulmonologist • Perform diagnostics to exclude infectious causes • If infectious cause excluded, consider use of corticosteroids • In presence of impending respiratory distress: consider use of concomitant corticosteroids and antibiotics	• Hold dose until recovery to grade ≤1 • Restart dose within 2 weeks at reduced dose if evidence of clinical benefit
4	Life threatening, ventilatory support indicated		• Discontinue everolimus

ADL, activities of daily living.

Porta C et al. *Eur J Cancer.* 2011;47:1287-1298. Moldawer NP, Wood LS. *Kidney Cancer J.* 2010;8(2):51-59. Eisen T et al. *J Natl Cancer Inst.* 2012;104:93-113.

Scenario Clinico

Febbraio 2012



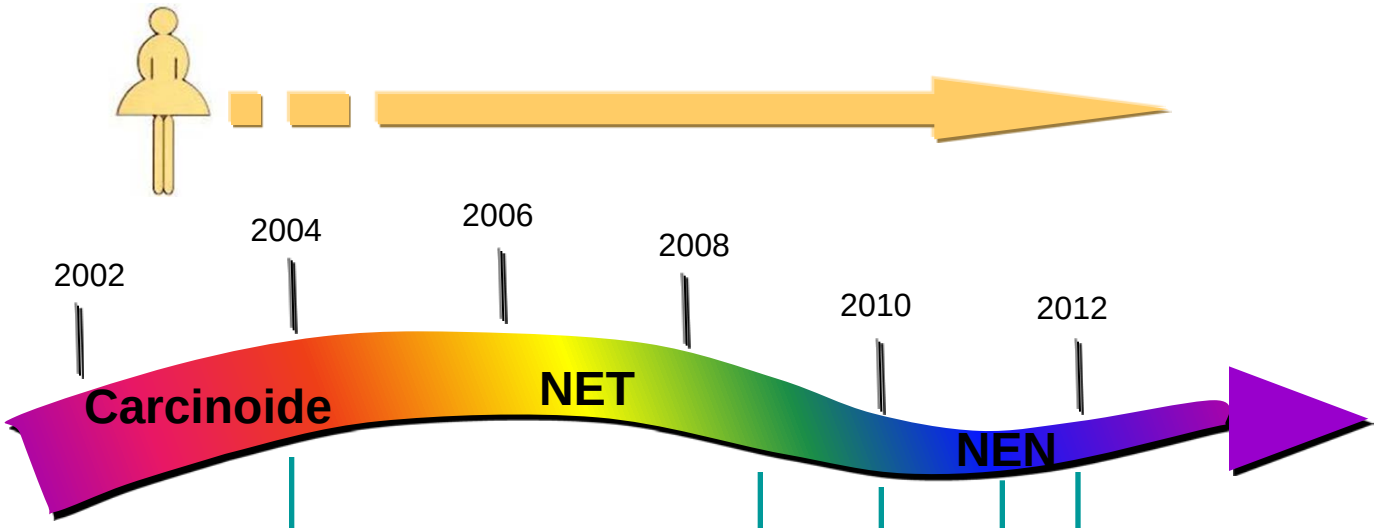
Prosegue RAD001 a 5 mg/die + Octreotide LAR 30 mg q 28

Discussione

Le peculiarità di questo caso sono in particolare legate a:

- ✓La persistenza di malattia dopo circa 10 anni
- ✓L'incognita della terapia adiuvante nell'*alto rischio*
- ✓La scelta dello switch con analoghi della SMS
- ✓Il senso della re-biopsia
- ✓Attività ed effetti collaterali dei *nuovi farmaci*
- ✓Valutazione delle risposte: RECIST *vs* CHOI

2003 - 2012: cosa c'è di nuovo?



Travis

ENETS

PROMID

WHO

NANETS Guideline

FDA: Everolimus, Sunitinib

ENETS Guidelines

UKINETS Guidelines

Pasireotide
Dopastatine
Bevacizumab
Sorafenib
Vatalanib
Pazopanib
Imatinib
Masatinib
Erlotinib
Cixutumumab

Grazie per l’attenzione

… e per la collaborazione

Dr. Felice Armienti – Radiologia Policlinico di Monza