

Gestione delle terapie biologiche nei pazienti con NET



Caso clinico 1

Maria Vittoria Davi

Medicina Interna D

Azienda Ospedaliera Universitaria Integrata

Verona

Caso clinico

- M, 69 anni (comorbilità : ernia discale L4-L5 operata nell' 81, stent iliaco sn '09, ipertrofia prostatica)
- pz asintomatico, in corso di ecografia addome, riscontro incidentale di 2 lesioni (17-32mm) al V-VI segmento epatico, confermate alla RMN e eco con mdc, compatibili con HCC (ipervascolarizzate in fase arteriosa, rapido wash-out in fase venosa)



Intervento chirurgico

(maggio 2009)

➔ riscontro intra-operatorio di metastasi epatiche di NET ileale

➔ resezione segmento ileale di 38 cm + linfadenomectomia + resezione del V-VI segmento epatico + metastasectomia al II segmento e al ligamento falciforme + colecistectomia

Esame istologico:

(maggio 2009)

- Carcinoma endocrino ileale ben differenziato multifocale
(2 formazioni nodulari di 0,6 e 0,8 cm), coinvolgimento sieroso, invasione vascolare e perineurale
- Ki 67 1%, cromogranina A +, sinaptofisina +, serotonina +
- metastasi in 1:16 linfonodi del meso ileale
- 4 metastasi epatiche: la maggiore di 2,7 cm in sottoglissoniana
- Ki 67 1%, cromogranina A+ , sinaptofisina +, serotonina +

TNM classification and disease staging (ENETS/UICC)

T-primary tumor

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor invades mucosa or submucosa and size ≤ 1 cm

T2 Tumor invades muscularis propria or size > 1 cm

T3 Tumor invades subserosa

T4 Tumor invades peritoneum/other organs

N -regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M -distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastases

M1 Distant metastasis

Stage I T1 N0 M0

Stage IIa T2 N0 M0

IIb T3 N0 M0

Stage IIIa T4 N0 M0

IIIb Any T N1 M0

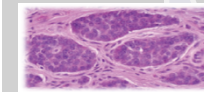
Stage IV Any T Any N M1

Classificazione WHO dei GEP-NET

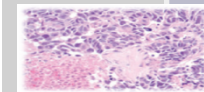
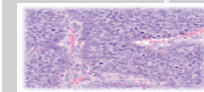
WHO 1980	WHO 2000	WHO 2010
Carcinoide	Tumore endocrino ben differenziato (WDET) ^a	NET G1 (carcinoide) ^b
	Carcinoma endocrino ben differenziato (WDEC) ^a	NET G2 ^b
	Tumore endocrino poco differenziato/ carcinoma a piccole cellule (PDEC)	NEC (tipo a larghe cellule o a piccole cellule) ^{b,c}

Modificato da (1)

Prognosi dei pazienti



Buona



Negativa

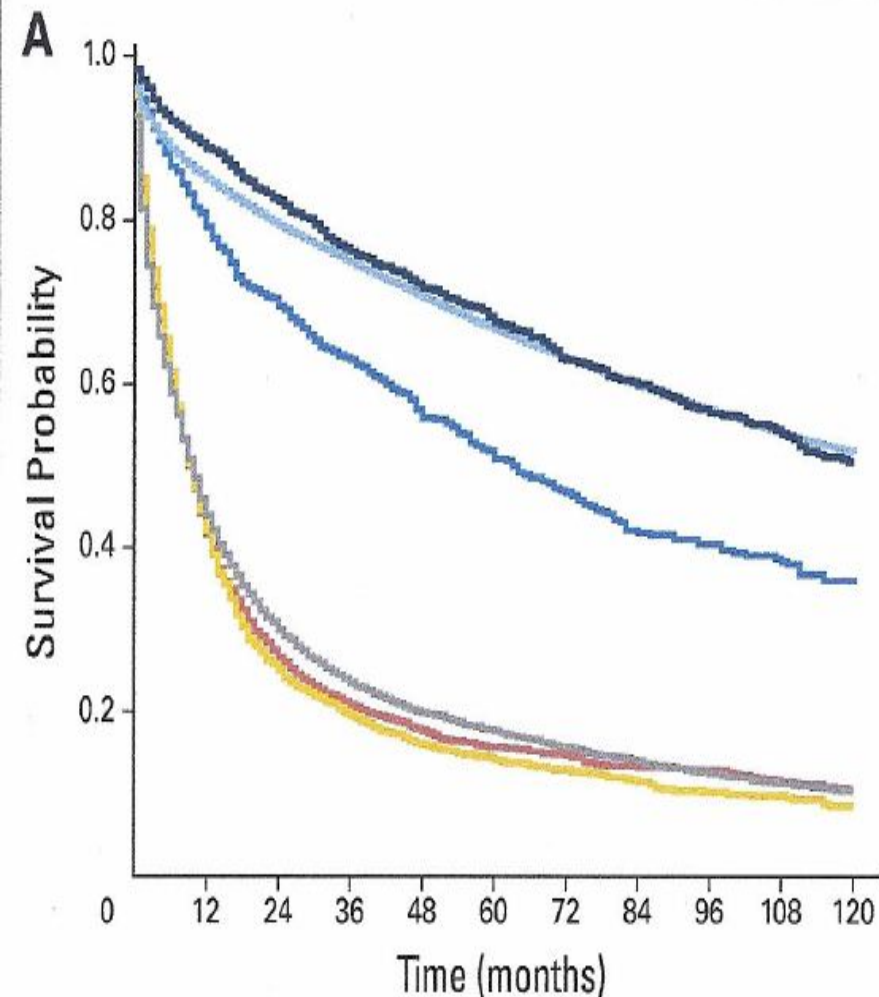
Modificato da (2,3)

Criteria di *grading* istopatologico (1,4,5)

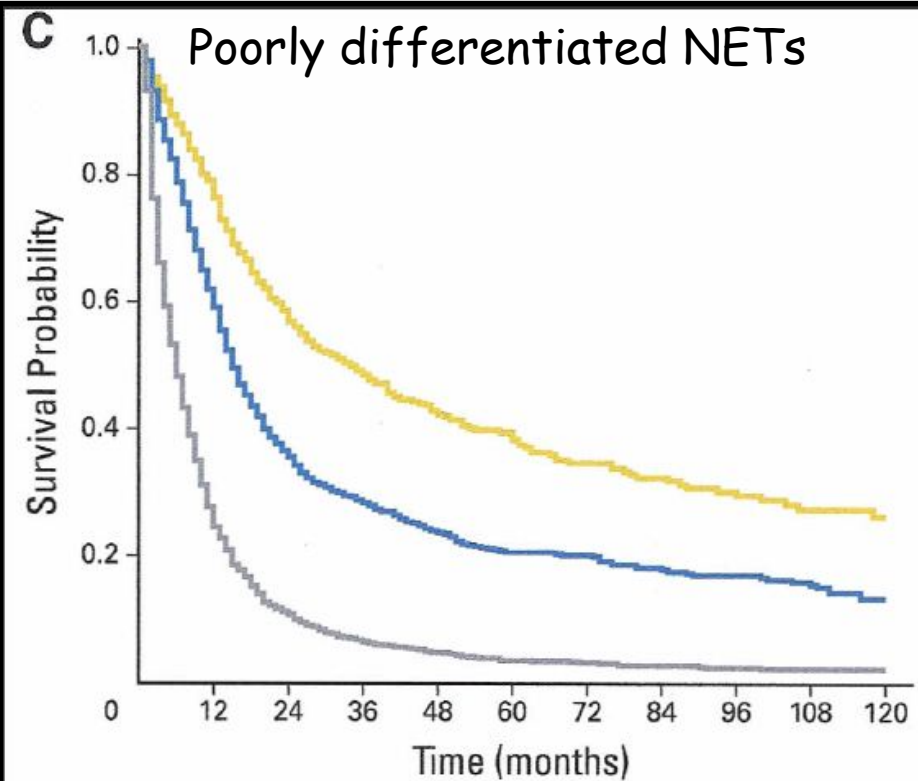
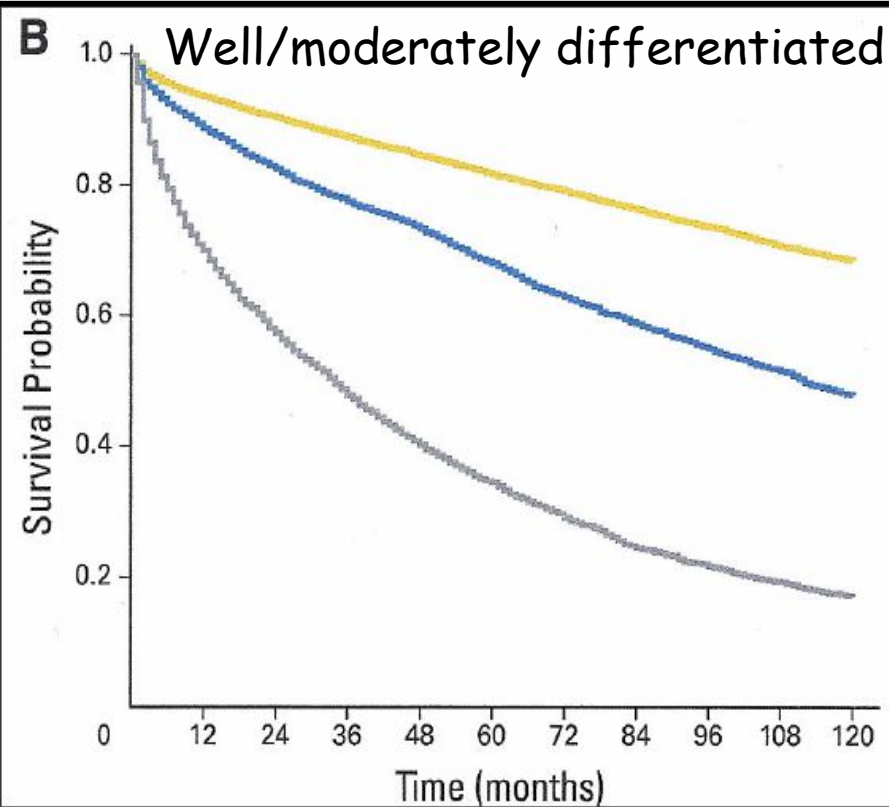
G1	<2 mitosi x 10 HPF e/o <2% Ki-67
G2	2-20 mitosi x 10 HPF e/o 3-20% Ki-67
G3	>20 mitosi x 10 HPF e/o >20% Ki-67

Elaborazione da (1,4,5)

Survival duration by histology



	Median Survival	
	Months	95%CI
■ Carcinoid/islet cell: well-differentiated	124	101 to 147
■ Carcinoid/islet cell: unspecified grade	129	124 to 134
■ Carcinoid/islet cell: moderately differentiated	64	56 to 72
■ Neuroendocrine: poorly differentiated	10	9 to 11
■ Neuroendocrine: anaplastic	10	9 to 11
■ Neuroendocrine: unspecified grade	10	9 to 11

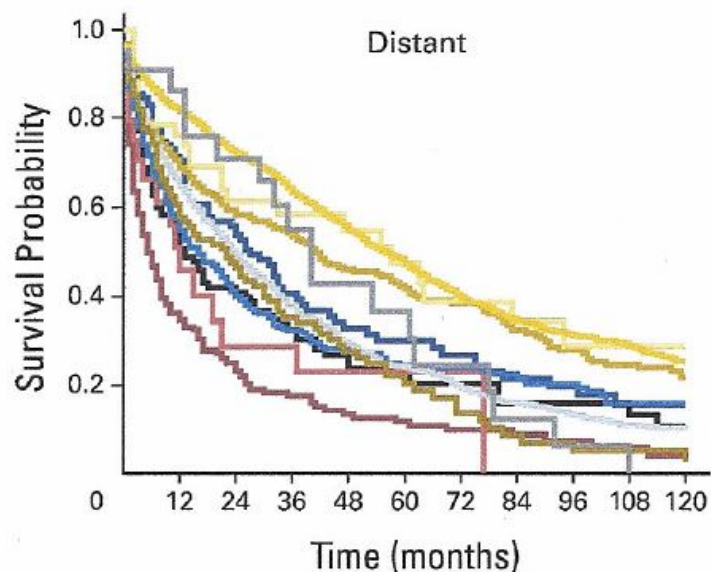
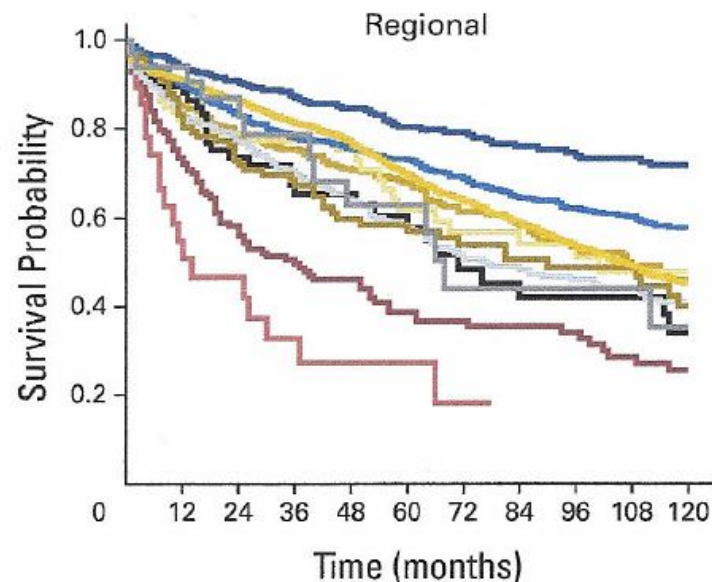
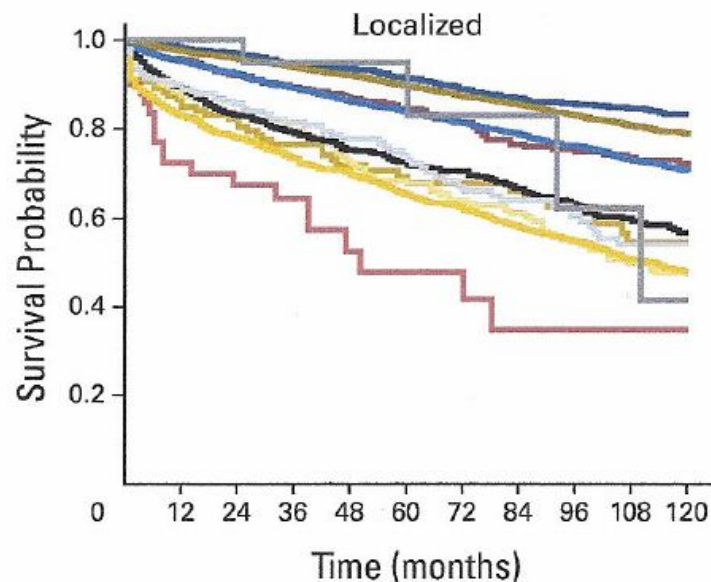


	Median Survival	
	Months	95%CI
Localized	223	208 to 238
Regional	111	104 to 118
Distant	33	31 to 35

	Median Survival	
	Months	95%CI
Localized	34	27 to 41
Regional	14	13 to 15
Distant	5	4.5 to 5.5

Survival duration by primary tumor site

A

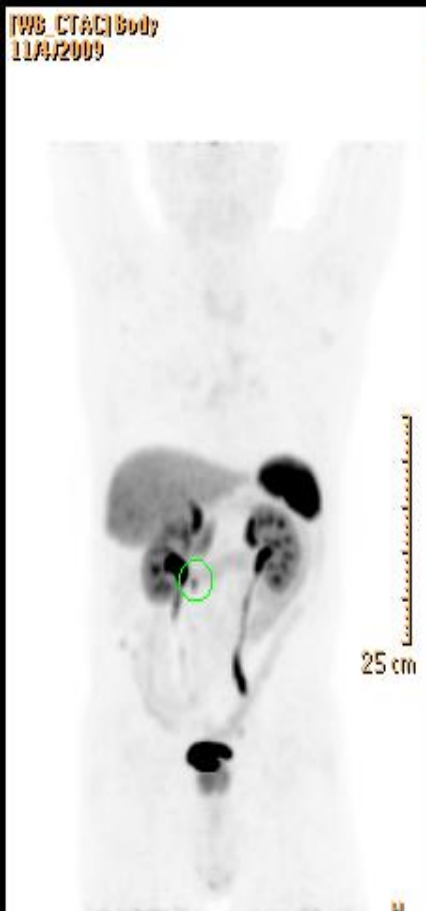


Color	Site	Median Survival (months)		
		Localized	Regional	Distant
Blue	Appendix	>360	>360	27
Yellow	Cecum	135	107	41
Brown	Colon	261	36	5
Light Yellow	Duodenum	107	101	57
Black	Gastric	154	71	13
Red	Liver	50	14	12
Dark Blue	Lung	227	154	16
Grey	Pancreas	136	77	24
Olive	Rectum	290	90	22
Gold	Small bowel	111	105	56
Light Blue	Thymus	110	68	40

1° follow up

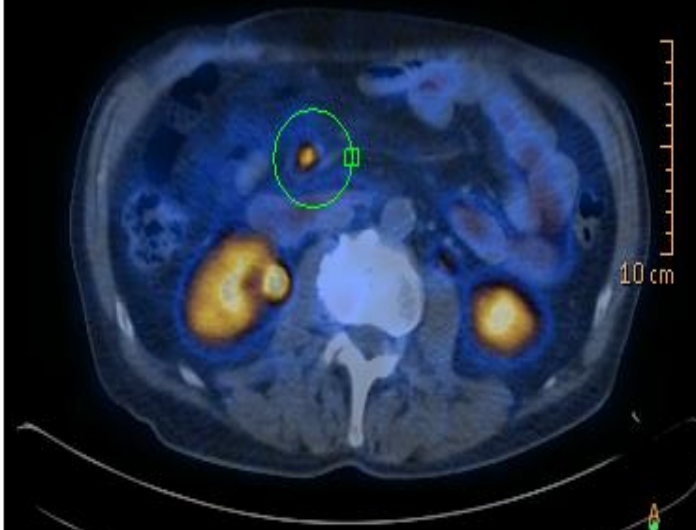
(sett. 2009)

- Karnofsky 100%
- Cromogranina A: 42 ng/ml (v.n. 19-98)
- 5-HIAA: 4,2 mg/24 h (v.n. 2-7)



PT: [WB_CTAC] Body
CT: Body-Low Dose CT
PT: 11/4/2009
CT: 11/4/2009

Body-Low Dose CT
11/4/2009



piccolo linfonodo mesenteriale in regione mesogastrica ds
ipercaptante

Terapia consigliata

(novembre 2009)

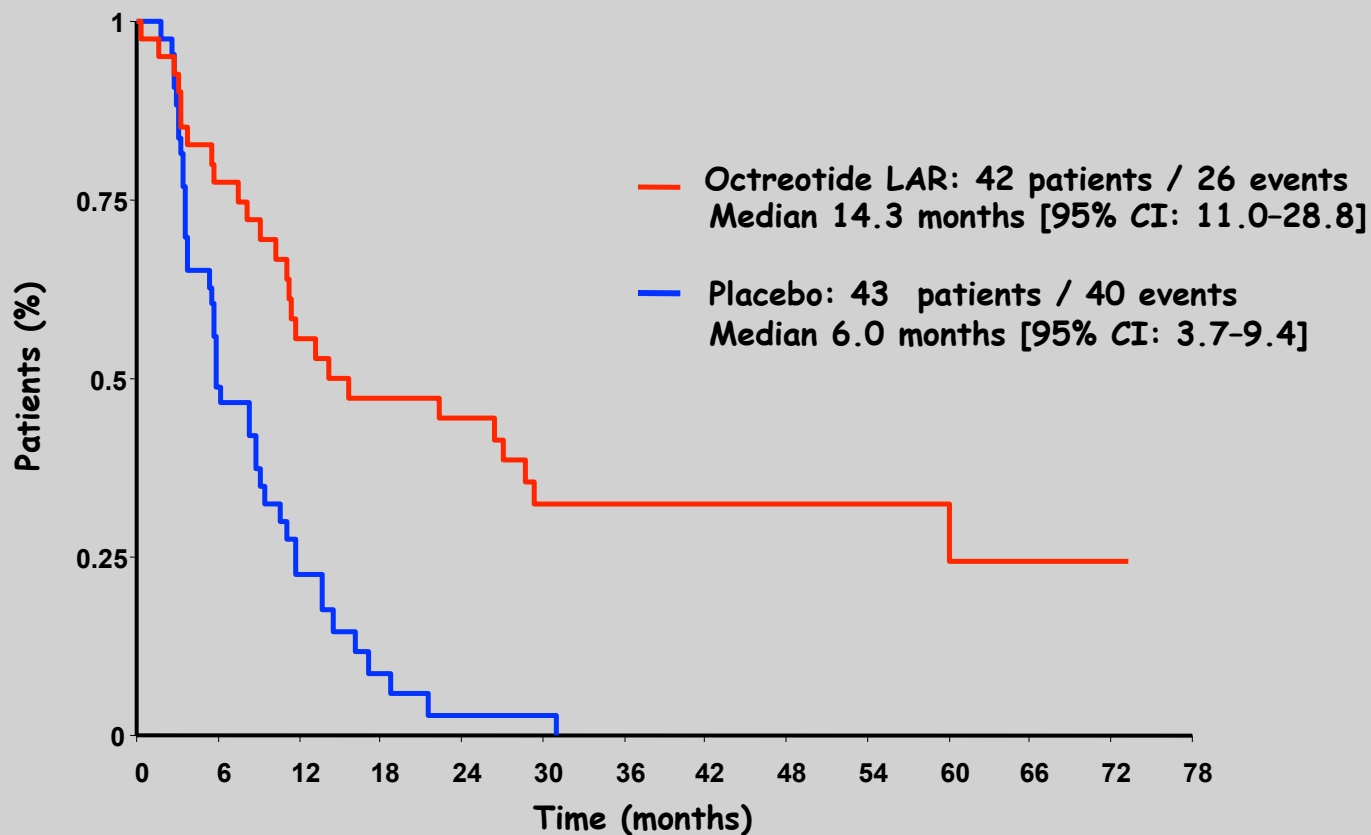
- Octreotide s.c. 0,1 mg 1 fl x 2/die s.c. x 7 gg
- Octreotide LAR 20 mg 1 fl/28 gg i.m.

- Controllo TAC addome dopo 6 mesi: linfonodo mesenteriale (9 mm) stazionario

- Prosegue octreotide LAR **➡** 30 mg/28 gg

Octreotide LAR 30 mg significantly prolongs time to tumor progression compared with placebo

66% reduction in the risk of tumour progression
 HR= 0.34 [95% CI: 0.20-0.59] $P=0.000072$



Neuroendocrinology 2012

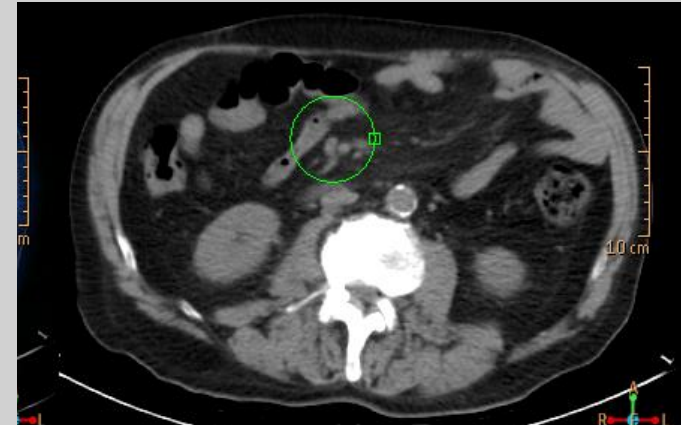
ENETS Consensus Guidelines

*Medical therapy in advanced disease:
Antiproliferative Treatment
Somatostatin Analogues (SSA)*

- ✓ In functioning and non-functioning midgut tumors
- ✓ First-line therapy in non-functioning, progressive, small intestinal G1 NET
- ✓ In individual cases of midgut NET G2, alternative therapies to SSA may be considered

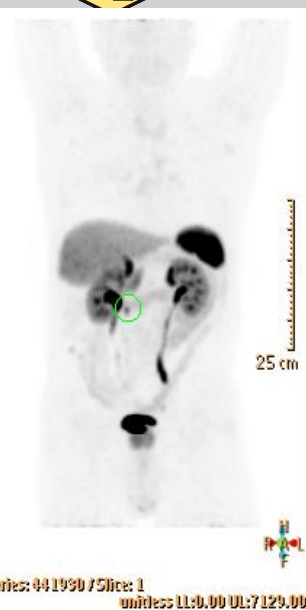
Follow up successivo

SD: nov.2009 → sett.2011:

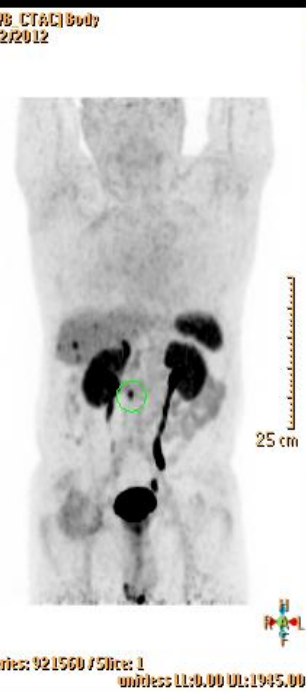
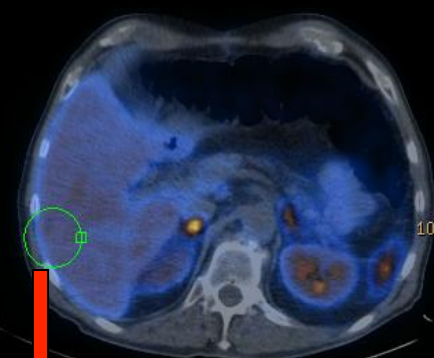
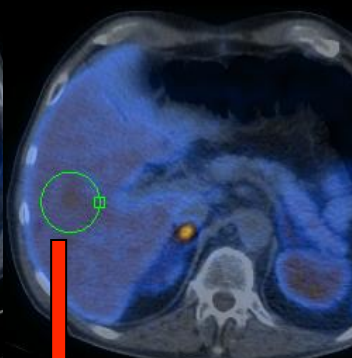
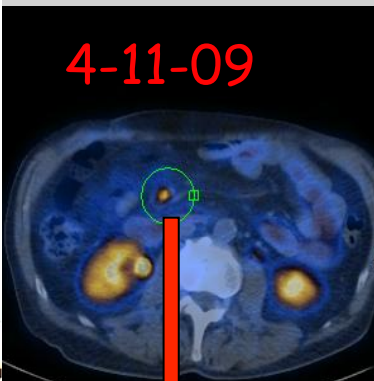


- Karnofsky 100%
- Cromogranina A 132 ng/ml (v.n. 19-98)
- 5-HIAA: nella norma
- PET-CT-⁶⁸GA-DOTANOC: comparsa di almeno 4 metastasi al lobo epatico ds

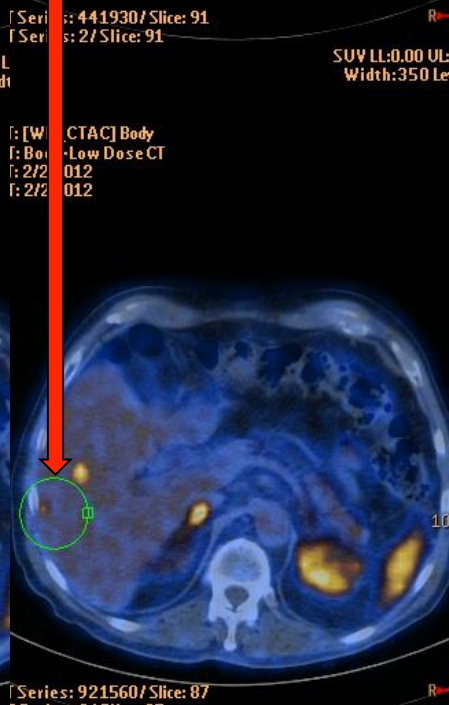
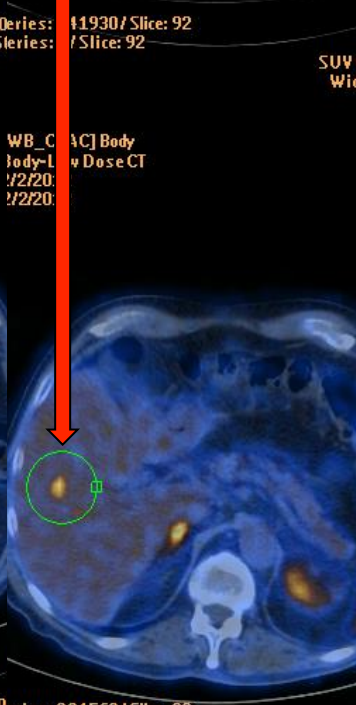
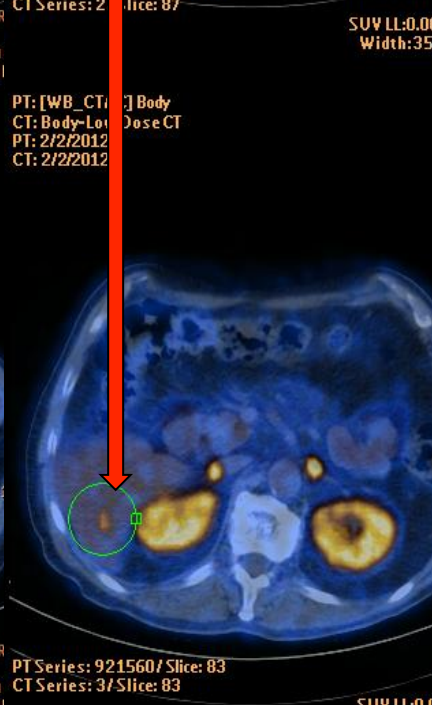
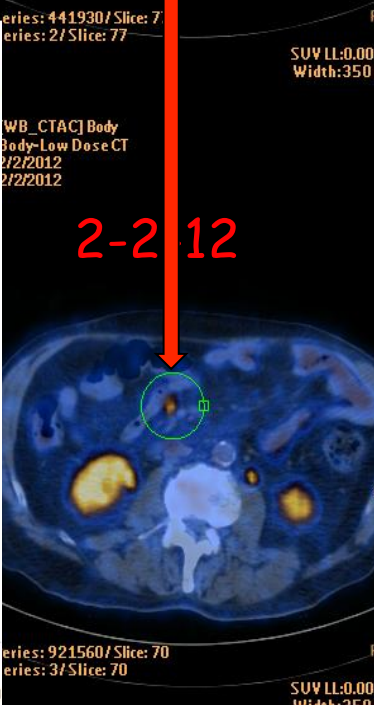
PET-CT-⁶⁸GA-DOTANOC



4-11-09



2-2-12



Series: 441930 / Slice: 77
Series: 2 / Slice: 77

PT Series: 441930 / Slice: 87
CT Series: 2 / Slice: 87

SUV LL: 0.00 Series: 441930 / Slice: 92
Width: 350 Series: 2 / Slice: 92

Series: 441930 / Slice: 91
Series: 2 / Slice: 91

SUV LL: 0.00 UL: 1.00
Width: 350

WB_CTAC] Body
Body-Low Dose CT
2/2/2012
2/2/2012

PT: [WB_CTAC] Body
CT: Body-Low Dose CT
PT: 2/2/2012
CT: 2/2/2012

WB_CTAC] Body
Body-Low Dose CT
2/2/2012
2/2/2012

[WB_CTAC] Body
Body-Low Dose CT
2/2/2012
2/2/2012

Series: 921560 / Slice: 70
Series: 3 / Slice: 70

PT Series: 921560 / Slice: 83
CT Series: 3 / Slice: 83

SUV LL: 0.00 Series: 921560 / Slice: 88

Series: 921560 / Slice: 87
Series: 3 / Slice: 87

Net ileale G1 in progressione epatica quale trattamento?

1. Aumento dosaggio/intervalli di octreotide
2. Terapia radiometabolica con ^{90}Y -dotatoc o ^{177}Lu -dotatate
3. HAE/TACE
4. Everolimus
5. Chemioterapia

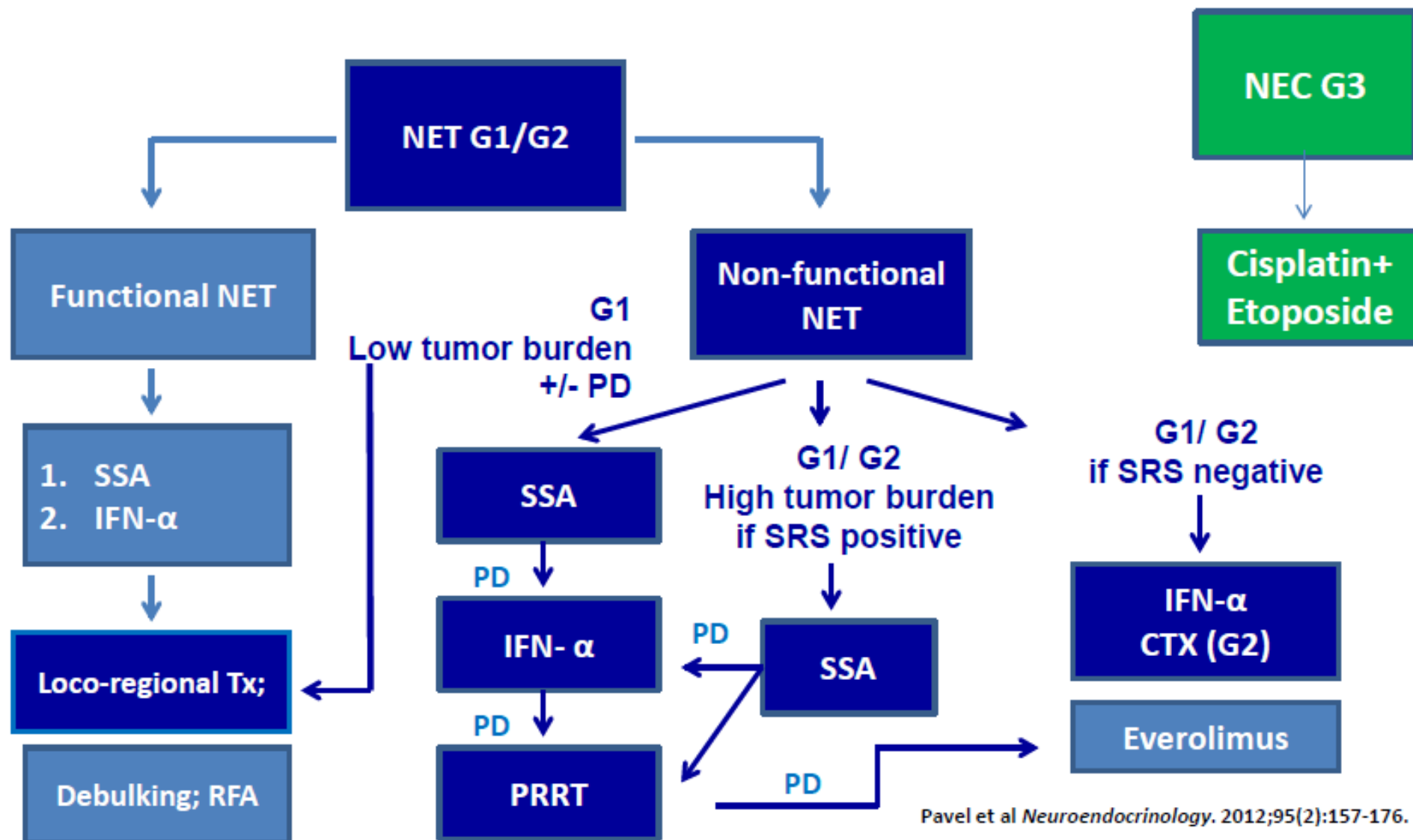
Cosa abbiamo fatto.....



- Continua octreotide LAR 30 mg/28 gg
- ^{177}Lu -dotatate 4 cicli: da 04/12 a 09/12 attivita' cumulativa 700 mC

Pharmacological Therapy in Metastatic Nonresectable Intestinal NET

ENETS Consensus Guidelines 2011



10 Novembre 2012
Giornata mondiale
dei tumori neuroendocrini

NET CANCER DAY