PROGRAMMA 6 APRILE 2018

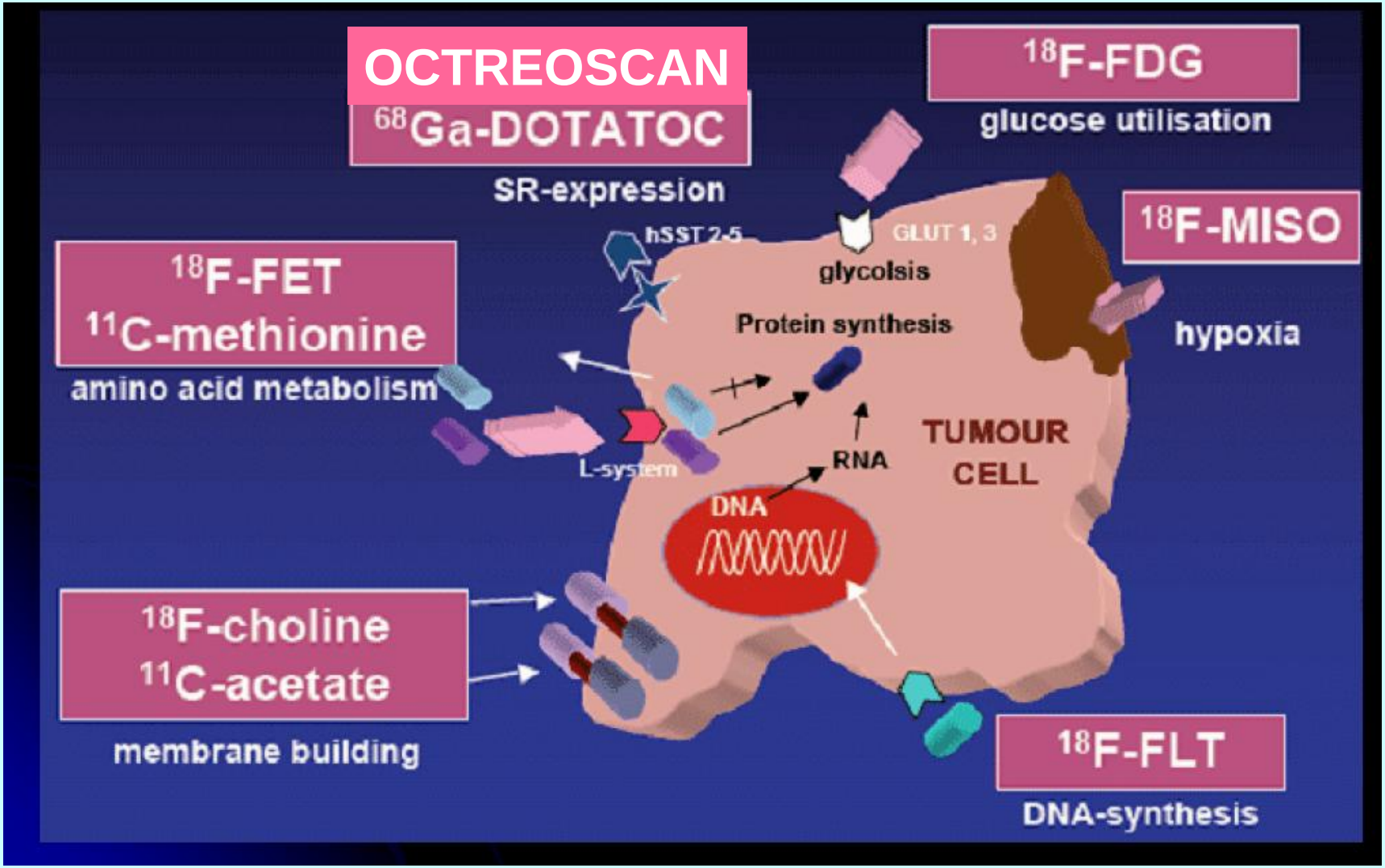
08:15 - 08:30	**INTRODUZIONE** - N. Fazio
08:30 - 08:40	**Terapie mediche** - M. Torniai
08:40 - 08:50	**Terapie locoregionali epatiche** - G. Bonomo
08.50 - 09:00	**PRRT** - C. Grana
09:00 - 10:30	**GEP NEN: Criteri di scelta della terapia e strategia terapeutica** – prima parte SHOOTER: N. Fazio
	Scenari clinici: Discussione del gruppo multidisciplinare IEO Panel: F. Spada, C. Grana, E. Pisa, G. Bonomo, D. Ravizza, B. Gibelli, E. Bertani, D. Zerini

TERAPIA RADIORECETTORIALE (PRRT)

THERANOSTIC…….. **Think different**….,
as a Nuclear Oncologist….

Chiara M Grana
Divisione Medicina Nucleare
Istituto Europeo di Oncologia, MIlano

LA CELLULA NET: il target



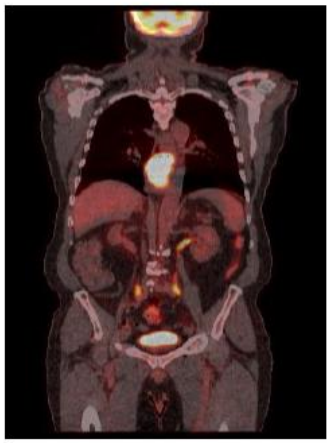
Molecular Imaging

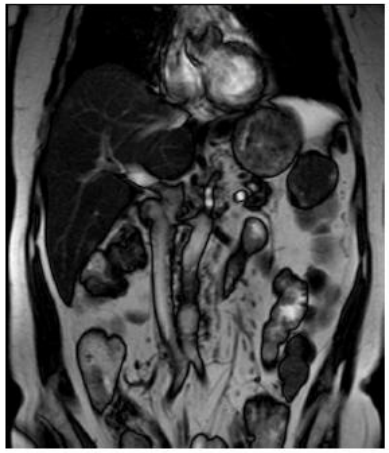
"Molecular imaging is aimed at the exploitation of specific molecules as the source of image contrast"

Weissleder R. *Radiology*. 1999;212(3):609-614.

Aims:

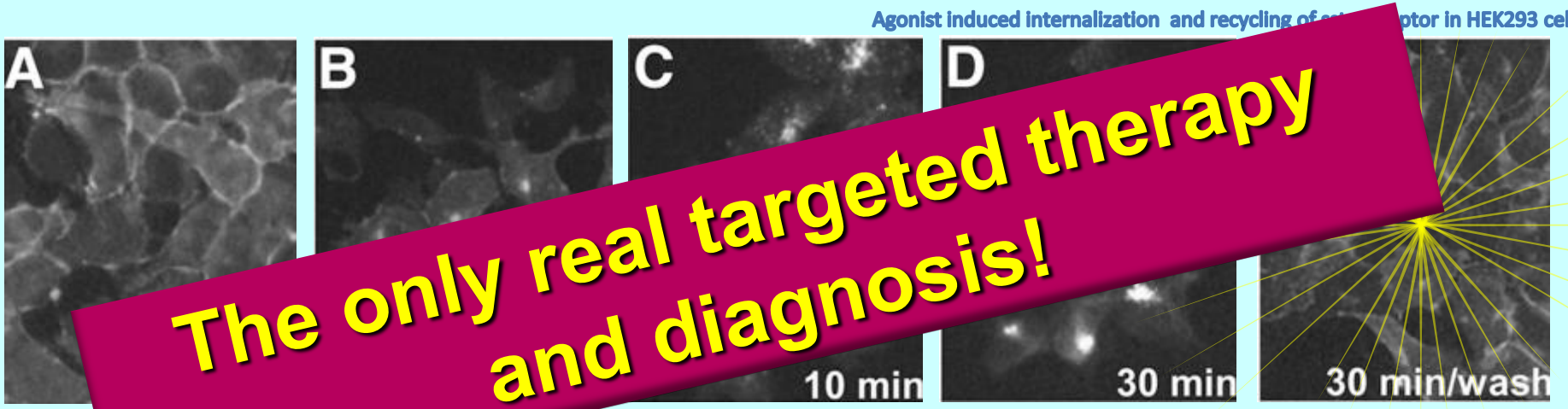
- **Earlier detection and characterization of disease ("molecular signature" prior to irreversible damage)** Ga-68-peptidi
- **Understanding of underlying biology** FDG PET
- **Selection of specific treatment option for targeted therapy** Ga-68-peptidi
- **Concept of THERANOSTICS nuclear medicine/molecular imaging ideally set for this dual role**





Manoharan, EANM 2016

Il Paradigma più utilizzato: THERANOSTIC



The only real targeted therapy and diagnosis!

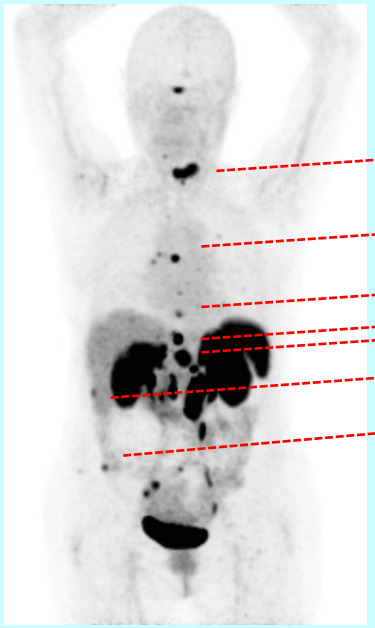
Legame con il recettore e Internalizzazione dello stesso Peptide, per Imaging & Terapia

^{68}Ga-DOTATATE → ^{177}Lu-DOTATATE

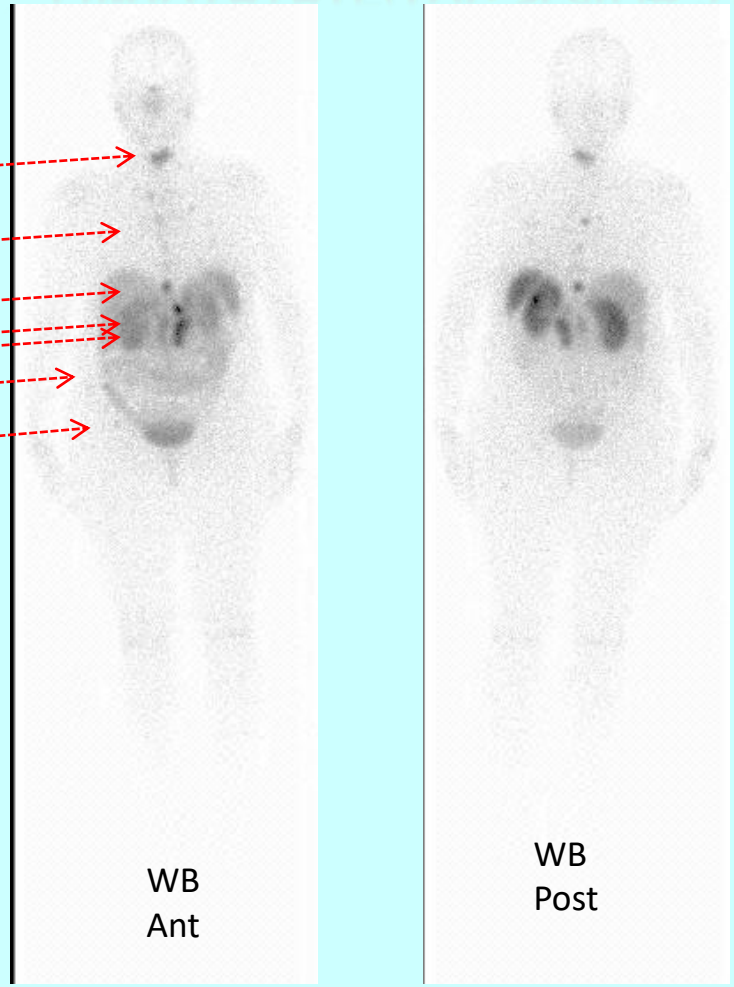
^{68}Ga-DOTATOC PET vs. ^{177}Lu-DOTATATE/TOC

Liver, LN and bone mets from ileal G1 NET (Ki67 <1%). Status post ileocolectomy; SSA ongoing

^{68}Ga-DOTATOC

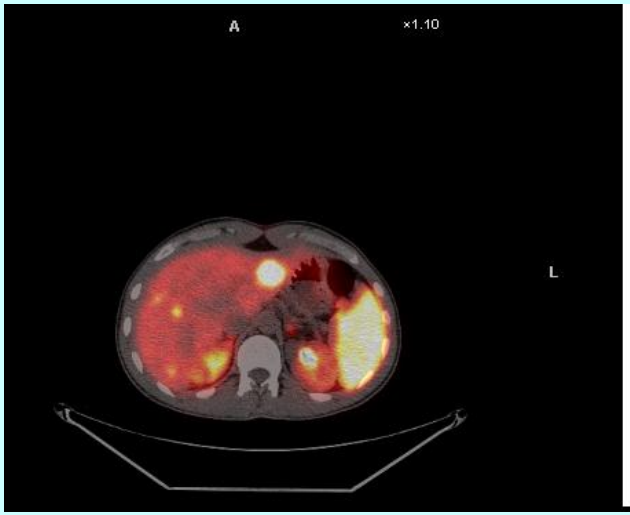


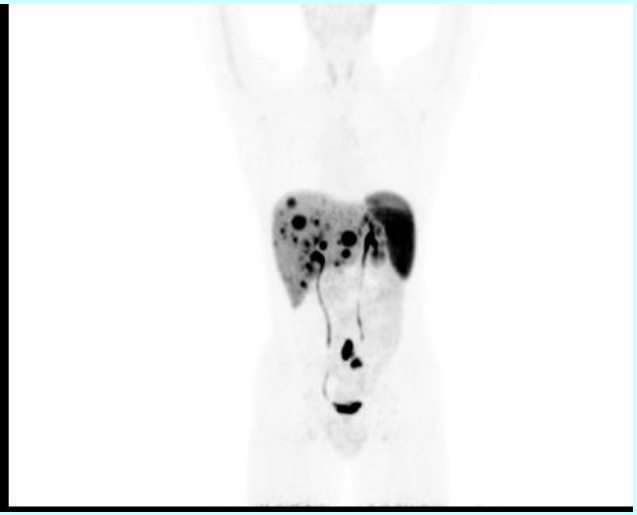
^{177}Lu-DOTATATE/TOC scan (4.5 GBq)



Imaging molecolare nei NET: obiettivi

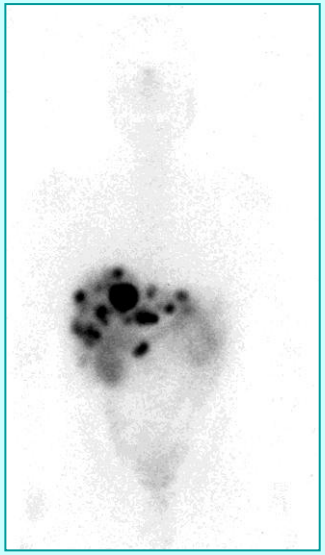
Localizzazione del tumore primitivo e delle mts

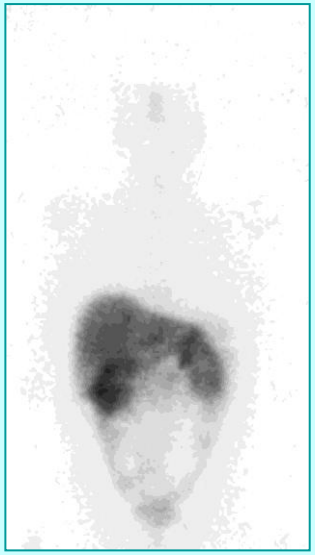




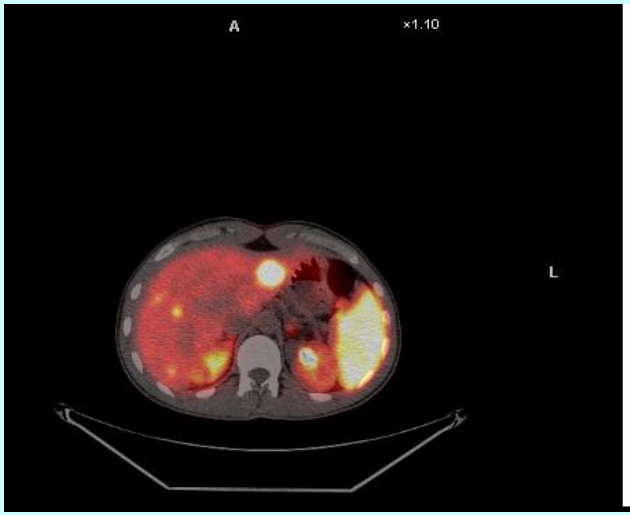
Decisione, strategia terapeutica e scelta del trattamento

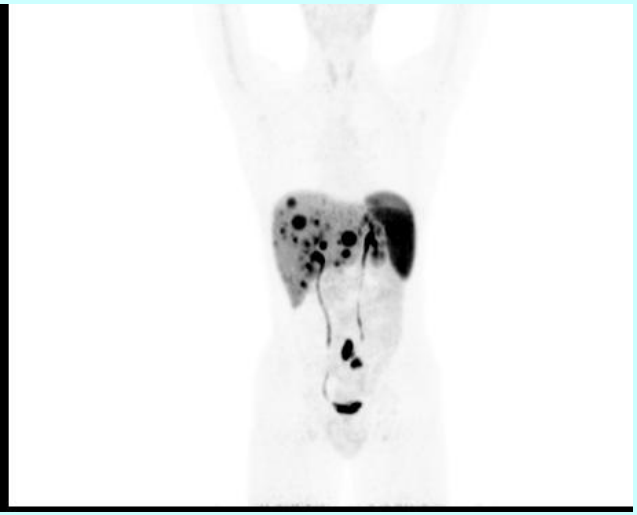
Valutazione della risposta alla terapia





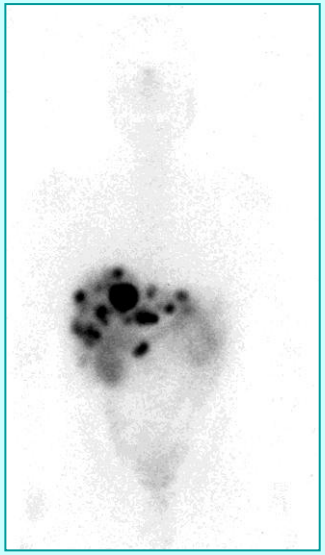
Imaging molecolare nei NET: obiettivi → PRRT

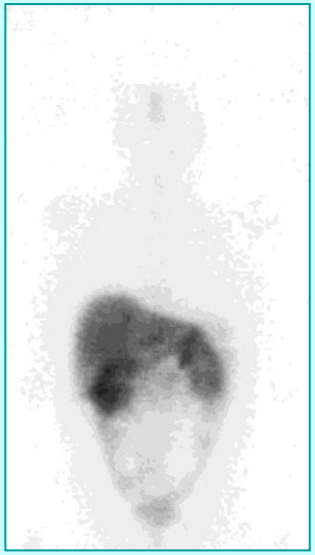




Decisione, strategia terapeutica e scelta del trattamento

Valutazione della risposta alla terapia





(K11)

Positron Emission Tomography (PET) Predictors of Tumor Response to Peptide Receptor Radionuclide Therapy (PRRT) in Metastatic Neuroendocrine Tumors (NET)

Ladwa R[A], Pattison D[B], Smith J[B], Goodman S[B], Burge M[C], Rose S[D], Dowson N[D], Wyld D[C];

[A]Department of Medical Oncology, Princess Alexandra Hospital. School of Medicine, University of Queensland, Brisbane, Australia

[B]Nuclear Medicine & Specialised PET Services, Royal Brisbane & Women's Hospital, Brisbane, Australia

[C]Cancer Care Services, Royal Brisbane and Women's Hospital. School of Medicine, University of Queensland, Brisbane, Australia

[D]Australian e-Health Research Centre, CSIRO Health and Biosecurity, Brisbane, Australia

Introduction: Pretherapeutic 68Gallium-DOTA-(0-Tyr3)-octreotate (68Ga-DOTATATE) PET standardised uptake value (SUV) has shown conflicting results in the prediction of tumor response to radionuclide therapy. **Aim(s):** We aimed to assess pretherapeutic SUV parameters with tumor lesion response in patients with metastatic NET. **Materials and methods:** Pre and post PRRT 68Ga-DOTATATE PET-CT were retrospectively analysed in patients who were treated with four cycles of 7.45GBq Lutetium octreotate PRRT. Pretreatment SUV parameters were correlated with response assessment at 6 months including change in lesion diameter (LD), morphologic tumor volume (ATV) and somatostatin receptor tumor volume (STV). **Results:** We analysed 111 lesions from 79 patients. Primary sites were predominately gastroenteropancreatic (87%) with hepatic metastasis (91%). Tumor grade G1 (46%), G2/3 (54%), Ki67 proliferation index ≤10% (75%) and >10% (25%) was measured. Concurrent chemotherapy was used (29%). Weak to moderate correlation between tumor response in LD and SUV max (Rs=0.298), SUV mean (Rs=0.408), tumor/spleen SUV mean (Rs=0.308) and tumor/liver SUV mean (Rs=0.264) was observed. Weak to moderate correlation was observed between SUV mean and change in ATV (Rs=0.368) or STV (Rs=0.454). Correlation did not vary by tumor site, grade or Ki67. Using a cut off SUV mean ≥15 (N=56), LD progression (≥20%), stable disease and response (≥30%) was observed in 0%, 61% and 39% compared with an SUV mean <15 (N=54) of 13%, 69% and 18% lesions respectively (P<0.01). **Conclusion:** SUV parameters had a weak to moderate correlation with lesion response however, no lesions progressed with a baseline SUV mean ≥15. **Keywords:** 68ga-dotatate pet-ct, suv parameters, tumor response, somatostatin receptor tumor volume

SRI: correlazione con la risposta alla PRRT

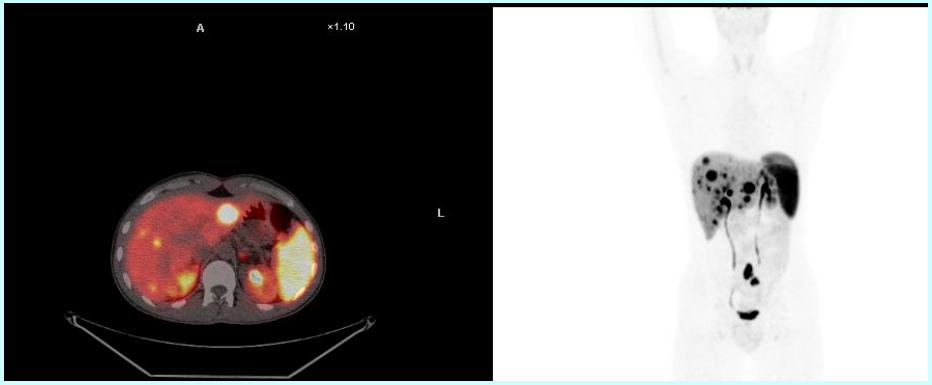
Ga-68-SSA-PET

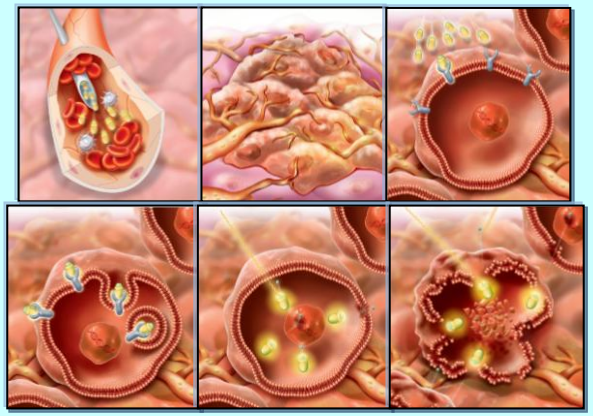
Elevata concentrazione di radioattività

Alta dose al tumore

Risposta

Captazione elevata



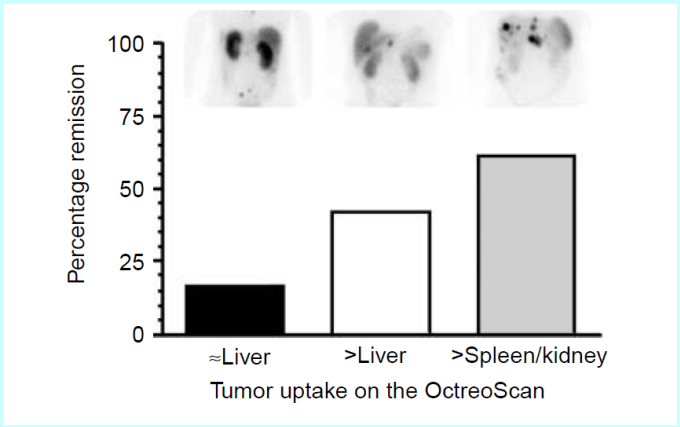


REVIEW

Endocrine-Related Cancer (2010) **17** R53–R73

Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors

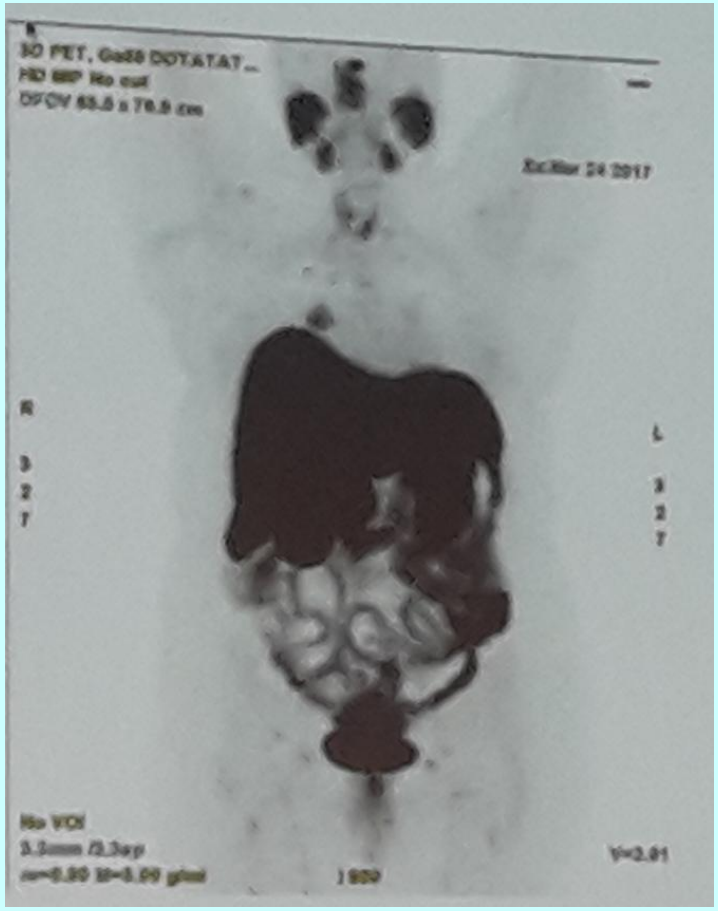
Dik J Kwekkeboom[1], Boen L Kam[1], Martijn van Essen[1], Jaap J M Teunissen[1], Casper H J van Eijck[2], Roelf Valkema[1], Marion de Jong[1], Wouter W de Herder[3] and Eric P Krenning[1]

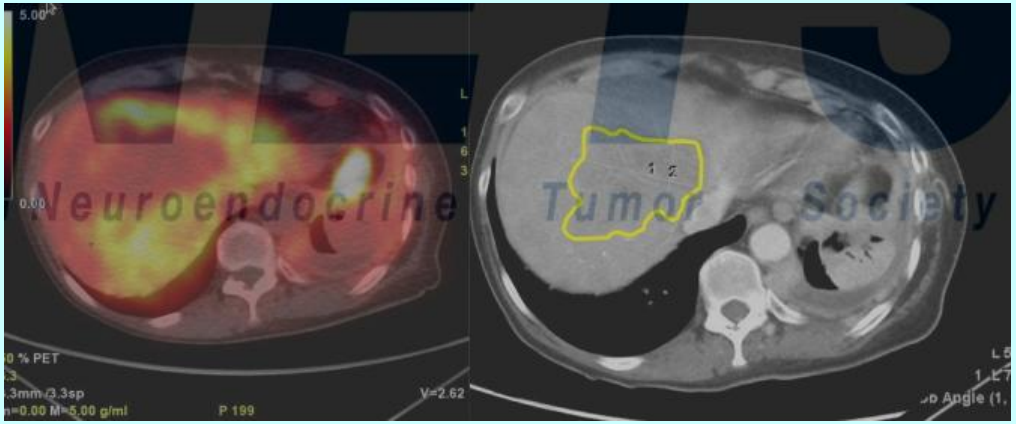


PRRT sempre indicata?

carcinoide atipico bronchiale,

mts ossee e ln, epatiche

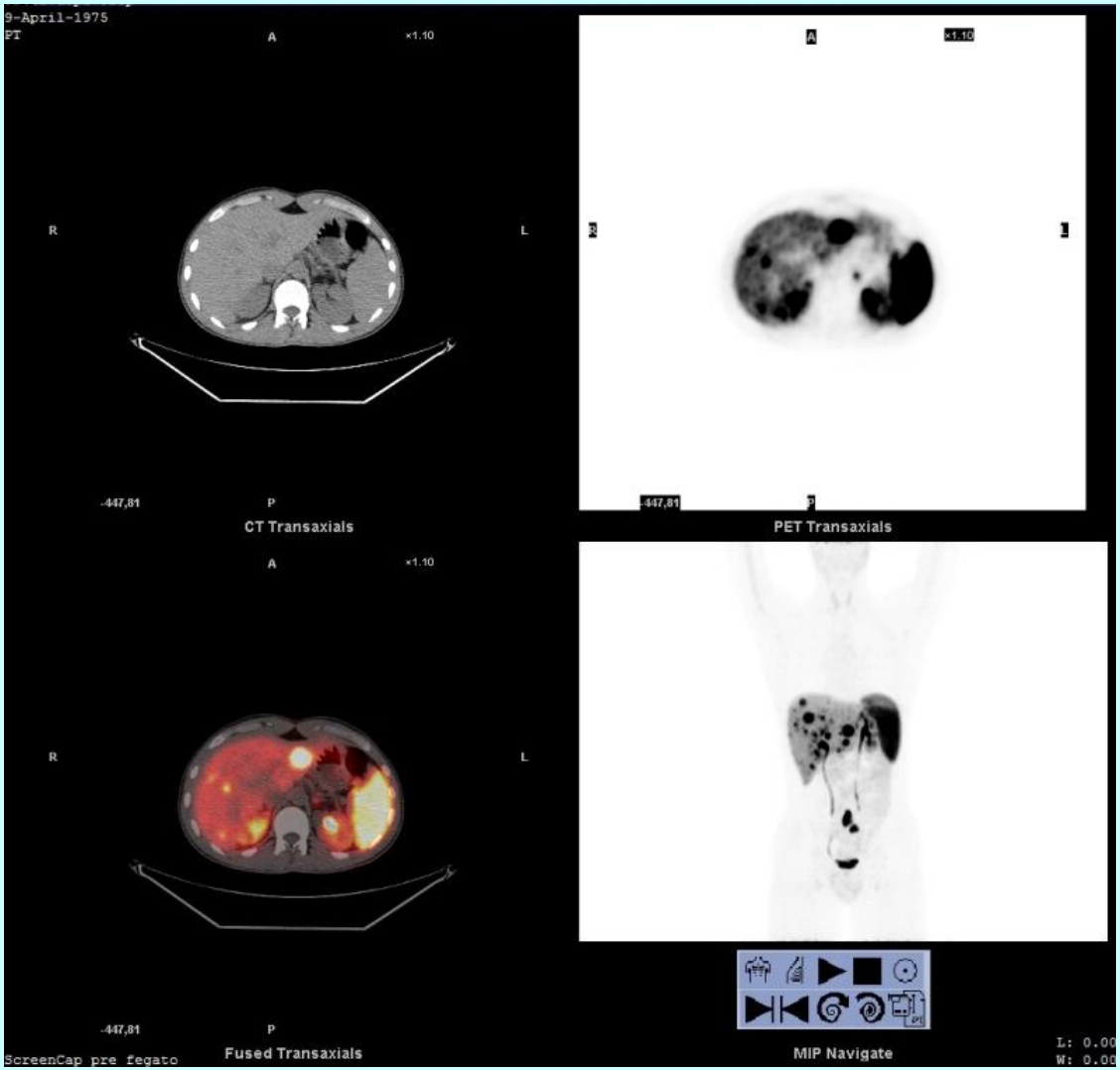




No uptake, no PRRT

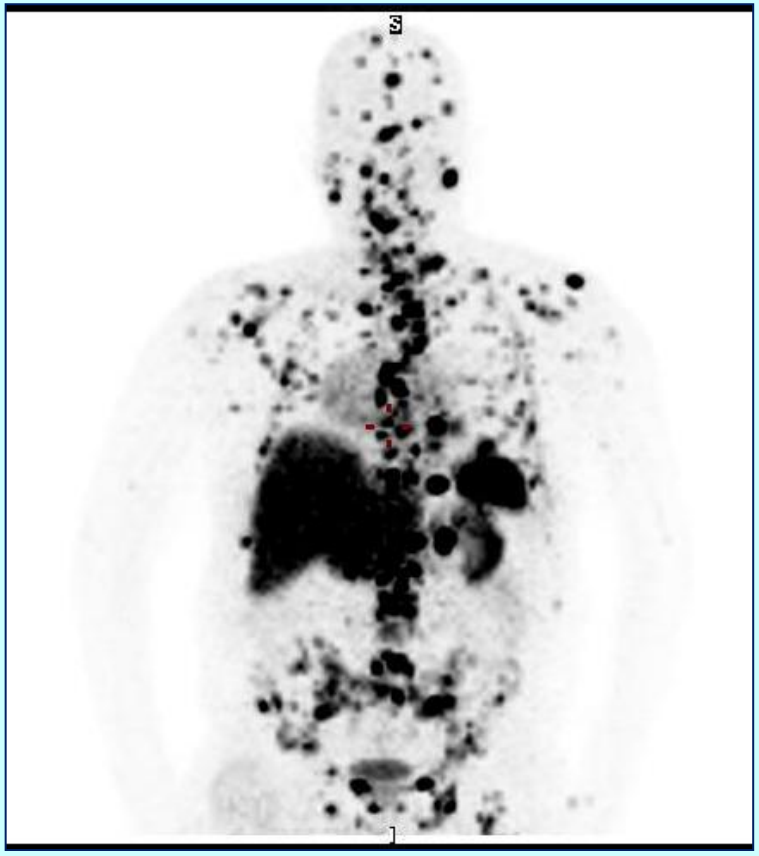
Courtesy of ENETS

Intensa captazione; ok per PRRT



T, SUV 28,2

Captazione intensa: è sempre indicata la PRRT?



ECOG 2, perdita peso

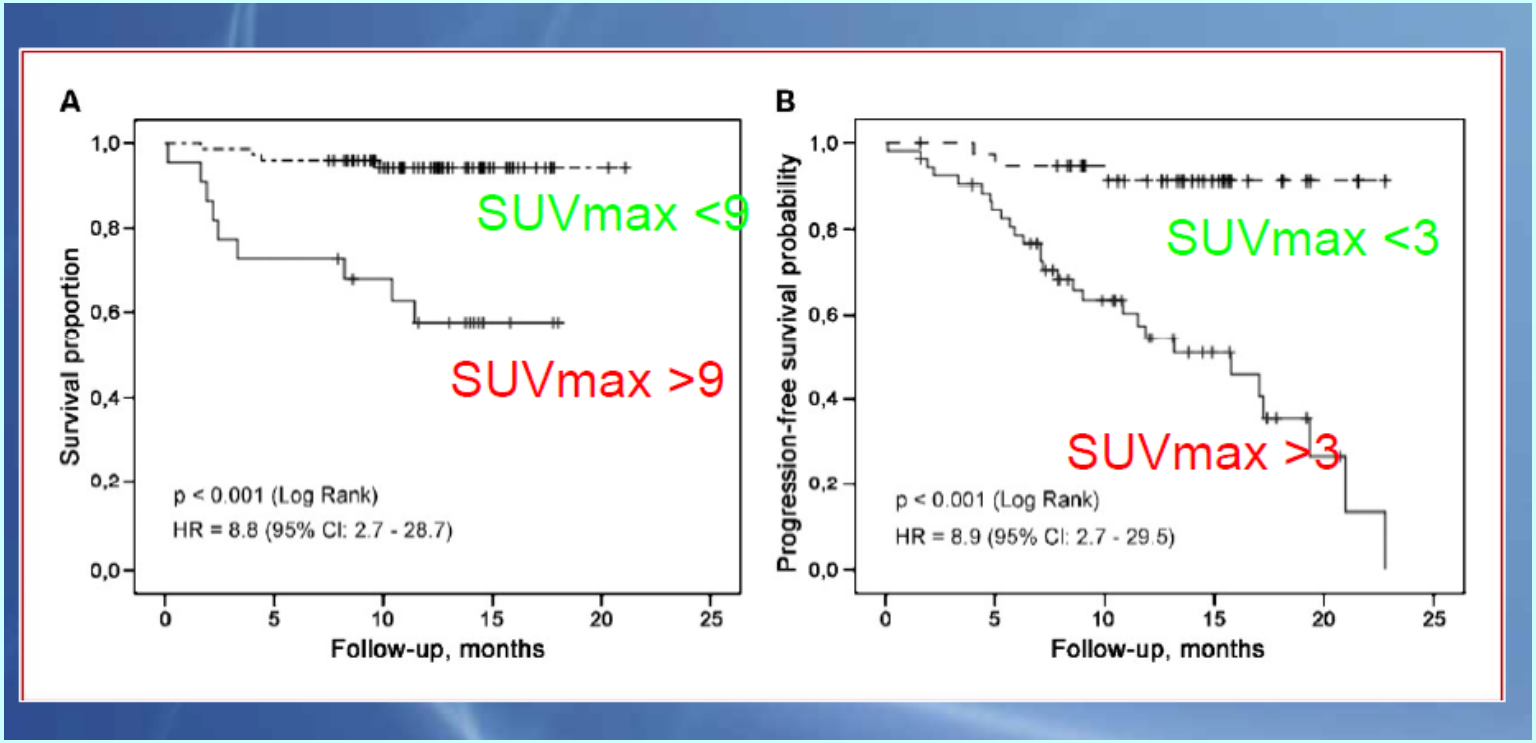
compromissione

funzionalità ematologica

basale

Valore predittivo della PET con FDG nei NETs: OS e PFS variano con il SUV max

Binderup T, et al. Clin Cancer Res; 2010

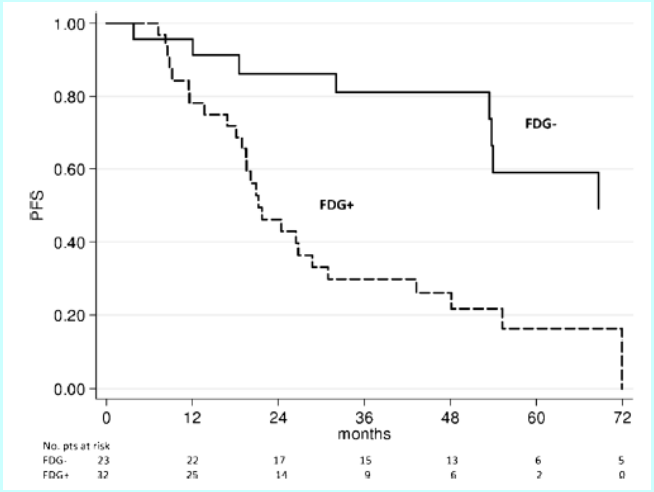


Eur J Nucl Med Mol Imaging (2017) 44:490–499
DOI 10.1007/s00259-016-3533-z

ORIGINAL ARTICLE

Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with ^{177}Lu-D OTATATE

Maddalena Sansovini[1] · Stefano Severi[1] · Annarita Ianniello[1] · Silvia Nicolini[1] · Lorenzo Fantini[1] · Emilio Mezzenga[2] · Fabio Ferroni[3] · Emanuela Scarpi[4] · Manuela Monti[4] · Alberto Bongiovanni[5] · Sara Cingarlini[6] · Chiara Maria Grana[7] · Lisa Bodei[7] · Giovanni Paganelli[1]



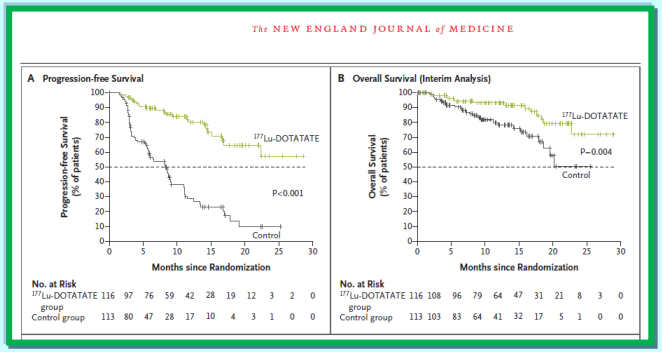
Cosa abbiamo imparato in 20 aa di Trial Clinici di PRRT

EFFICACIA

- ✓ Tumor shrinkage
- ✓ Miglioramento sintomi e QoL
- ✓ Ruduzione marcatore
- ✓ Impatto sulla SV

Currently mostly used:

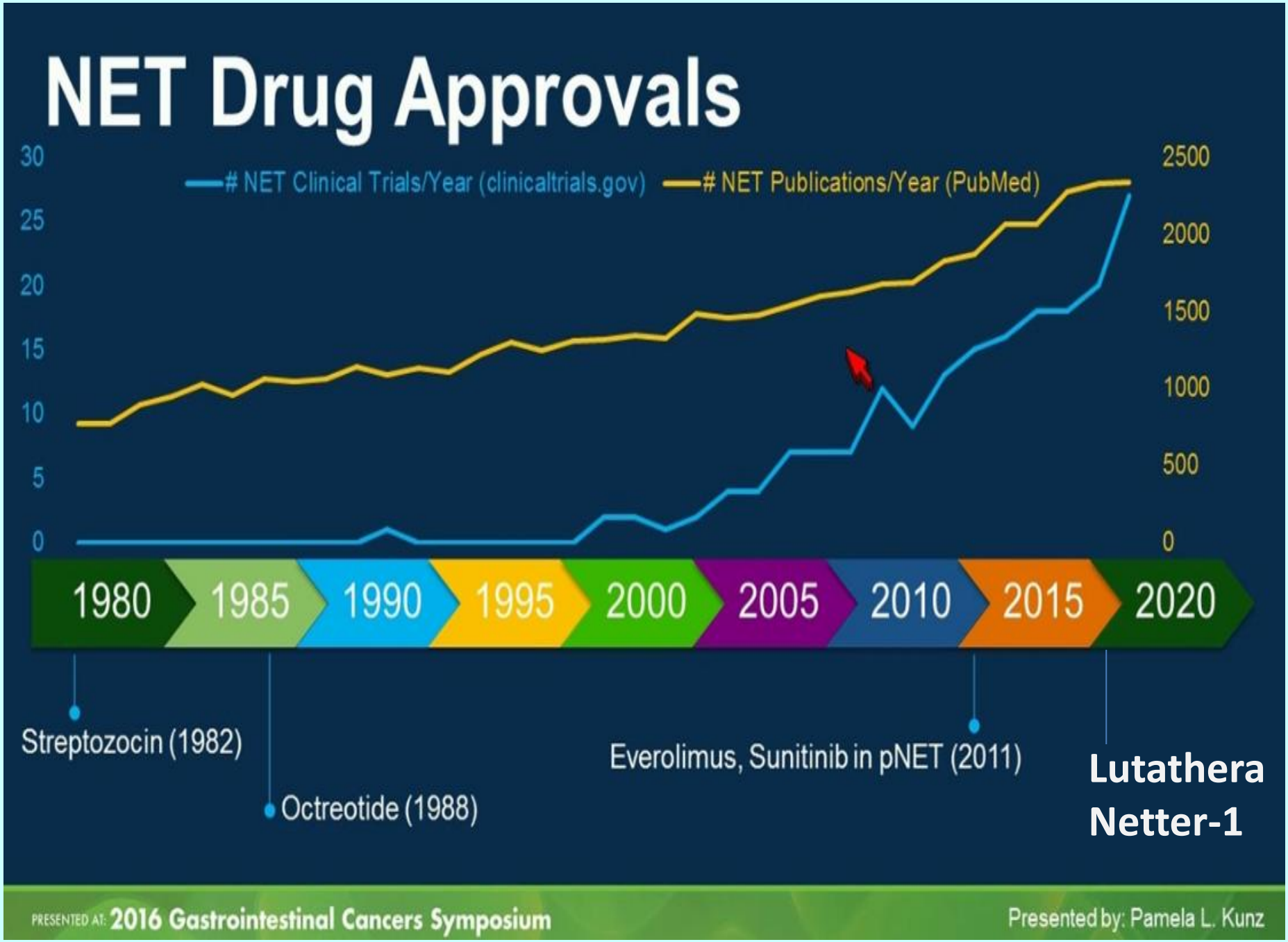
^{177}Lu-DOTATATE

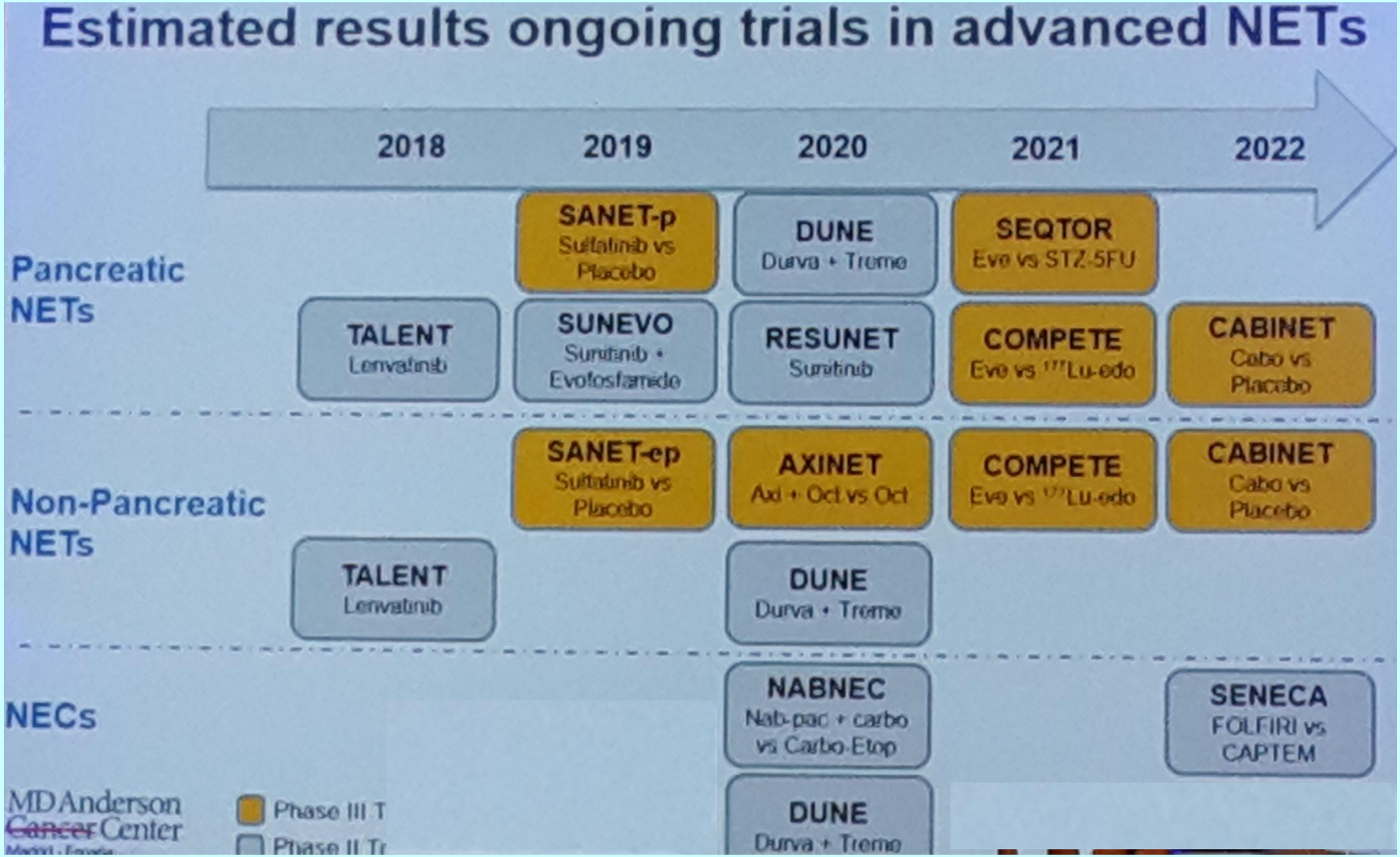


TOLLERABILITA'

- ✓ Generalmente ben tollerata
- ✓ Generalmente effetti collaterali acuti minimi:
  - AA-correlati: nausea, vomito
  - PRRT-correlati: astenia, ricambio capelli (Lu-tate), rara esacerbazione sdr
- ✓ Effetti cronici e permanenti (rene, BM)
  - Generalmente lievi se opportune precauzioni

Kwekkeboom DJ et al. JNM 2005
Bodei L et al. Eur J Nucl Med Mol Imaging 2004
Bodei et al. J Endocrinol Invest 2009
Kwekkeboom DJ et al. Endocrine Rel Cancer 2010
Brans B et al. Eur J Nucl Med 2007
Cremonesi M et al. Q J Nucl Med Mol Imaging 2011


NET Drug Approvals
NET Clinical Trials/Year (clinicaltrials.gov)
NET Publications/Year (PubMed)
30
25
20
15
10
5
0
2500
2000
1500
1000
500
0
1980
1985
1990
1995
2000
2005
2010
2015
2020
Streptozocin (1982)
Octreotide (1988)
Everolimus, Sunitinib in pNET (2011)
Lutathera
Netter-1
PRESENTED AT: 2016 Gastrointestinal Cancers Symposium
Presented by: Pamela L. Kunz



Courtesy of ENETS

NETTER-1: Quality of Life

		^{177}Lu arm Av. % of pts	60mg Oct arm Av. % of pts	Comments
Global Health Status	Improvement	28%	15%	Statistically significant improvement in ^{177}Lu arm
	Worsening	18%	26%	
Diarrhea	Improvement	39%	23%	Statistically significant improvement in ^{177}Lu arm
	Worsening	19%	23%	
Pain	Improvement	41%	28%	Trend towards improvement in ^{177}Lu arm not statistically significant
	Worsening	17%	25%	
Flushing	Improvement	42%	38%	Improvement in both arms with no clear advantage in ^{177}Lu arm
	Worsening	22%	19%	

- Benefit in important domains associated with ^{177}Lu treatment Vs. HD octreotide.
- Confirmed treatment value of ^{177}Lu on patient QoL, in addition to the meaningful increase in PFS already reported.

Strosberg J et al. JNM 2017 Abs.

Controllo dei sintomi, post PRRT con Lu-177-DOTATATE

NET type	Schedule	Pts	Symptom	Concomitant SSA	Symptomatic Response	Author
All NETs	22.2-29.6 GBq	111	Diarrhea	62%	67%	Khan S 2011
All NETs	31 GBq + 5FU	10	Diarrhea, flushing, pain	n.a.	9/10	Kong G 2014
P-NETs	28.2 GBq	68	Fatigue, pain, nausea	36%	Significant improvement	Marinova M 2017

Significant symptomatic improvement regardless of the objective response

Efficacy of ^{177}Lu-DOTATATE in **P-NETs** Non-controlled studies

Schedule	Pts	Best response	PFS	TTP	OS	Authors
25.5 GBq (5 cycles, normal pts; 18 GBq in risk pts)	52	29% PR+CR	-	36 mo	-	Sansovini 2013
32 GBq in 4 cycles	68	60% PR	34 mo	-	-	Ezziddin 2014
22.2-29.6 GBq in 4 cycles	133	55% CR+PR	30 mo	31 mo	71 mo	Brabander 2017

PRRT with ^{177}Lu-DOTATATE is a favorable therapeutic option in patients with pancreatic NETs with objective responses and impact on survival parameters

Efficacy of ^{117}Lu-DOTATATE in **BP-NETs** Non-controlled studies

Schedule	Pts	Best response	PFS	TTP	OS	Authors
^{90}Y-DOTATOC (11 GBq); ^{177}Lu-DOTATATE (21GBq) ; ^{90}Y-TOC+^{177}Lu-TATE (7+13 GBq)	114	18% PR+MR 29% PR+MR 38% PR+MR	23 mo 31 mo 31 mo	-	46 mo >110 mo 61 mo	Mariniello 2015
27 GBq in 4 cycles	22	27% PR	27 mo	-	42 mo	Sabet 2017
22.2-29.6 GBq in 4 cycles	23	30% CR+PR	20 mo	25 mo	52 mo	Brabander 2017

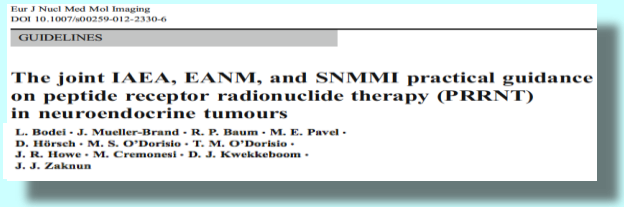
PRRT with ^{177}Lu-DOTATATE is a favorable therapeutic option in patients with broncho-pulmonary NETs with objective responses and impact on survival parameters

The IAEA – EANM - SNMMI Practical Guidance Document on PRRT in NETs

IAEA International Atomic Energy Agency

EANM European Association of Nuclear Medicine

SNMMI Society of Nuclear Medicine and Molecular Imaging


Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-012-2330-6

GUIDELINES

The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

L. Bodei · J. Mueller-Brand · R. P. Baum · M. E. Pavel · D. Hörsch · M. S. O'Dorisio · T. M. O'Dorisio · J. R. Howe · M. Cremonesi · D. J. Kwekkeboom · J. J. Zaknun

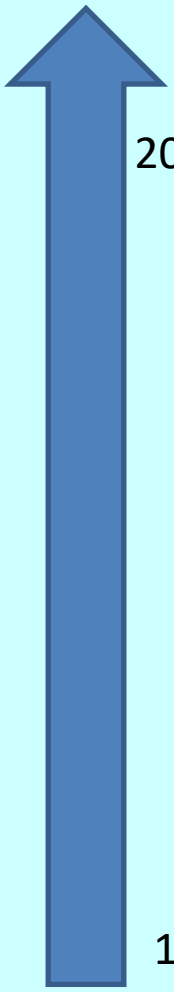
AIOM Associazione Italiana di Oncologia Medica

Single country guidelines

European ENETS Neuroendocrine Tumor Society

FDA (26 gennaio 2018)/EMA (29 settembre 2017) Approval: LUTATHERA® is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

E nei prossimi anni?



2015

Registration in BP NETs

New RCTs and other trials:

in GEP-NETs vs other STD of care (e.g. EVE)
in BP-NETs vs STD of care
PPGL, NB, liver mets, etc.

Validation of new strategies

Combinations with chemo or biologics or immunotherapies
Intra-arterial
New theranostics (SS-ANT, GLP-1R, GIP) and new isotopes (Sc-44-47, Cu-64-67, Tb-152/Tb-149)

Targeted Alpha Radiation Therapy

Personalization

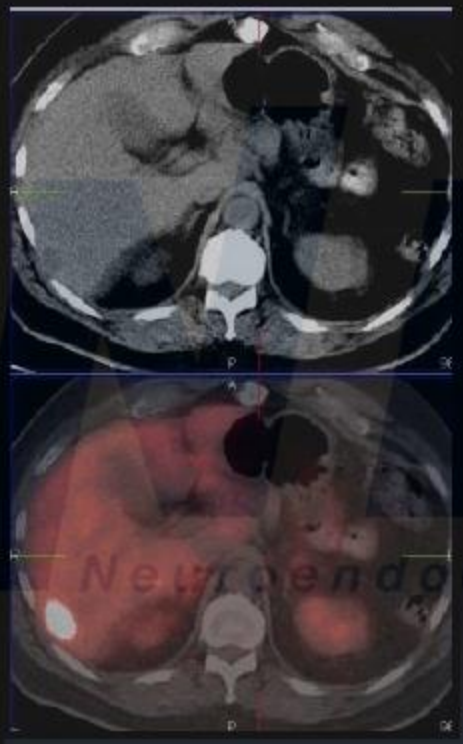
1994

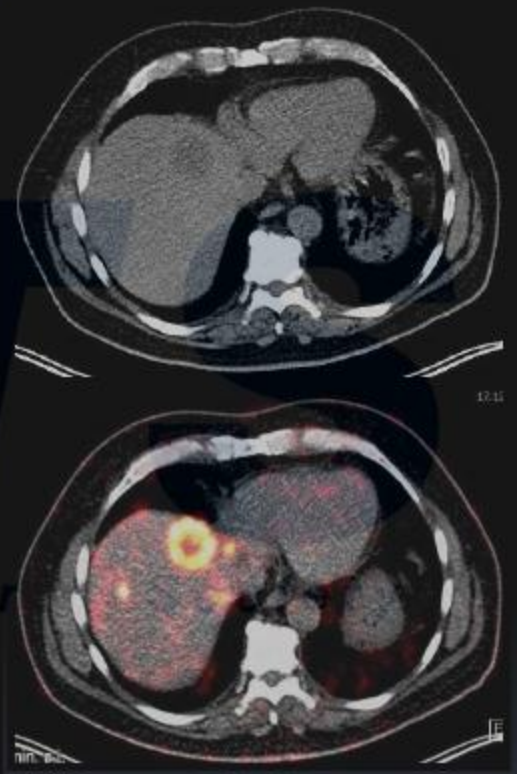
Based upon: risk factors FDG status, dosimetry

Personalisation of individual response and tolerability: (circulating NET transcripts)

The results of NETTER-1 registration trial has increased the utilization of PRRT in the NET tumor boards.

Ga-68 DOTATOC --- PET/CT --- Sc-44 DOTATOC





Personalized dosimetry and new isotopes

COMPETE study

^{177}Lu-Edotreotide (^{177}Lu-DOTATOC) vs. Everolimus in GEP-NETs

Prospective randomized Controlled Open-label Multicentre phase III study to evaluate efficacy and safety of Peptide Receptor Radionuclide Therapy with ^{177}Lu-edotreotide compared to targetedd molecular therapy with Everolimus in patients with inoperable, progressive, somatostatin receptor-positive gastro-entero-pancreatic neuroendocrine tumors

STARTED RECRUITING IN EUROPE

TO BE STARTED SOON IN THE US

Peptide Receptor Radionuclide Therapy (PRRT) in Gastroenteropancreatic Grade 3 Neuroendocrine Neoplasms: A Retrospective International Multicenter Study

Skovgaard D[A], Fazio N[B], Granberg D[C], Grozinsky-Glasberg S[D], Ahmadzadehfar H[E], Zandee W[F], Ćwikła J[G], Walter M[H], Ringe A[I], Frilling A[J], Grana C[B], Horbye H[K];
[A]Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet Copenhagen, Denmark, Copenhagen, Denmark
[B]Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milan, Italy
[C]Department of Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden
[D]Neuroendocrine Tumor Unit, Endocrinology & Metabolism Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[E]Department of Nuclear Medicine, University Hospital Bo
[F]Department of Internal Medicine, Erasmus MC, Rotterd
[G]Postgraduate Medical Centre and Central Clinical Hosp
[H]Nuclear Medicine Service, University Hospital Geneva,
[I]Department of Gastroenterology and Endocrinology Ph
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Introduction: Gastroenteropancreatic (GEP) grade 3 neuroendocrine neoplasms (NEN G3) are rare, highly malignant neoplasms with poor prognosis and limited therapeutic options. Median survival following chemotherapy is only 10-12 months. **Aim(s):** Our aim was to assess the outcome after peptide receptor radionuclide therapy (PRRT) in patients with GEP NEN G3. **Materials and methods:** In a retrospective international multicenter study we analyzed the outcome of PRRT in patients with GEP NEN G3, defined as Ki67>20%. Using Kaplan-Meier estimation, Progression Free Survival (PFS) and overall survival (OS) were calculated. **Results:** 149 pts were included (primary tumor: pancreatic n=88, other GI n=34, unknown primary n=27), 147 with metastatic disease. 98 pts fulfilled the planned protocol (median 20.48 GBq). The main reason for not completing PRRT was progressive disease (n=19). PRRT was mainly given as 2-line (n=62) or later line of treatment (n=47). Of 114 pts that were evaluable by RECIST, 48 (42%) experienced complete or partial response, 43 (38%) stable disease and 23 (20%) progressive disease. Median follow up was 34 m (0-210); 107 pts died. PFS was 14 m and OS was 29 m for all pts. There was a difference in PFS (16 vs. 5 m; p<0.001) and OS (31 vs. 8 m; p<0.001) in pts with Ki67 below (n=126) or above (n=22) 55%. Similarly, there was a difference in PFS (8 vs. 18 vs. 19 m; p=0.032) and OS (19 vs. 42 vs. 44 m; p<0.001) for pts with poorly (n= 62), intermediate (n=9), and well-differentiated tumors (n=60). **Conclusion:** This large multicenter study demonstrates promising results regarding tumor response, PFS and OS after PRRT in patients with GEP NEN G3. Based on these results, PRRT might become a relevant treatment option for these patients. **Keywords:** neuroendocrine neoplasms, who grade 3, prrt, progression-free survival, overall survival

Retrospettivo
Multicentrico
G3
PRRT

Combinations with Chemo or Biologics

Schedule	Pts	CR	PR	DCR	PD at baseline	Response criteria	Outcome (PFS/TTP)
Lu-PRRT+ CAP, Claringbold 2011	33 GEP	0%	24%	94%	100%	RECIST	Median PFS not reached
Lu-PRRT+ CAPTEM Claringbold 2012	33 GEP	16%	41%	94%	100%	RECIST	PFS 31 m
Lu-PRRT + EVE Claringbold 2015	16 GEP	0%	44%	94%	100%	RECIST	n.a.

Adequately powered, prospective and rigorously analyzed studies are underway

New combinations with check point inhibitors planned in high grade NENs

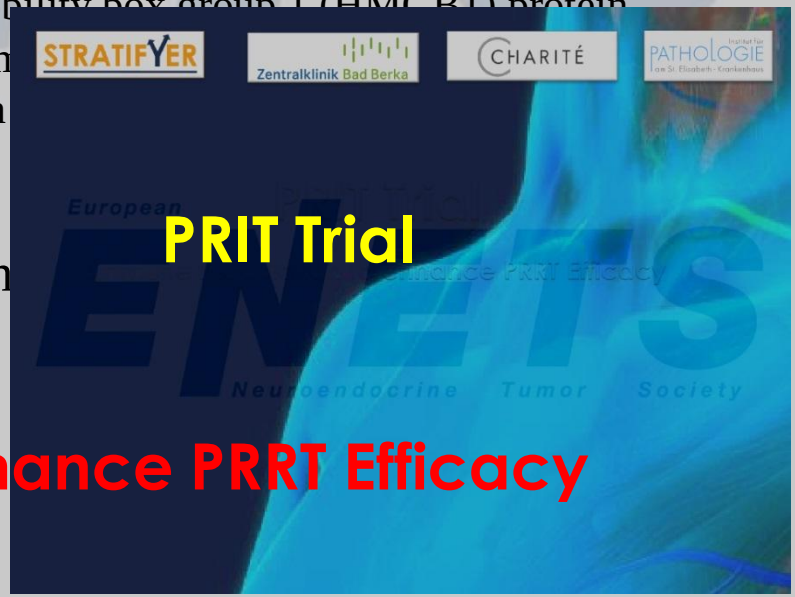
Bodei L et al. Sem Nucl Med 2016

PeptideRadioImmunoTherapy: PRIT
Endoradiotherapy + Immunotherapy

Immunomodulation by radiotherapy

Radiation therapy in combination with immunotherapeutic approaches has synergistic efficacy:

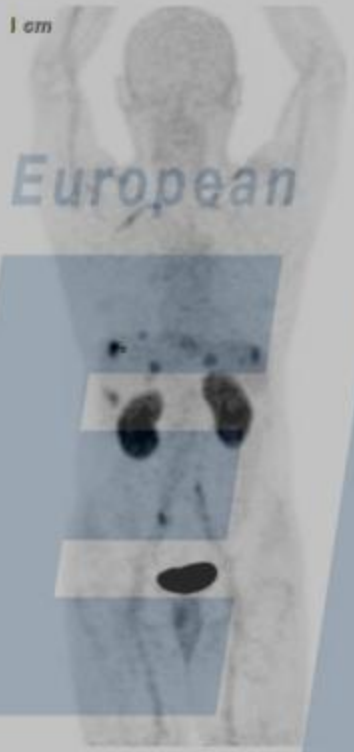
- **radiation induced tumor cell death**
  - increased supply of tumor specific antigens for presentation / cross presentation by antigen presenting cells
  - leads to the release of signal molecules like high mobility box group 1 (HMGB1) protein that attrack immune cells to the tumor microenvironm
    dendritic cells resulted in efficient cross-presentation
- **radiation increased the expression of MHC**
  among other cell surface proteins leading to in
  T cell mediated lysis.



Immune Modulation to enhance PRRT Efficacy

Courtesy: Patricia Grabowski

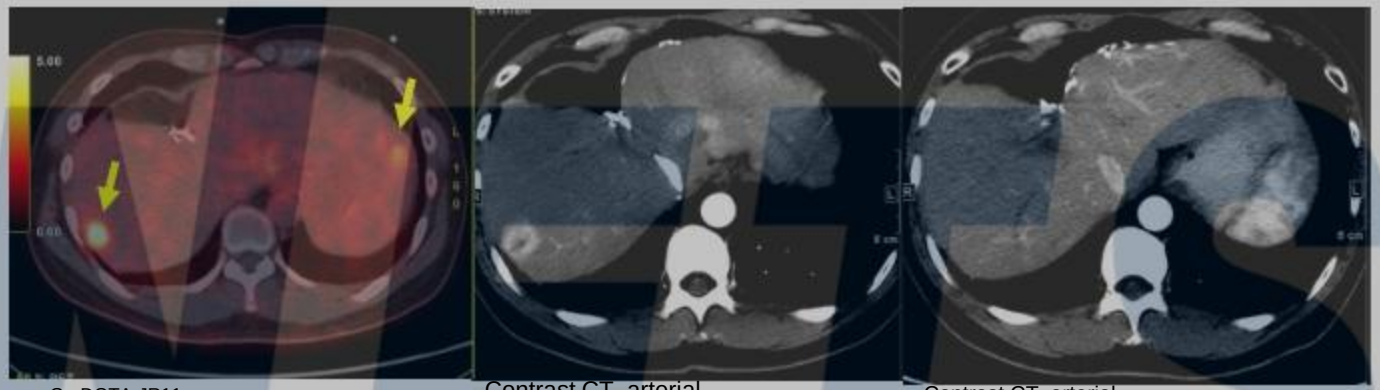
PRRT with SSR-ANTAGONISTS ^{177}Lu-DOTA-JR11 in NETs → OPS101 trial



^{68}Ga-DOTA-JR11
60 min p.i. (MIP)

Baseline

Follow up



^{68}Ga-DOTA-JR11
fused transaxial image

Contrast CT, arterial phase

Contrast CT, arterial phase

Complete response!

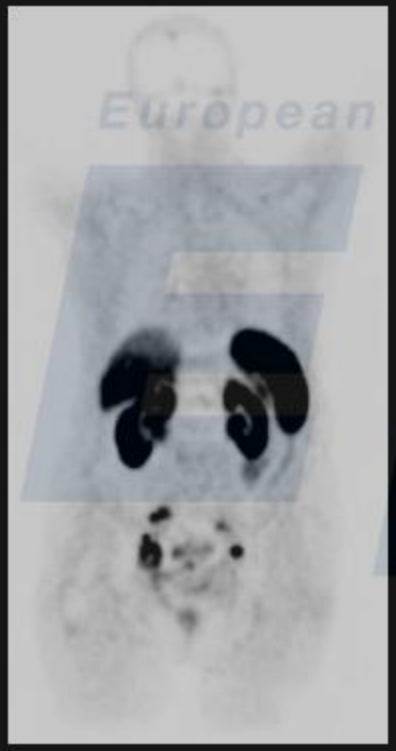
- 20 heavily pretreated pts: 10 completed 2 cycles, 10 had 1 cycle
- After only 1 cycle, evaluable pts had (RECIST 1.1):
  - PR in 7/19 (37%), SD in 9/19 (47%), PD in 3/19 (16%)
- Prolonged but reversible G3/4 toxicity in 4/10 pts treated with 2 full dose cycles
- Favorable response justifies continuation

Weber W, Bodei L. et al. 2015-17

Comparison of ^{177}Lu-DOTATATE and ^{177}Lu-DOTA-JR11 dosimetry

Patient with NEC (G3) of the bladder with lymphnode and uterus metastases, shows progression after surgery and treatment with Somatostatin analogues

^{68}Ga-DOTA-TATE PET



Limited kidney function
Creatinine clearence: 54 ml/min
(norm 90 – 179 ml/min)

^{177}Lu-DOTA-TATE (Agonist)

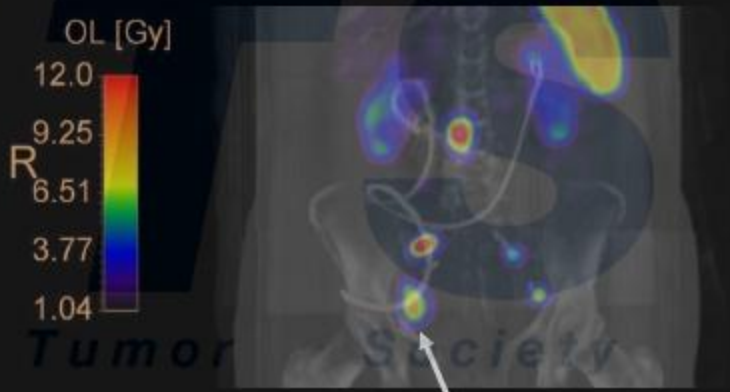
Isodose curves based on 3D voxel dosimetry analysis

mean dose: 1.4 Gy/GBq
Tumor-to-kidney dose ratio: 1.1

sst$_2$ affinity profile(IC$_{50}$)
0.7 ± 0.15 nM

^{177}Lu-DOTA-JR11 (Antagonist)

Isodose curves based on 3D voxel dosimetry analysis



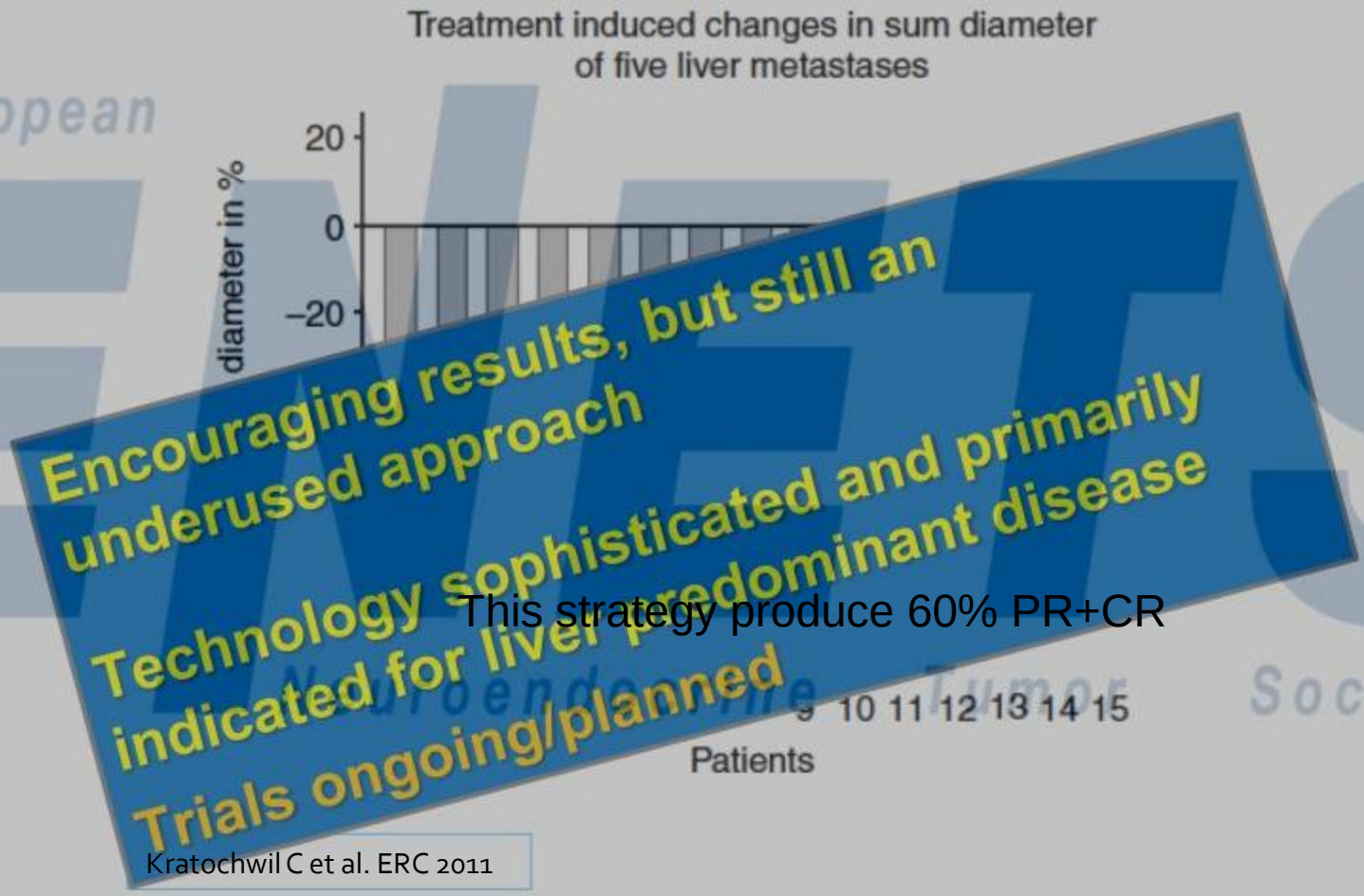
mean dose: 5.7 Gy/GBq
Tumor-to-kidney dose ratio: 2.5

sst$_2$ affinity profile(IC$_{50}$)
1.5 ± 0.4 nM

UNIVERSITÄTS KLINIKUM FREIBURG

Courtesy Damian Wild

Intra-arterial PRRT



Encouraging results, but still an underused approach

Technology sophisticated and primarily indicated for liver predominant disease

Trials ongoing/planned

This strategy produce 60% PR+CR

Kratochwil C et al. ERC 2011

Altro ruolo dei radionuclidi:
SIRT prior PRRT/MIBG

International Multicentre Retrospective Study on the Safety of Radioembolization with Yttrium-90 Resin Microspheres after Systemic Radionuclide Therapy in Neuroendocrine Tumors

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[B]MD Anderson Cancer Center, Houston, TX USA
[C]University Hospital Bonn, Bonn, Germany
[D]Vanderbilt University, Nashville, TN, USA
[E]University Hospital Leuven, Leuven, Belgium
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[H]Stanford University, Palo Alto, CA, USA

Introduction: In the treatment metastatic neuroendocrine tumors (mNET) safety concerns exist when treating patients with radioembolization (RE) after prior systemic radionuclide therapy (SRT) **Aim(s):** The aim of this study was to assess safety and efficacy of yttrium-90 resin microspheres RE in mNET after prior systemic radionuclide therapies (SRT). **Materials and methods:** Patients treated with SRT before RE and with at least baseline and follow-up CT/MRI imaging after 3 months were included. Clinical, laboratory, and imaging parameters were retrospectively collected. Efficacy was based on imaging response according to RECIST 1.1 (liver-only) and clinical response. Biochemical toxicity data was based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03. **Results:** 44 patients received SRT prior to 58 RE procedures. One patient received M131IBG only, 3 patients 90Y-PRRT only, 31 patients 177Lu-PRRT only and 9 patients a combination of different SRT compounds. Median cumulative activity administered during prior SRT was 30.4 GBq (10–61.6 GBq) in a median of 4 cycles (2-9). Median interval between SRT and RE was 353 days. Median activity administered during RE was 1.67 GBq (range 0.4–5.5 GBq). RE resulted in CR 2%, PR 14%, SD 75%, and PD 9% according to RECIST 1.1. New grade 3-4 laboratory toxicities were limited in these heavily pre-treated patients; lymphocytopenia in 10% and others <5%. Improvement and resolution of symptoms in symptomatic patients occurred in 30% and 35%, respectively. Adverse events within 3 months were mainly abdominal pain (27%), nausea (20%) and vomiting (16%). Radioembolization induced liver disease occurred in 1 patient and radiation pneumonitis in 1 patient. **Conclusion:** Yttrium-90 resin microspheres RE in mNET after SRT is safe and effective. **Keywords:** prrt, radioembolization,

Trattamento combinato: ^{90}Y-DOTATATE e ^{177}Lu-DOTATATE

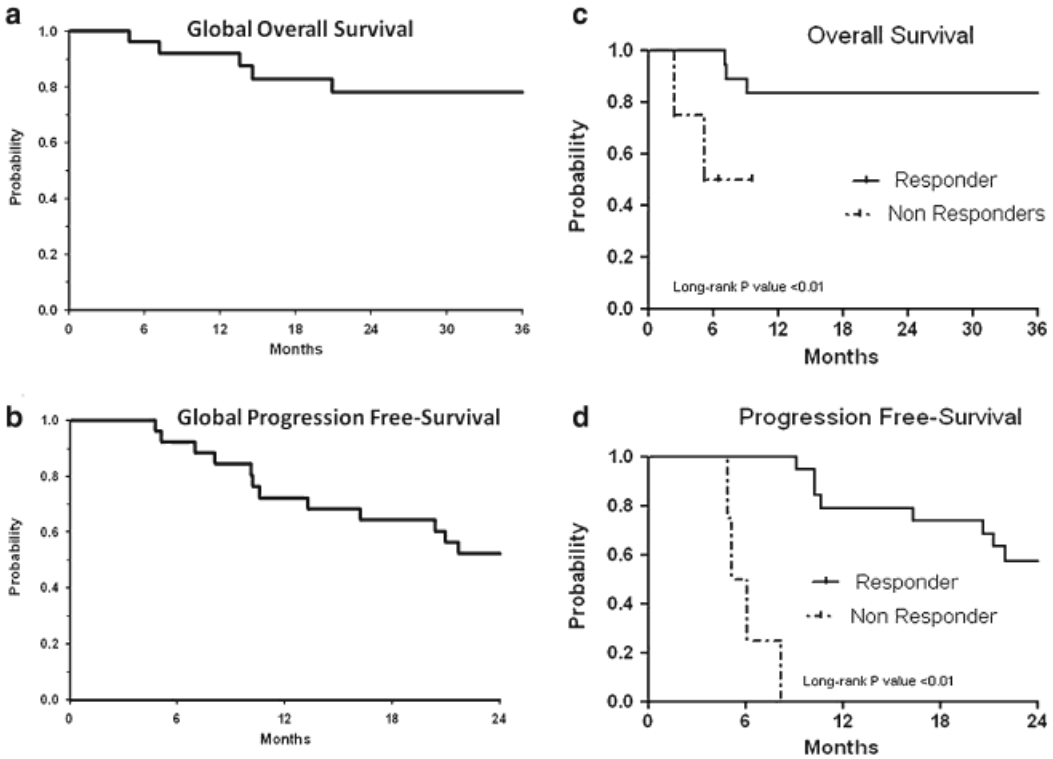
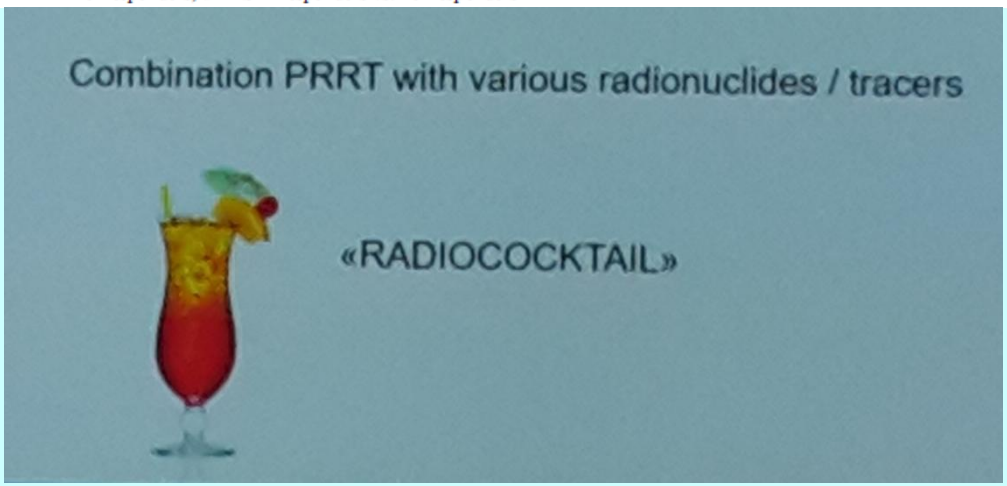


Fig. 3 Survival parameters: a global OS (estimated 78. 1 % at 24 months), b global PFS (estimated 52.2 % at 24 months), c OS in responders vs. nonresponders, d PFS in responders vs. nonresponders

OS a 24 m: 78.1%

PFS: 25.0 m
PFS a 24 m: 52.2%



Eur J Nucl Med Mol Imaging (2014) 41:223–230
DOI 10.1007/s00259-013-2578-5

ORIGINAL ARTICLE

Treatment with tandem [^{90}Y]DOTA-TATE and [^{177}Lu] DOTA-TATE of neuroendocrine tumours refractory to conventional therapy

E. Seregni · M. Maccauro · C. Chiesa · L. Mariani · C. Pascali · V. Mazzaferro · F. De Braud · R. Buzzoni · M. Milione · A. Lorenzoni · A. Bogni · A. Coliva · S. Lo Vullo · E. Bombardieri

213 Bi and Ac 225 DOTATOC Receptor Labeled Targeted Alpha-Radionuclide Therapy in Neuroendocrine Tumors Refractory to Beta Radiation - Early Experience

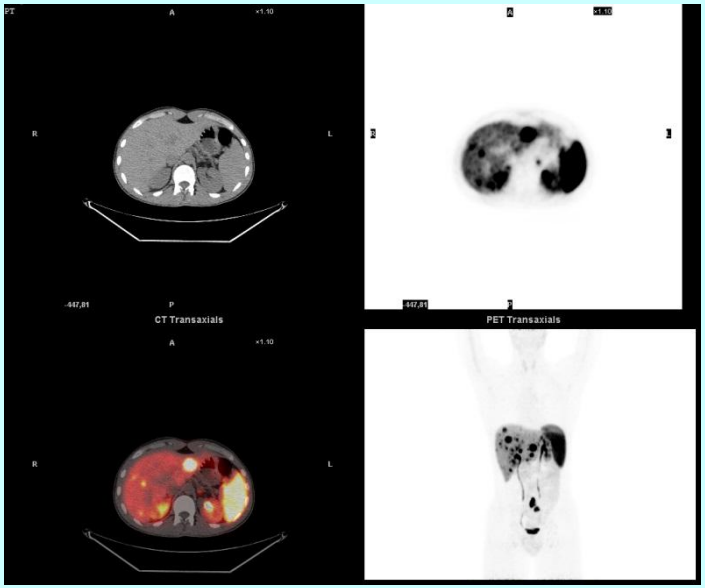
Dureja S[A], Sen I[B], Pant V[C], Thak P[C];
[A]Carcinoid Neuroendocrine Tumor Society India, New Delhi, India
[B]Fortis Memorial Research Institute, Delhi-NCR, india
[C]Fortis Memorial Research Institute, Delhi-NCR, India

Targeted Alpha Therapy

Introduction: Radiopeptide therapy using a somatostatin analogue labeled with alpha emitters Actinium 225 and Bismuth 213 DOTATOC is a novel therapeutic option in metastatic neuroendocrine tumors (NET), with few alternative therapeutic options for patients with beta refractory disease. We report the first experience with 213Bi and Ac225 DOTATOC targeted alpha therapy (TAT) in treatment of well differentiated metastatic NETs at a tertiary care hospital in India. **Aim(s):** To assess safety and efficacy of alpha emitter labeled somatostatin analogue therapy in well differentiated NETs To evaluate radiological response and its correlation with clinical parameters. **Materials and methods:** Ten patients with progressive metastatic neuroendocrine tumors, refractory to 177Lu-DOTATATE therapy were treated with 1-2 cycles (average 1.2) of 213Bi or Ac225 labeled DOTATOC, with two patients receiving intraarterial infusion of 213Bi-DOTATOC for extensive liver disease. Haematological, hepatic, renal and endocrine toxicities were assessed according to CTCAE criteria. Radiological response was assessed on 68Ga-DOTANOC-PET imaging 8 weeks post therapy. **Results:** The biodistribution of 213Bi-DOTATOC was evaluated with 440 keV gamma emission scans, and demonstrated specific tumor binding. Non progression of disease (stable disease/partial response) was seen on response assessment PET CT scans done in 60% of treated patients with upto 40% reduction of target tumor volume seen post therapy. Grade 1 to 2 hematological toxicity was seen. No grade 3 or 4 toxicity was seen, warranting active intervention. **Conclusion:** TAT can induce early response in tumors refractory to beta radiation with favourable acute toxicity profile at therapeutic doses. Long term toxicity and progression free survival analyses are ongoing. **Keywords:** targeted alpha

Caso clinico: midgut

Uomo, 37 aa; dolori addominali e flushing



→eco, TC: lesioni epatiche e piccoli linfonodi

→**Biopsia: mts da tumore NE,** Ki-67 4%.

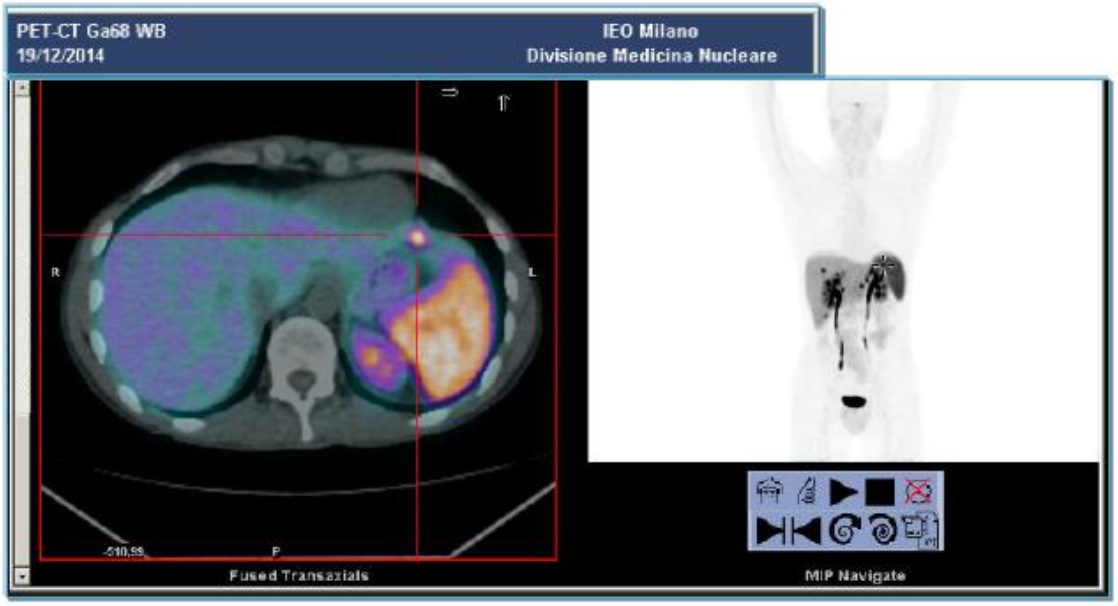
→**Ottobre 2008 Ga-68-DOTATOC PET/CT**:
Multiple lesioni epatiche, sst2-5 + ln e intestino

→ **SSA**

→**Gennaio 2009 resezione ileale: tumore NE** Ki-67: 5%N+

→ **PRRT alternata a TAE**

→ **PR e poi SD, marzo 2018 ultimo controllo**

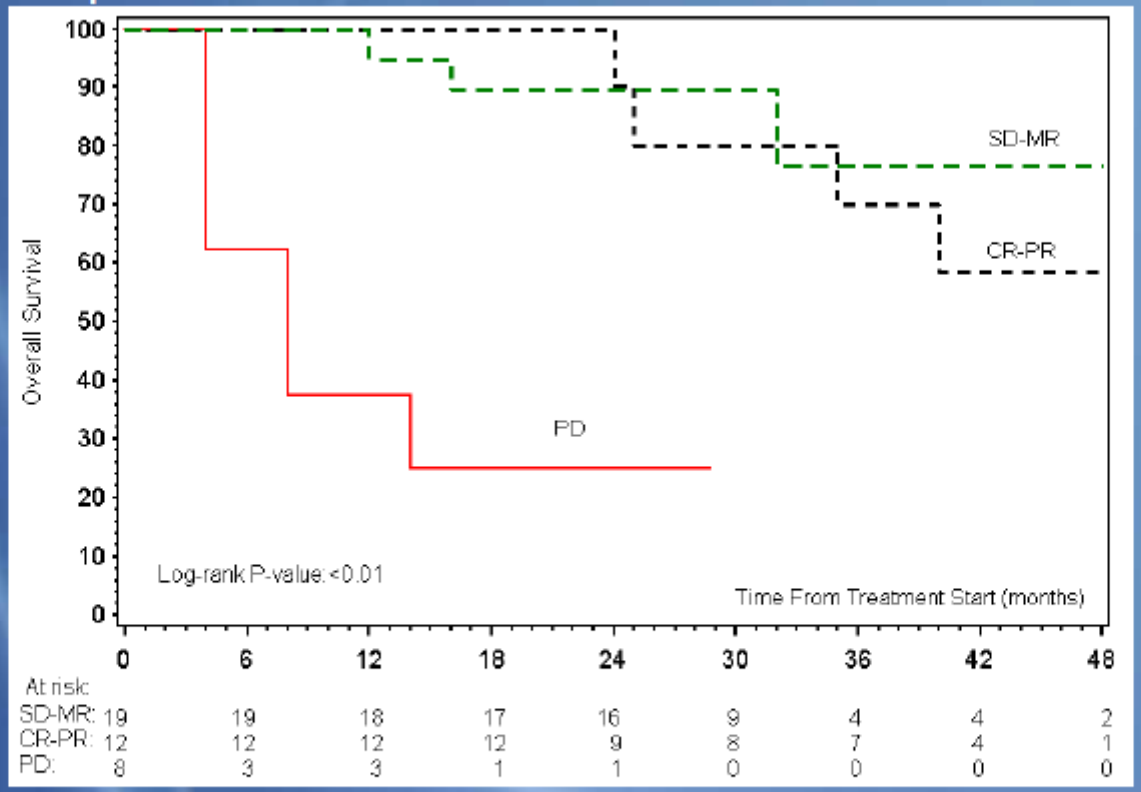


Follow up, 2014 and 2016

Nel follow up: PET/CT con Ga-68-DOTATOC? TC total-body? RM addome?

Quali criteri di risposta? Come dobbiamo considerare le risposte?

39 paz



Dal punto di vista prognostico, stabilizzazione e risposta obiettiva hanno la stessa probabilità di sopravvivenza

Bodei et al, Eur J Nucl Med Mol Imaging, 2011

KEY POINTS: 1

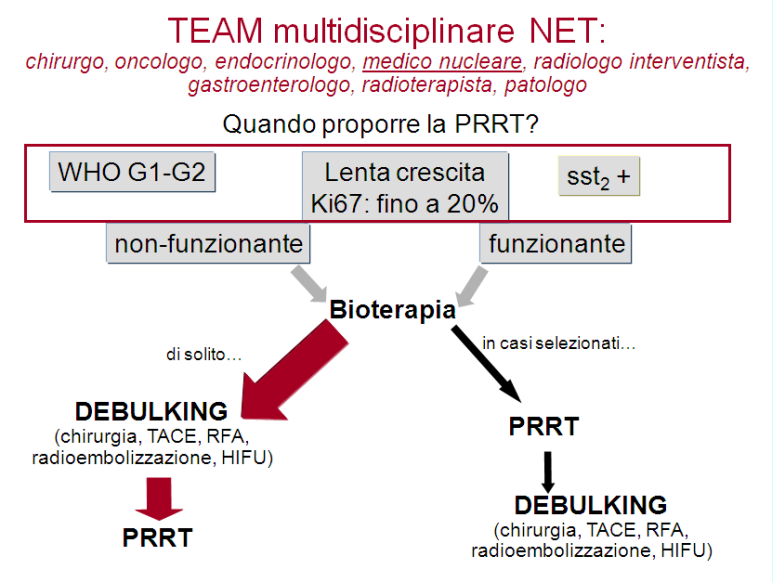
THE PATIENT:

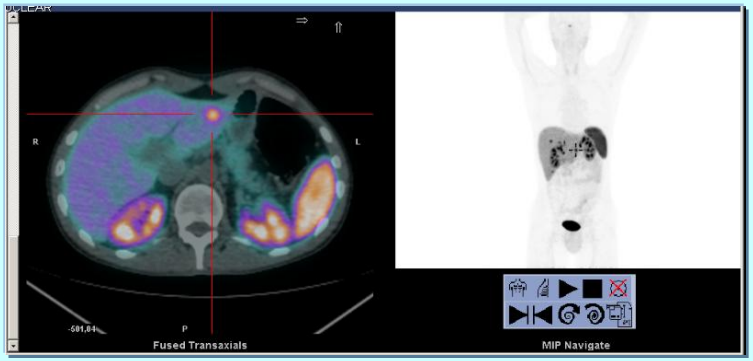
Neuroendocrine tumors and receptor evaluation IN VIVO

Morphological and functional imaging – staging

Patient's preference and convenience

Multidisciplinary tumor board to write a therapeutic path



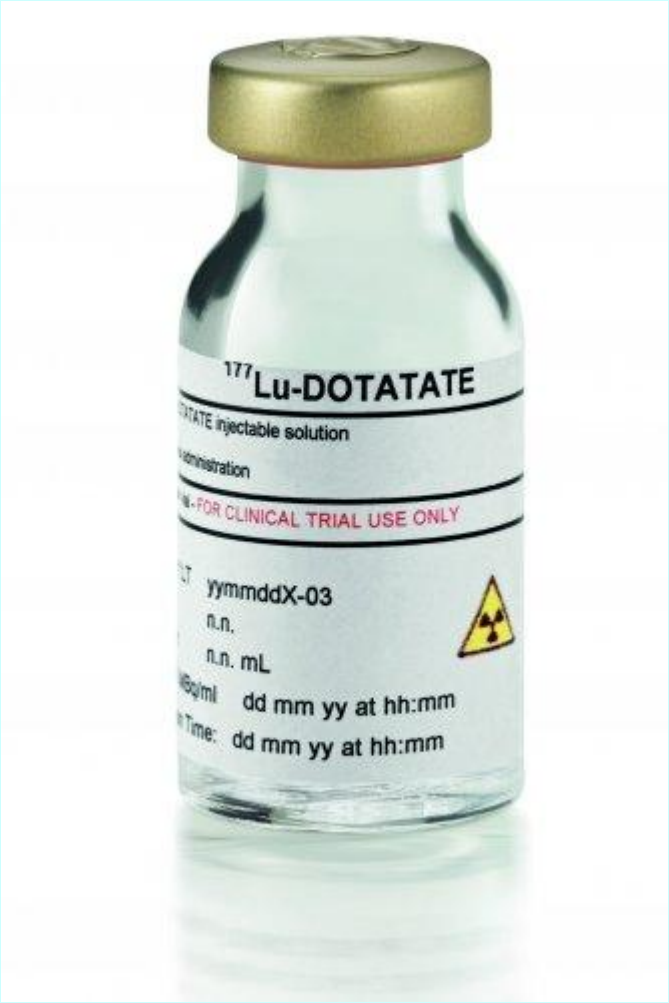


KEY POINTS: 2

PRRT:

- Clinical evaluation
- Lab examinations
- Syndrome control
- Radioprotection
- Follow up
- Is it available?

NEWS????



KEY POINTS: 3

FOLLOW UP:

- Clinical evaluation
- Lab examinations
- QoL
- Morphological and functional evaluation
- **Always discuss in a Multidisciplinary Tumor Board**

Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: Possible indications for a multimodal approach

Emilio Bertani, MD,[a] Nicola Fazio, MD,[b] Edoardo Botteri, PhD,[c] Antonio Chiappa, MD, FACS,[a] Massimo Falconi, MD,[d] Chiara Grana, MD,[c] Lisa Bodei, MD,[c] Davide Papis, MD,[a] Francesca Spada, MD,[b] Barbara Bazolli, MSc,[c] *and* Bruno Andreoni, MD,[a] *Milan and Ancona, Italy*

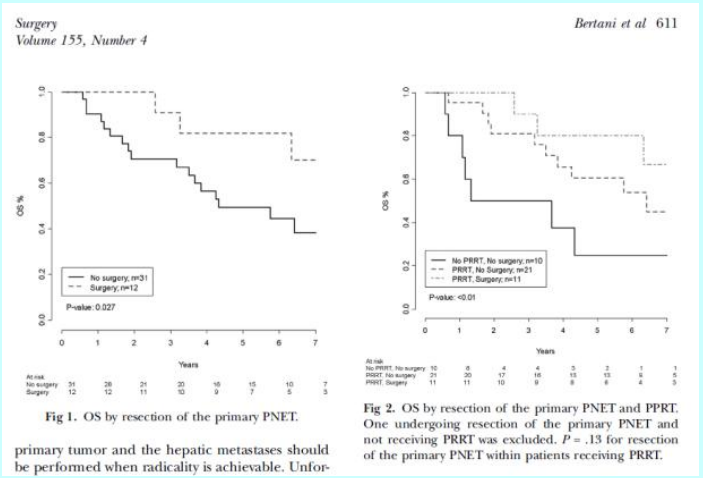


Fig 1. OS by resection of the primary PNET.

Fig 2. OS by resection of the primary PNET and PPRT. One undergoing resection of the primary PNET and not receiving PRRT was excluded. $P = .13$ for resection of the primary PNET within patients receiving PRRT.

primary tumor and the hepatic metastases should be performed when radicality is achievable. Unfor-

→ New theranostic apporoaches, new modalities

Conclusions

Theranostics, particularly of SSR, are the mostly utilized paradigm in NET diagnosis and therapy; new isotopes (alpha, theranostic pairs)

Ga-SSA-PET/CT is the most accurate dg tool and is used in combination with morphological imaging

Novel peptides (antagonists) for dg and TH and molecular strategies are being developed (tandem PRRT, IA)

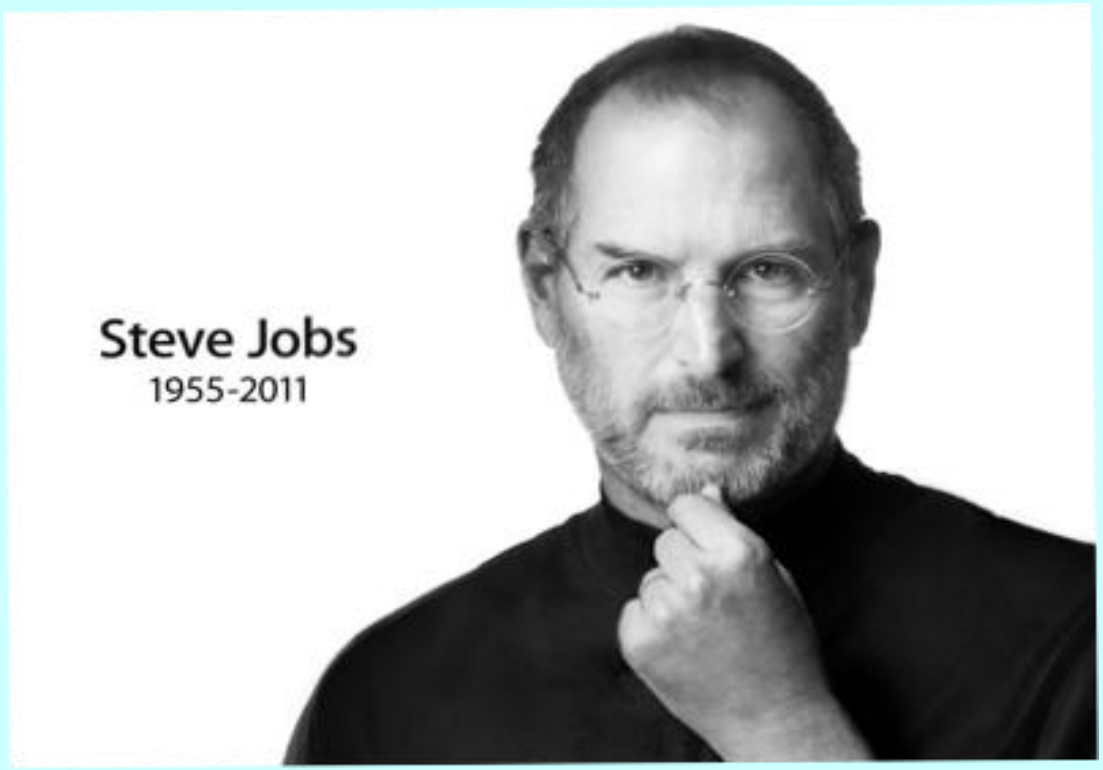
PRRT has been accepted in the clinical algorithms of the major scientific societies and is now approved for GEP

SI NETs: Lu demonstrated efficacy in a RCT

P NETs: Lu demonstrated efficacy in non controlled trials

Molecular genomics: required to predict and define efficacy and tolerability
in conjunction with imaging

New combinations (biol, CT, Immuno, SIRT, surgery)



Grazie per l'attenzione

Think different.

www.eanm.org

Present and Future of NET Management: "PRRT of NET".

Chiara M Grana
Nuclear Medicine Division
European Institute of Oncology
Milano, Italy