RADIO-LIGAND THERAPY NEI TUMORI NEUROENDOCRINI

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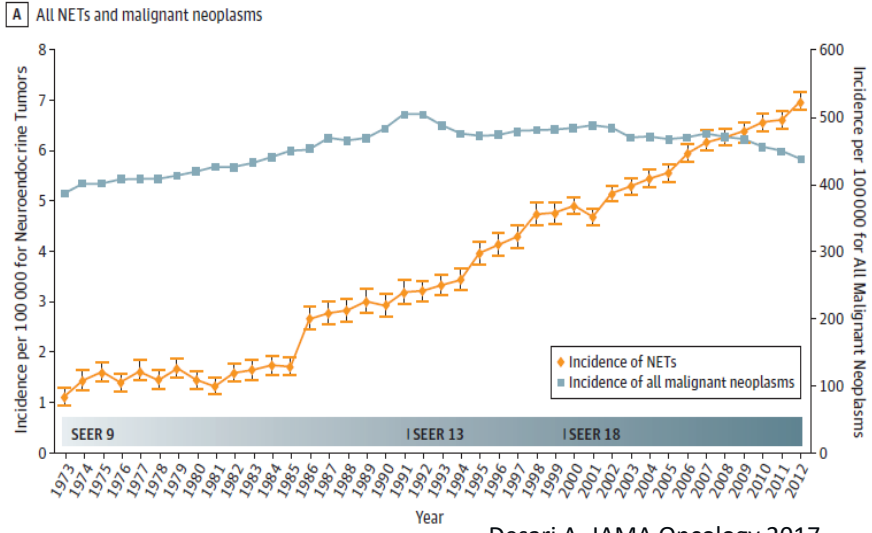
EPIDEMIOLOGY: RARE TUMOR

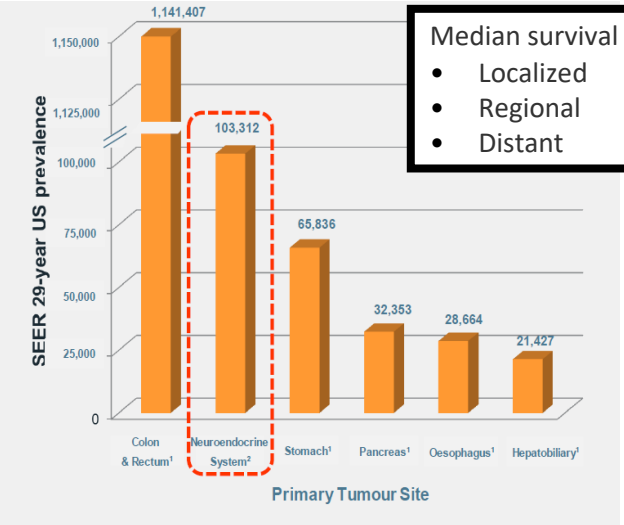
0.5% of all malignancies → NETs are considered rare

Incidence trends of NETs from 1973 to 2012



Desari A. JAMA Oncology 2017

NETs Are Second Most Prevalent Gastrointestinal Tumor



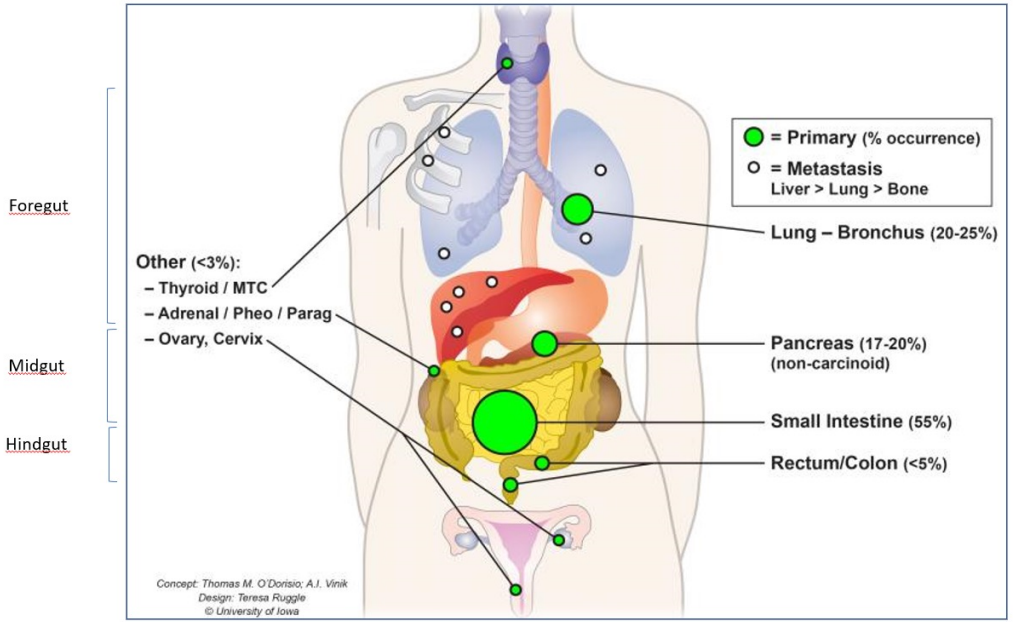
Median survival (1988 – 2004)

- Localized 203 months
- Regional 114 months
- Distant 39 months

Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072.
SEER Cancer Ststistics Review 1975-2004

PRIMARY SITE

Heterogeneous Neoplasms



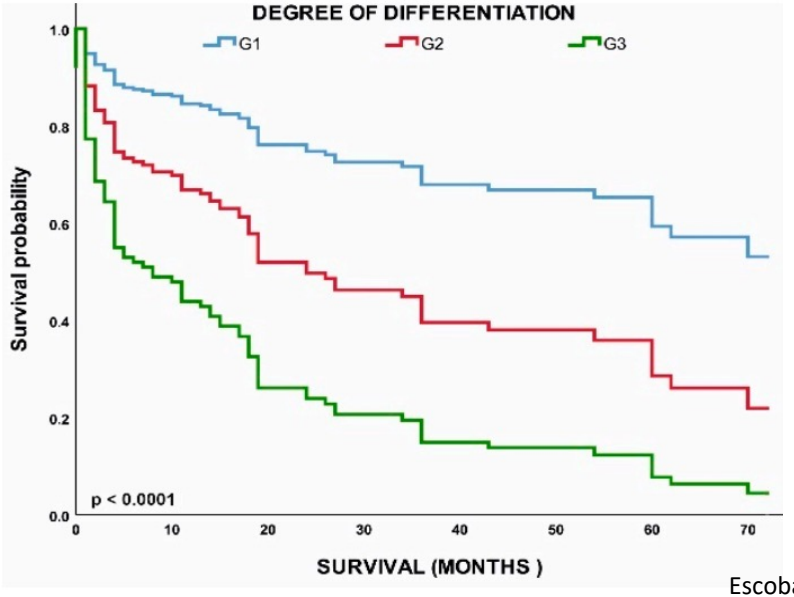
NEN CLASSIFICATION & GRADING

WHO 2017 Grading System

	Ki 67	
NETumor G1	≤2%	Well differentiated NET
NETumor G2	2-20%	
NETumor G3	>20%	
NECarcinoma	>20%	Poorly differentiated NEC

<55% less responsive to platinum
>55% more responsive (but still recurred quicker and worse survival)

Survival Patients By Tumor Grade



Escobar 2022

NEN CLASSIFICATION & FUNCTIONALITY

20 – 30% Functional NETs

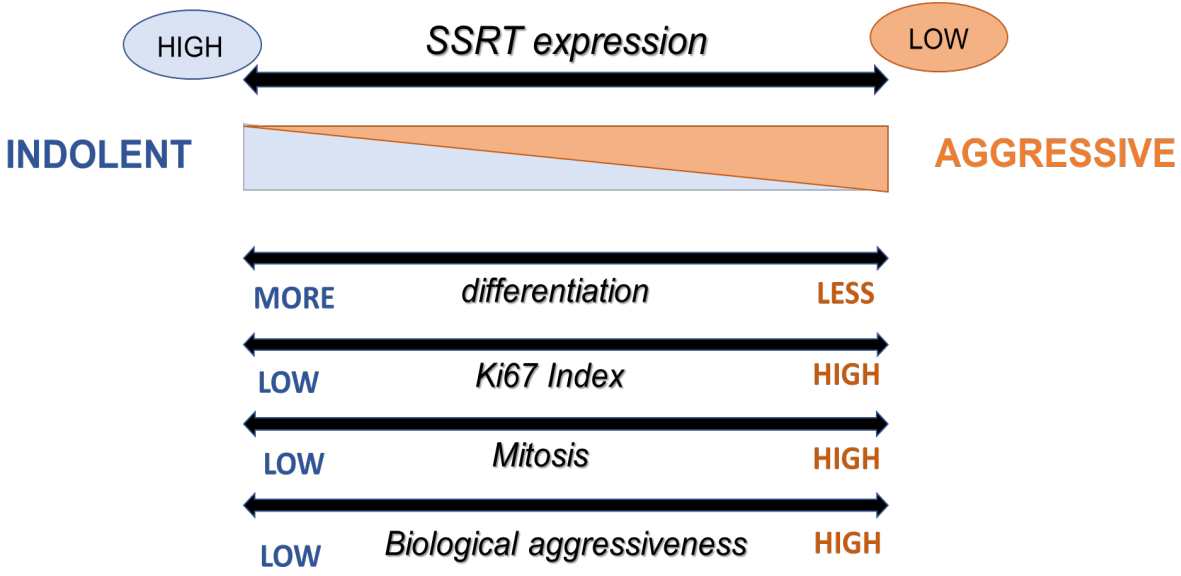
Secrete hormones / growth factors / neurotransmitters that lead to **typical clinical symptoms**:

- Diarrhoea, Flushing (Carcinoid Syndrome)
- Ulcer Symptoms
- Hypoglycaemia
- Wheezing, Bronchial Obstruction

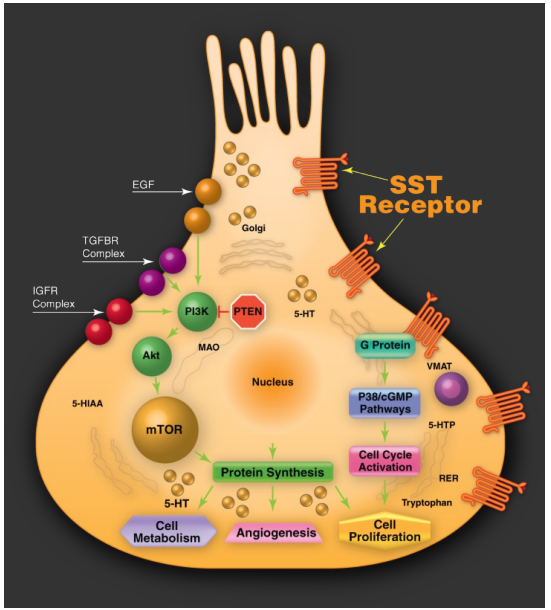
70 – 80% Non-functional NETs

- May be secretory (>50% secrete peptides or amines used as tumour markers)
- **No typical clinical symptoms**
- Often show **symptoms related to tumor progression or invasion** (late disease stages):
  - addominal pain
  - weight loss/anorressia
  - obstructive symptoms
  - jaundice

SSR EXPRESSION



Targeting SST receptors can provide symptom and disease control



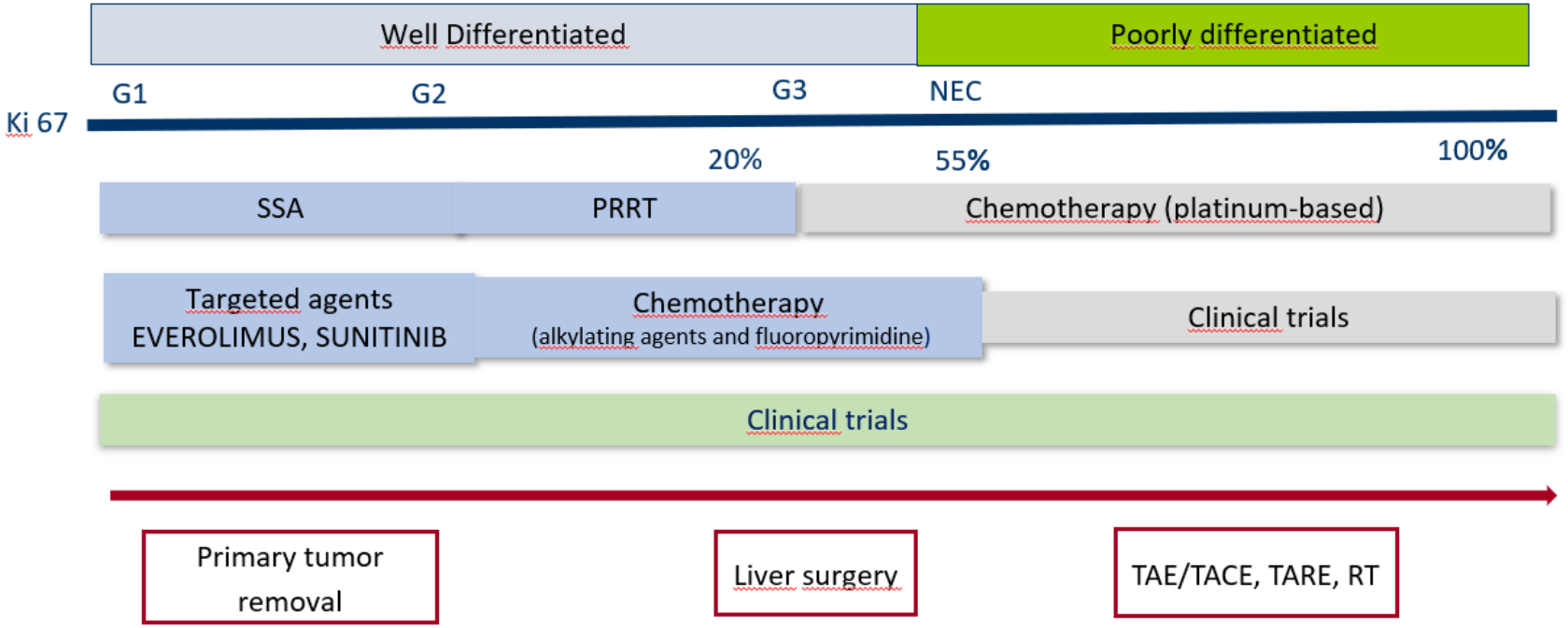
NEN TREATMENT

- The cornerstone of therapy is still SURGERY with curative intent, whenever possible. However, in the case of metastatic disease, total excision is generally not possible due to the infiltration of other tissues and/or blood vessels or the number of metastatic.
- SSAs (or interferon-α) may improve symptoms caused by hormonal excess or even lengthen the time to disease progression by offering hormonal and antiproliferative control over NETs, but rarely lead to partial or complete tumor response .
- Targeted Agents may improve symptoms and offer tumor response with disease stabilization.
- PRRT has long been considered as a palliative treatment for NETs, but is now attracting more and more attention as a very effective symptomatic and well-tolerated treatment prolonging progression-free (and possibly overall) survival.
- Systemic chemotherapy provides only modest benefit in rapidly proliferating tumors (grade 3).
- EBRT unfortunately is not effective for the treatment of metastasized and secondary cancer sites beyond the treatment area.

NEN TREATMENT

Patient	Disease	Aim of Treatment	Treatment availability
Age PS Comorbidity	Primary – Stage Grade –Ki67 SSr expression Functionality Liver dominant	Syndrome control Tumor growth control → Disease cronicization	Logistic Clinical Trials Regulatory AIFA

NEN TREATMENT



SSTR THERANOSTICS

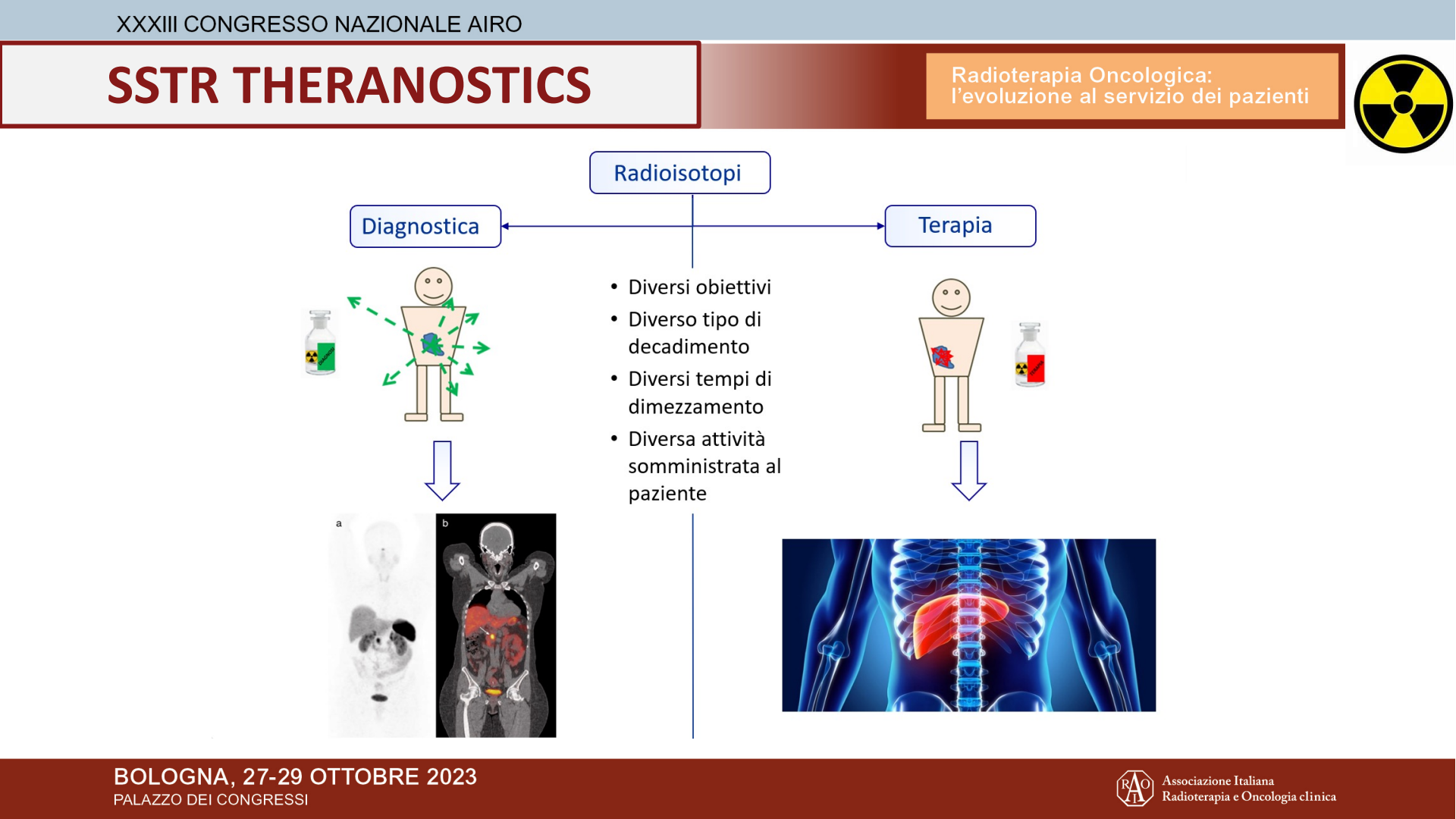
I radioisotopi utilizzati in diagnostica

- devono localizzarsi con la massima selettività possibile nell'organo/tessuto bersaglio.
- non devono emettere o il meno possibile particelle alfa o beta (per non sottoporre l'organismo a un inutile rischio da radiazioni)
- sono usati a concentrazioni molto basse e non ci si aspetta che abbiano alcun effetto farmacologico né rilevante tossicità biologica.

I radiofarmaci terapeutici

- sono molecole progettate per rilasciare dosi terapeutiche di radiazioni ionizzanti sotto forma di particelle alfa o beta a siti specifici (siti tumorali).
- dovrebbero essere in grado di accumularsi presso il sito malato fino a raggiungere una concentrazione tale da rilasciare una dose di radiazione citotossica per le cellule tumorali
- avere una rapida eliminazione (clearance) dal sangue e dagli altri organi per minimizzare i danni da radiazione ai tessuti normali.

SSTR THERANOSTICS



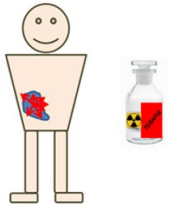
SSTR THERANOSTICS

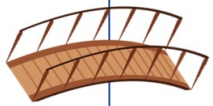
Radioisotopi

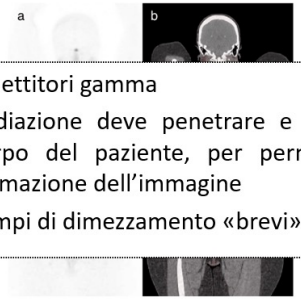
Diagnostica

Terapia

Teranostica







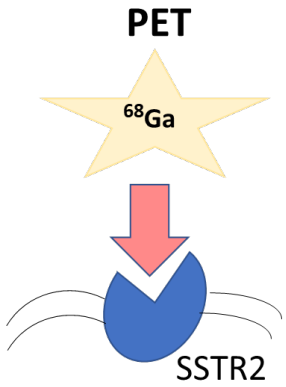
- Emettitori gamma
- Radiazione deve penetrare e uscire dal corpo del paziente, per permettere la formazione dell'immagine
- Tempi di dimezzamento «brevi»*

- Emettitori beta, alpha ed elettroni Auger, per irradiare volumi di tessuti di dimensioni multicellulari, cellulari o subcellulari
- Tempi di dimezzamento più lunghi (giorni, settimane)

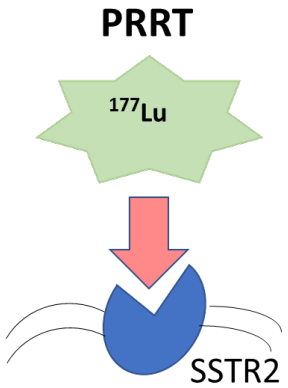
SSTR THERANOSTICS

THERANOSTICS is a combination of the terms **thera**peutics and diag**nostics**.

- one radioactive drug to identify (diagnose)
- a second radioactive drug to deliver therapy to treat the main tumor and any metastatic tumors.



Diagnostics



Therapy

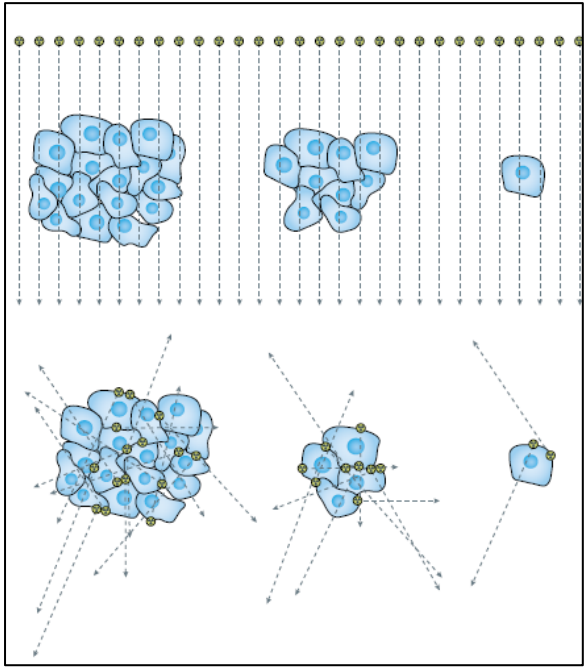
What you see is what you treat

Pene Crit Care Med 2009

SSTR THERANOSTICS

TUMOUR CELL IRRADIATION: RADIO-THERAPY VERSUS RADIO-PHARMACEUTICAL THERAPY

- La radiazione viene somministrata all'interno del corpo.
- Il trattamento è sistemico: è possibile raggiungere sia il sito del tumore primitivo, che metastasi a distanza (potenzialmente, anche se non note all'imaging).
- La radiazione è rilasciata alle cellule cancerogene o al loro micro-environment direttamente o attraverso veicoli che si legano specificatamente al target.
- By-stander or cross-fire effect: possibilità di danneggiare anche le cellule tumorali adiacenti al target anche se mancano dello specifico recettore o antigene.
- Confrontata con altre opzioni terapeutiche sistemiche, ha mostrato efficacia con tossicità minime.



Sgouros Nat Rev Drug Disc 2020

SSTR THERANOSTICS

PET con ^{18}FDG e con ^{68}Gallio

L'uso della PET con FDG nello studio delle neoplasie neuroendocrine serve per valutazione degli istotipi sdifferenziati o nella valutazione della differenziazione delle lesioni secondarie, in quanto le lesioni ben differenziate captano poco o nulla questo tracciante.
La perdita di differenziazione correla con l'uptake di FDG da un lato e con la perdita di uptake dei radiofarmaci marcati con Gallio-68 (fenomeno *flip-flop*).

SUVmax of ^{68}Ga-DOTATATE and ^{18}F-FDG According to Tumor Grade

	^{68}Ga-DOTATATE	^{18}F-FDG	*P*
All NET	16.9 (1.6–50)	4.2 (1.4–16.4)	.005
Low-grade NET Ki67 index ≤2%	29 (3.3–45)	2.9 (1.5–12)	<.001
Intermediate NET Ki67 index 3%–20%	15.5 (1.8–50)	10.5 (2.0–13.9)	NS
High-grade NET Ki67 index >20%	4.4 (1.6–8.9)	11.7 (4.1–16.4)	.03

SUVmax is the median SUVmax with range in parentheses.
SUVmax indicates maximum standardized uptake value; NET, neuroendocrine tumor; ^{68}Ga-DOTATATE, ^{68}Ga-DOTA-[SCAP]D[R]Phe^{1},Tyr^{3}-octreotate; ^{18}F-FDG, ^{18}F-Fluorodeoxyglucose.

Kayani Cancer 2008

SSTR THERANOSTICS

^{68}Ga-DOTA PET & ^{18}FDG PET

- Localizzazione tumore primitivo e stadiazione
- Monitoraggio della risposta ai trattamenti
- Valutazione stato recettoriale (i pazienti con elevata positività hanno una maggiore possibilità di risposta)
- Selezioni dei pazienti per PRRT

PRRT: Peptide Receptors Radiolabelled Therapy

PRRT o RLT

Le prime esperienze con PRRT risalgono agli anni Novanta con l'utilizzo di 111In-octeotride, poi nel 1996 con Y90 e nel 2000 con Lu177.

Entrambi questi ultimi due tipi di radionuclidi sono *beta-emittenti*, ma:

- Y90 ha un potere di penetrazione maggiore e lo rende adatto anche nella terapia di tumori di grosse dimensioni e con densità eterogenea
- Lu177 ha potere di penetrazione meno elevato che lo rende più adatto nella terapia di localizzazioni meno voluminose e dalla densità più omogenea.

Per contro il Lu177 ha due tipi di emissione, la maggiore beta come l'Y90 e una seconda, inferiore, gamma che lo rendono maggiormente indicato per l'effettuazione degli studi dosimetrici.

	β - (Mev)	γ (Kev)	T ½ (gg)	penetrazione
177 Lu	0,13 (max 0,49)	113-208	6,7	0,23-1,7 mm
90Y	2,27		2,7	3-11 mm

PRRT o RLT

Therapeutic radionuclides currently in clinical and/or translational use in NET.

Radionuclide	Mode of decay	Half-life	Therapeutic use
Lutetium-177	Beta minus Gamma emission	6.7 days	Most commonly used NET PRRT Prostate cancer radio-ligand therapy
Yttrium-90	Beta minus	2.7 h	NET PRRT Super-selective intra-arterial radio-embolization of liver lesions
Actinium-225	Alpha decay	10 days	Prostate cancer bone disease Potential role in NET alpha PRRT
Copper-67	Beta minus Gamma rays	61.7 h	NET PRRT Prostate cancer
Bismuth-212	Alpha decay Beta minus	60.6 min	Clinical trials with monoclonal antibodies attachment Leukemia, brain tumors
Lead-212	Alpha decay Beta minus	10.6 h	Monotherapy for various cancers Under investigation for alpha PRRT

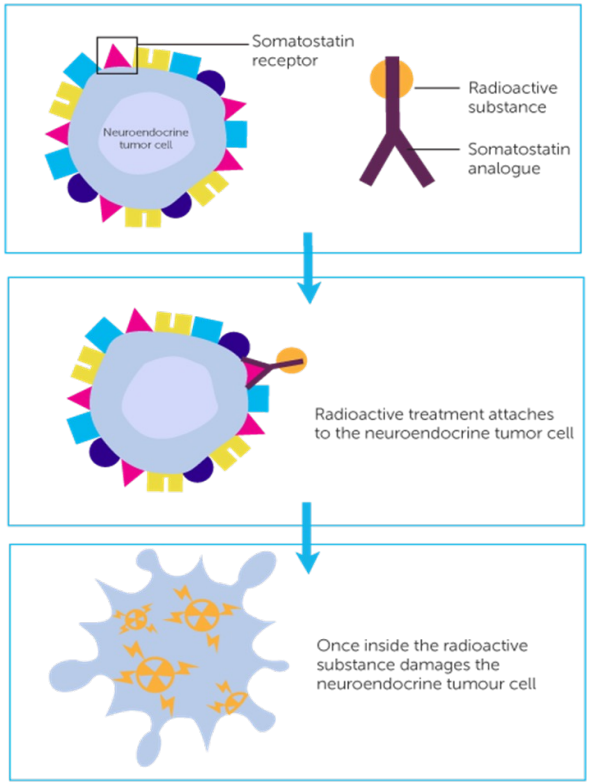
Haq, Clin Endoc & Metab. In Press

PRRT o RLT

Il radiofarmaco (Lutetium - Lu 177 dotatate) presente in commercio per la cura delle neoplasie neuroendocrine, è composto da

- un radioisotopo (Lu177), da
- un ligando o molecola carrier (l'oxodoteotride)
- un chelante (DOTA) che mantiene uniti tra di loro i due componenti sopradescritti.

La molecola carrier ***riconosce i recettori per la somatostatina espressi sulla superficie cellulare*** e il radiofarmaco viene internalizzato nella cellula, degradato all'interno dei lisosomi, dove intrappolato esplica la sua azione tossica sulla cellula portando alla rottura del DNA cellulare.

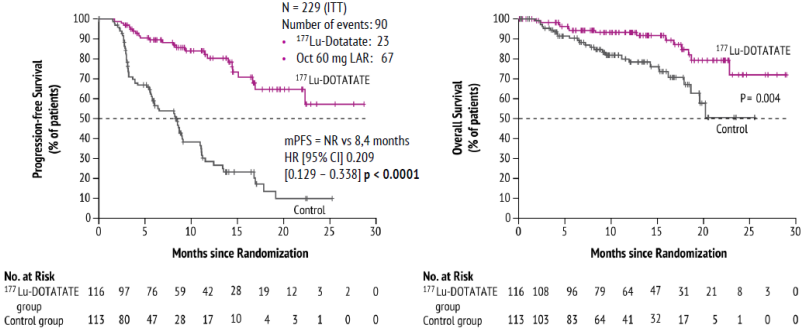


PRRT o RLT

Center	Reference	Ligand	Patient, *n*	Tumour response					
				CR	PR	MR	SD	PD	CR + PR
Studies using PRRT									
Rotterdam	Valkema et al., 2002	[^{111}In-DTPA^0] octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0%
New Orleans	Anthony et al., 2002	[^{111}In-DTPA^0] octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8%
Milan	Bodei et al., 2003	[^{90}Y-DOTA^0,Tyr^3] octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29%
Basel	Waldherr et al., 2001	[^{90}Y-DOTA^0,Tyr^3] octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24%
Basel	Waldherr et al., 2002	[^{90}Y-DOTA^0,Tyr^3] octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33%
Multicenter	Valkema et al., 2006	[^{90}Y-DOTA^0,Tyr^3] octreotide	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)	9%
Multicenter	Bushnell, 2010	[^{90}Y-DOTA^0,Tyr^3] octreotide	90	0	4 (4%)	NA	63 (70%)	11 (12%)	4%
Copenhagen	Pfeifer, 2011	[^{90}Y-DOTA^0,Tyr^3] octreotide	53	2 (4%)	10 (19%)	NA	34 (64%)	7 (13%)	23%
Warsaw	Cwikla, 2010	[^{90}Y-DOTA^0,Tyr^3] octreotate	58	0	13 (23%)	NA	44 (73%)	3 (5%)	23%
Warsaw	Kunikowska et al., 2011	[^{90}Y-DOTA^0,Tyr^3] octreotate	25	0	5 (20%)	NA	13 (52%)	7 (28%)	20%
Rotterdam	Kwekkeboom et al., 2008	[^{177}Lu-DOTA^0,Tyr^3] octreotate	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29%
Gothenburg	Sward et al., 2010	[^{177}Lu-DOTA^0,Tyr^3] octreotate	26	0	6 (38%)	NA	8 (50%)	2 (13%)	38%
Lund	Garkavij et al., 2010	[^{177}Lu-DOTA^0,Tyr^3] octreotate	12	0	2 (17%)	3 (25%)	5 (40%)	2 (17%)	17%
Milan	Bodei et al., 2011	[^{177}Lu-DOTA^0,Tyr^3] octreotate	42	1 (2%)	12 (29%)	9 (21%)	11 (26%)	9 (21%)	31%
Bonn	Ezziddin et al., 2014	[^{177}Lu-DOTA^0,Tyr^3] octreotate[e]	68	0	41 (60%)	8 (12%)	9 (13%)	10 (15%)	60%
Bonn	Sabet et al., 2015	[^{177}Lu-DOTA^0,Tyr^3] octreotate[f]	61	0	8 (13%)	19 (31%)	29 (47.5%)	5 (8.2%)	13%
Meldola	Sansovini et al., 2013	[^{177}Lu-DOTA^0,Tyr^3] octreotate[e]	26[a]	3 (12%)	7 (27%)	NA	12 (46%)	4 (15%	30%
Meldola	Paganelli et al., 2014	[^{177}Lu-DOTA^0,Tyr^3] octreotate[f]	25[a]	1 (4%)	0	NA	20 (80%)	4 (16%)	4%
Bad Berka	Baum et al., 2016	[^{177}Lu-DOTA^0,Tyr^3] octreotide	43	9 (20.9%)	10 (23.3%)	NA	12 (27.9%)	12 (27.9%)	41%
Multicentre	Strosberg et al., 2017	[^{177}Lu-DOTA^0,Tyr^3] octreotide	101	1 (1%)	17 (17%)	NA	NA	NA	18%

PRRT o RLT

NETTER-1: phase III multicenter trial



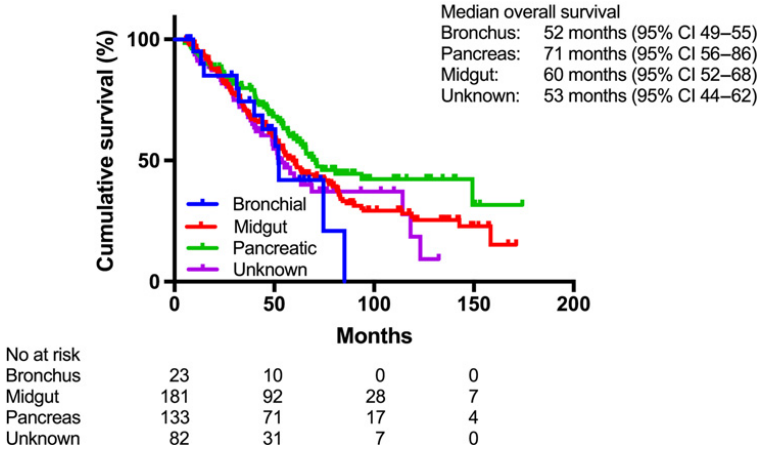
HR, hazard ratio; LAR, long acting release; mPFS, median progression free survival; NR, not reported; LAR, long acting release; Lu, lutetium; Oct, ocreotide

229 patients who had well-differentiated, metastatic midgut NET

- PFS 65.2% vs 10.8% at 20 months
- OR 18% vs 3%

Strosberg, J. NEJM 2017

ERASMUS study: phase I/II single arm



696 pts with well diff GEP and bronchial NET. Median follow-up: 78 months

- PFS 29 months
- time to progression 36 months
- OS 63 months

Brabander CCR 2017

PRRT o RLT

With NETTER-1 results started a new era and 177LuDOTATATE was finally approved by:

- the EMA in September 2017,
- the FDA in January 2018,
- the Canada Health in January 2019,
- the State of Israel Ministry of Health in July 2019

Currently, 177Lu-DOTATATE is approved in 23 countries worldwide.
However, this should be considered only a partial achievement as ***a large portion of tumors overexpressing somatostatin receptors (SSTR) still cannot be treated with 177Lu-DOTATATE***, giving rise to the so-called "Lutathera Orphans".
Indeed, 177Lu-DOTATATE is currently administered in a protected hospitalization regime and is indicated in adult patients diagnosed with well-differentiated (G1 and G2) gastroenteropancreatic neuroendocrine tumors (GEP-NET) that are progressive, non-removable or metastatic, and positive to the receptors for somatostatin.
Therefore, ***paediatric patients cannot be treated with 177Lu-DOTATATE***. Similarly, patients with ***newly diagnosed or stable metastatic disease, even if symptomatic or affected by a large burden of disease, are not eligible*** for this therapy despite promising literature evidences. Finally, ***G3 NET, neuroendocrine carcinomas (NEC), or extra-GEP-NET patients are still 177Lu-DOTATATE orphans*** as well, even though they often show intense overexpression of SSTRs at functional imaging.

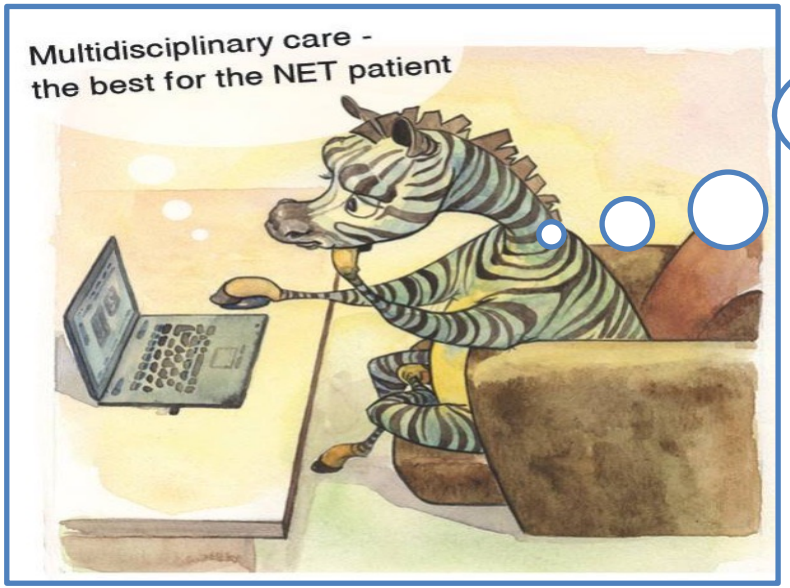
PRRT o RLT

ELEGGIBILITA'

- NEN del tratto GEP
  - G1 (Ki-67: <3%)
  - G2 (Ki-67: 3-20%)
- Espressione e densità Rc SSA nei siti di malattia
- Progressione (RECIST) in corso di standard-dose SSA
- Esami ematochimici

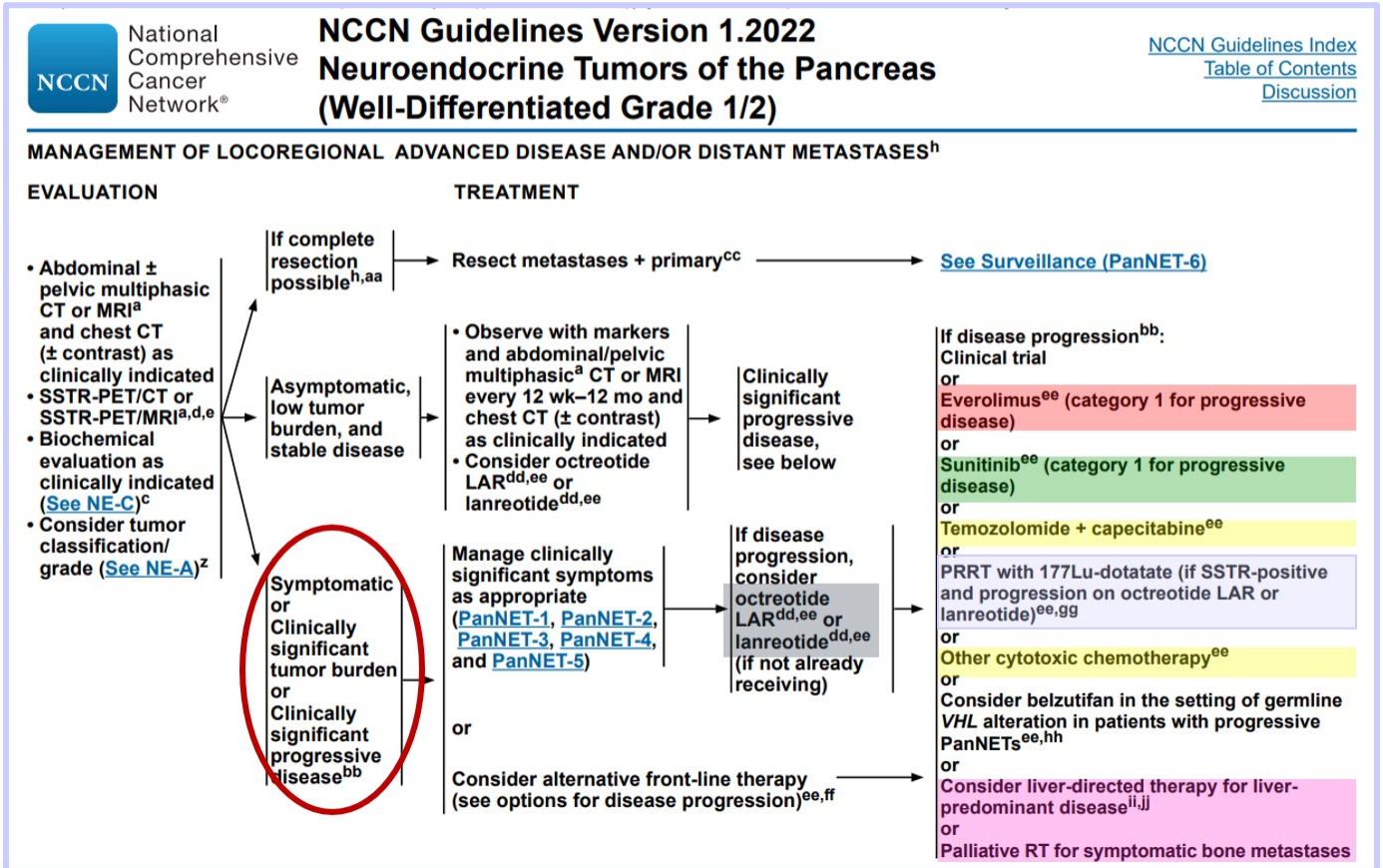
Creatinina < 1.7 mg/dL (o Clearance >50mL/min)
Emoglobina > 8g/dL
WBC > 2.000/mL, PLT > 75.000/mL
Bilirubina totale < 3 volte il limite sup normalità
Albumina > 3g/dL

TREATMENT CHOICE



- ✓ *Treat who should be treated*
- ✓ *Start treatment at right time*
- ✓ *Give the best drug for each patient*
- ✓ *Avoid therapy in patients with risk factors*

TREATMENT CHOICE



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Neuroendocrine Tumors of the Pancreas
(Well-Differentiated Grade 1/2)

NCCN Guidelines Index
Table of Contents
Discussion

MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES[h]

EVALUATION

- Abdominal ± pelvic multiphasic CT or MRI[a] and chest CT (± contrast) as clinically indicated
- SSTR-PET/CT or SSTR-PET/MRI[a,d,e]
- Biochemical evaluation as clinically indicated (See NE-C)[c]
- Consider tumor classification/ grade (See NE-A)[z]

TREATMENT

If complete resection possible[h,aa] → Resect metastases + primary[cc] → See Surveillance (PanNET-6)

Asymptomatic, low tumor burden, and stable disease
- Observe with markers and abdominal/pelvic multiphasic[a] CT or MRI every 12 wk–12 mo and chest CT (± contrast) as clinically indicated
- Consider octreotide LAR[dd,ee] or lanreotide[dd,ee]

→ Clinically significant progressive disease, see below

Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease[bb]

Manage clinically significant symptoms as appropriate (PanNET-1, PanNET-2, PanNET-3, PanNET-4, and PanNET-5)

→ If disease progression, consider octreotide LAR[dd,ee] or lanreotide[dd,ee] (if not already receiving)

or

Consider alternative front-line therapy (see options for disease progression)[ee,ff]

If disease progression[bb]:
Clinical trial
or
Everolimus[ee] (category 1 for progressive disease)
or
Sunitinib[ee] (category 1 for progressive disease)
or
Temozolomide + capecitabine[ee]
or
PRRT with 177Lu-dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide)[ee,gg]
or
Other cytotoxic chemotherapy[ee]
or
Consider belzutifan in the setting of germline *VHL* alteration in patients with progressive PanNETs[ee,hh]
or
Consider liver-directed therapy for liver-predominant disease[ii,jj]
or
Palliative RT for symptomatic bone metastases

Surveillance

SSTAs

Everolimus

Sunitinib

PRRT

Chemotherapy

Hepatic Direct Therapy - EBRT

TREATMENT CHOICE

… NEED A TREATMENT

Systematic Review and Meta-Analysis

The therapeutic efficacy of ^{177}Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors

A meta-analysis

Li-fan Wang, BD, Lin Lin, MD, Meng-jiao Wang, MD, Yong Li, PhD*

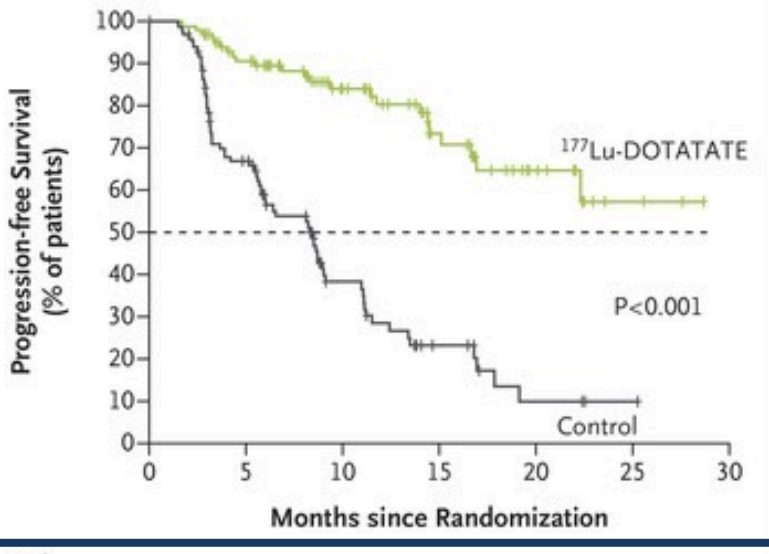
A total of 22 studies (1758 patients) were included in this meta-analysis

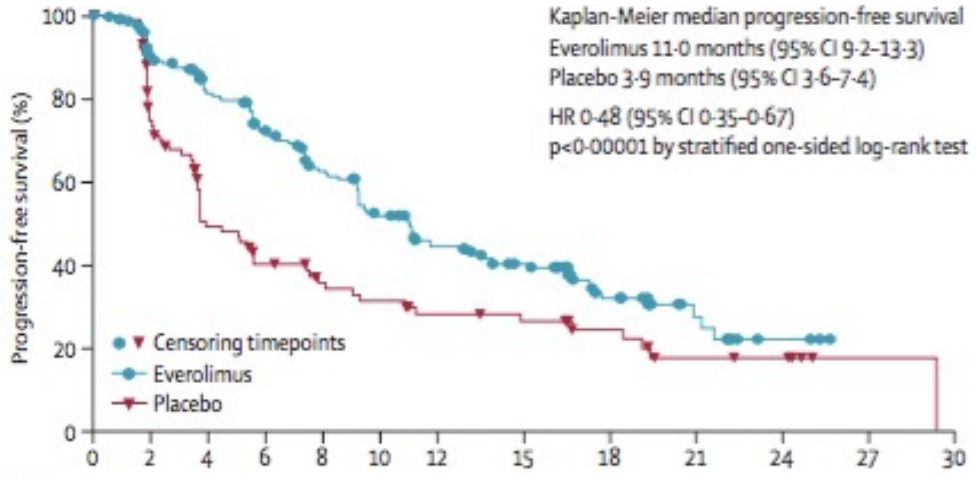
NEN patients treated with PRRT:

- complete response (CR) + partial response (PR) → OBJECTIVE RESPONSE 35%
- CR or PR or stable disease (SD) → DISEASE CONTROL RATE 83%

Wang Medicine 2020

TREATMENT CHOICE





PRRT
GI NET

Do we really need to select the patients?

Everolimus
GI and lung NET

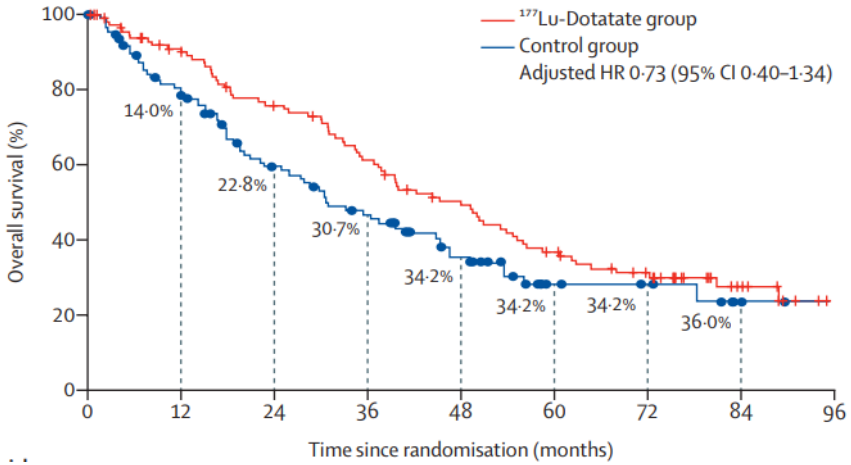
Strosberg, J. NEJM 2017

Yao Lancet 2015

RLT & OS

^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial

*Jonathan R Strosberg, Martyn E Caplin, Pamela L Kunz, Philippe B Ruszniewski, Lisa Bodei, Andrew Hendifar, Erik Mittra, Edward M Wolin, James C Yao, Marianne E Pavel, Enrique Grande, Eric Van Cutsem, Ettore Seregni, Hugo Duarte, Germo Gericke, Amy Bartalotta, Maurizio F Mariani, Arnaud Demange, Sakir Mutevelic, Eric P Krenning, on behalf of the NETTER-1 investigators**



- In the phase 3 NETTER-1 study (with a mFU of more than 6,3ys) ^{177}Lu-Dotatate treatment **did not significantly improve mOS** versus high-dose longacting octreotide.

→ ***Potentially impacted by high rate of cross-over (36%) of patients in the control arm to PRRT***

- the **11,7 month difference in mOS** with ^{177}Lu-Dotatate (48 months) treatment versus high-dose long-acting octreotide alone (36,3 months) might be considered clinically relevant.
- No new safety signals were reported during long-term follow-up

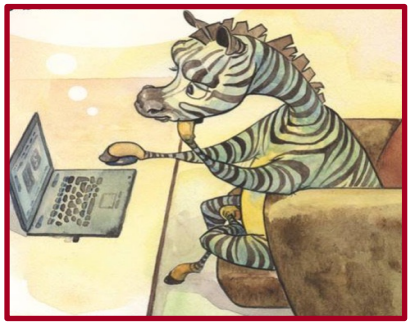
Lancet Oncol 2021

RLT & TIMING

Overall survival results from the NETTER-1 trial in neuroendocrine tumours: an important milestone

The Netter-1 safety data show a low incidence of long-term side-effect regarding hematotoxicity and nefhrotoxicity (5% had >G3 nefhotoxicity vs 4% control group, no new cases of MDS, AML).

→ *These data are very important because the results suggest that PRRT could be applied earlier in the course of the disease*



The optimal patient to be treated by 177Lu-DOTATAE:

- high SSTR expression as assessed by PET-TC
- a relatively good Karnofsky performance status score
- is progressive under treatment long-acting SST analogues

Virgolini Lancet Oncol 2021

RLT & TIMING

2019
AIOM GUIDELINES

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione clinica
ALTA	Nei pazienti adulti con neoplasia neuroendocrina gastroenteropancreatica (GEP_NET) ben differenziata (G1 e G2), progressiva, non asportabile o metastatica, positiva ai recettori della somatostatina, la PRRT dovrebbe essere presa in considerazione	Positiva Forte

2022
AIOM GUIDELINES

Qualità globale delle evidenze	**Raccomandazione**	**Forza della raccomandazione clinica**
Bassa	Nei pazienti adulti con GEP-NET G1 o G2 non resecabile o metastatico, funzionante o non funzionante, positivo ai recettori per la somatostatina, in progressione all'analogo della somatostatina, la PRRT dovrebbe essere presa in considerazione come opzione di prima scelta (27).	**Forte a favore**

WHAT'S NEXT?

GEP NET	OCCLURANDOM	PRRT vs Sunitinib
	COMPETE (phase III)	PRRT vs Everolimus
	CONTROL NETS	PRRT vs PRRT+CAPTEM vs CAPTEM
GEP NET G2/G3	NETTER 2	PRRT vs Octreotide LAR
	COMPOSE (phase III)	PRRT vs Best Standard of Care

- PRRT with SST-antagonist
- PRRT with alpha emitters

WHAT'S NEXT?

OCCLURANDOM

Patients with progressive advanced PaNET according to RECIST1.1 were randomized 1:1 to
-OCLU (7.4 GBqX4/8w)
-or sunitinib (SUN) 37.5 mg/d.

84 pts were enrolled. Main characteristics were well balanced.

1.Primary Outcome Measures: To determine the 12 months PFS [Assessed 12 months after randomization]

2. Secondary Outcome Measures:
- Overall Survival [Assessed every 3 months until death]
- Best response [Assessed every 12 weeks until progression up to 48 months] According to RECIST V1.1

The primary endpoint was met with

- a 12m-PFS rate at 80.5% in the OCLU arm (IC90%: 67.5–89.9, *n* = 33 pts without progression at 12 months/41) vs. 41.9% in the SUN arm (IC90%: 29.1–55.5,including 35% the null hypothesis; *n* = 18/43).

- Median PFS was 20.7 in the OCLU arm (90CI: 17.2–23.7) vs. 11 months in the SUN arm (90CI: 8.8–12.4).

The OCLURANDOM study met its primary endpoint.

Boudine 2022

WHAT'S NEXT?

NETTER 2

NETTER-2 (NCT03972488) is an open-label, multi-center, randomized, comparator-controlled Phase III trial assessing whether Lutathera® plus long-acting octreotide when taken as a first line treatment can prolong PFS in patients with high-proliferation rate tumors (G2 and G3), compared to treatment with high-dose (60 mg) long-acting octreotide. Eligible patients were diagnosed with SSTR-positive advanced GEP-NETs within 6 months before enrollment.

- Phase III NETTER-2 trial *met primary endpoint of improvement in progression-free survival (PFS) and key secondary endpoint of objective response rate (ORR)* in patients with Grade 2 and 3 advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs) who received first line treatment with Lutathera® in combination with long-acting octreotide, versus high-dose long-acting octreotide alone.

- Lutathera is the first radioligand therapy (RLT) to demonstrate clinically meaningful benefit in a first line setting

WHAT'S NEXT?

PRRT & SOMATOSTATIN RECEPTOR ANTAGONISTS

The use of radiolabelled-SSTR antagonists instead of agonists is based on some studies that refer their ***bigger uptake***.
This behaviour can be justified by the fact that antagonists, which are ***not internalized***, can bind to a larger number of receptors because they are independent of the receptor activation state.

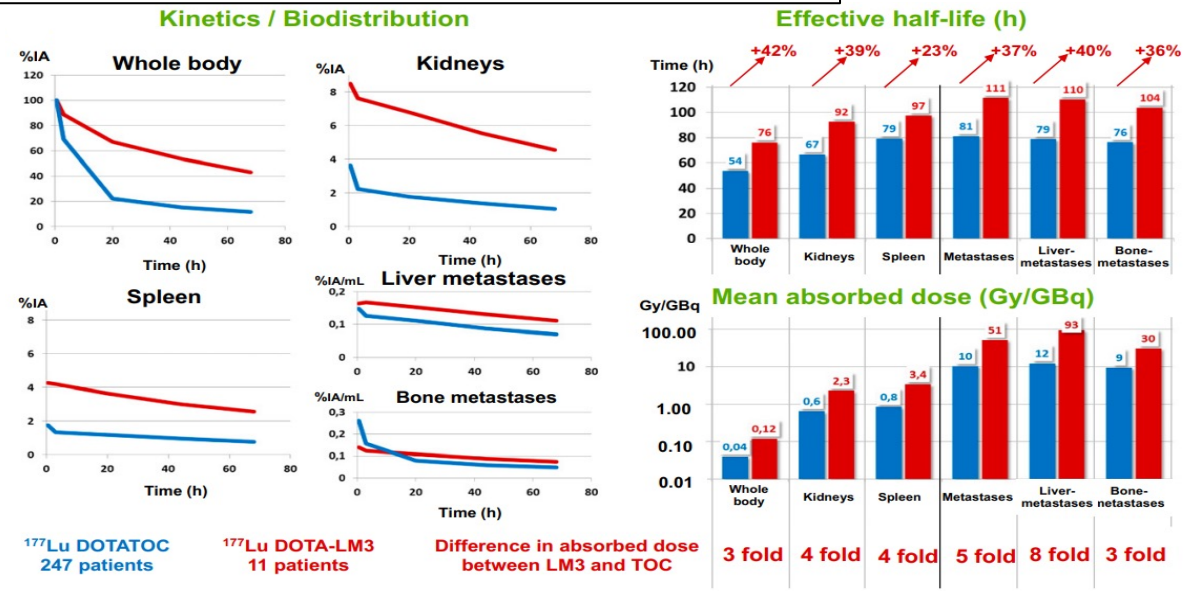
Due to the greater number of binding sites, the ^{68}Ga-labelled SSTR antagonists have the potential to increase image sensitivity for NET detection, comparing to agonists.

Among all the potential SSTR2 antagonists, ***LM3 and JR11*** were the most interesting, having the highest hydrophilicity and best affinity.

WHAT'S NEXT?

First-in-Humans Study of the SSTR Antagonist ^{177}Lu-DOTA-LM3 for Peptide Receptor Radionuclide Therapy in Patients with Metastatic Neuroendocrine Neoplasms: Dosimetry, Safety, and Efficacy

Richard P. Baum[*1,2], Jingjing Zhang[*1,3,4], Christiane Schuchardt[1], Dirk Müller[1], and Helmut Mäcke[5]



Higher uptake and a longer effective half-life were found for 177Lu-DOTALM3 than for the agonist 177Lu-DOTATOC *in the whole body and in the kidneys, spleen, and metastases, resulting in higher mean absorbed organ and tumor doses*. All patients tolerated therapy without any serious acute adverse effects.

Antagonist 177Lu-DOTA-LM3 PRRT resulted in an excellent tumor response, with a disease control rate of 85.1%.

The renal absorbed dose of 177Lu-DOTA-LM3 was noticeably higher than that of the patient cohort receiving 177Lu-DOTATOC

J Nucl Med 2021

WHAT'S NEXT?

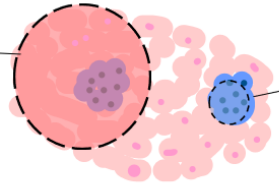
PRRT & ALPHA EMITTERS

Beta Particle Radiation

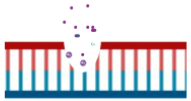
- Energy 50-2300 keV
- Range: 2-12 mm
- LET: 0,3 keV/µm

Alpha Particle Radiation

- Energy: 5-9 MeV
- Range: 40-100 µm
- LET: 100 kev/µm



Single-strand DNA Breaks



Moderate generation of ROS

Moderate bystander effect

Moderate bystander immune activation

Healthy Cell

Tumor Cell

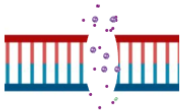
Particle Range

Reactive oxygenated species: a type of unstable molecule that contains oxygen and that easily reacts with other molecules in a cell

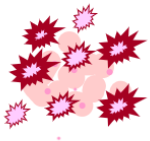
Cytokines

T-cell

induction of biological effects in cells that are not directly traversed by particle

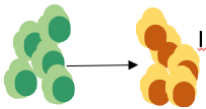


Double-strand DNA Breaks



Increased generation of ROS

Increased bystander effect



Increased bystander immune activation

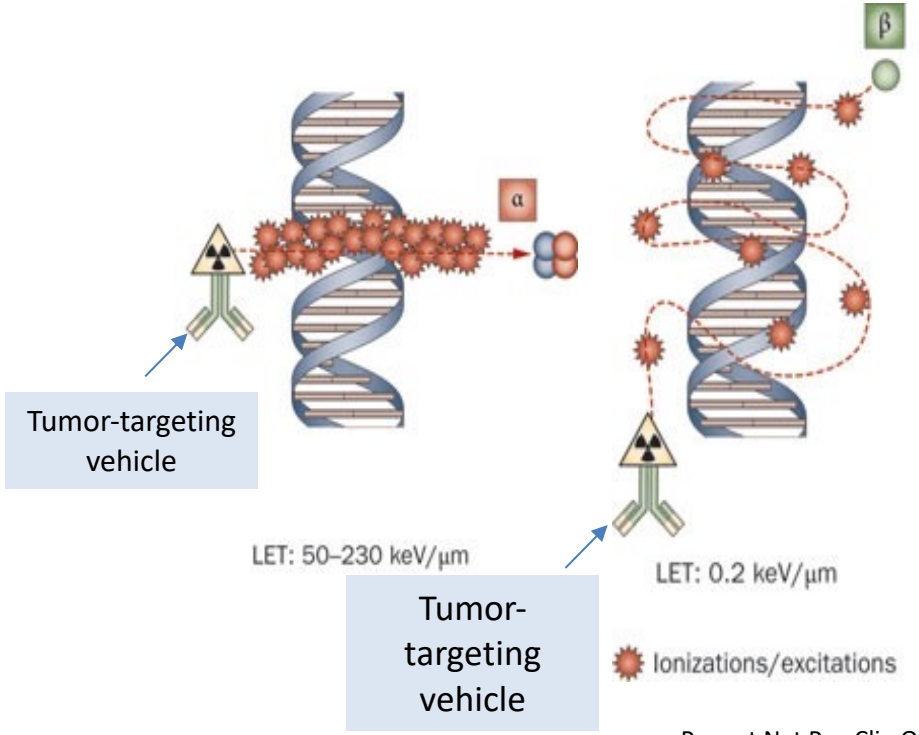
WHAT'S NEXT?

PRRT & ALPHA EMITTERS

The first commercially available alpha therapy was 223Ra (Xofigo®), licensed for the treatment of bone metastases; approximately 95% of emission energy is via alpha emission.
As 223Ra has a natural predilection for osteoblastic bone turnover, 223Ra does not need to be labelled with an antibody/peptide to ensure targeting.

Indeed, subsequent attempts to label 223Ra with antibodies/peptides have not been successful, and thus 223Ra has not been used in other TATs.

The two principal therapeutic radionuclides used in preclinical and clinical TAT of the SSR are 213Bi and 225Ac.



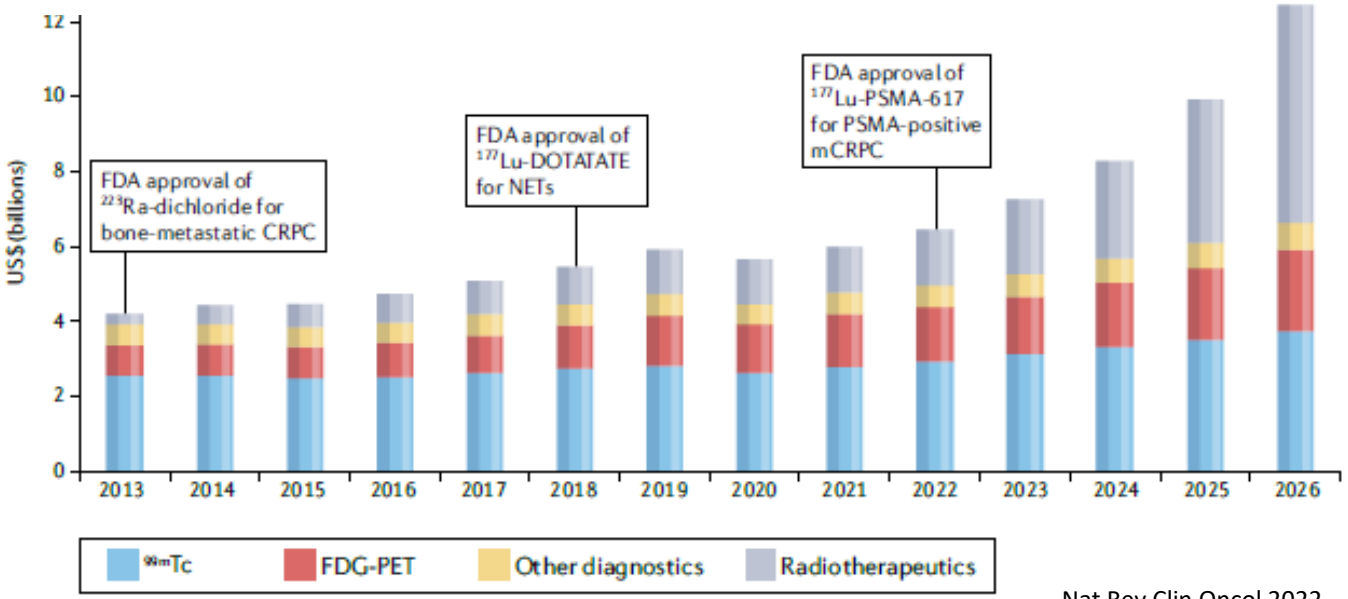
Pouget Nat Rev Clin Oncol 2011

FUTURE

Radiotheranostics in oncology: current challenges and emerging opportunities

Lisa Bodei[1,2], Ken Herrmann[3,4], Heiko Schöder[1,2], Andrew M. Scott[5,6,7,8] and Jason S. Lewis[1,2,9,10]

Predizione global market 2013-2026



Nat Rev Clin Oncol 2022

TAKE HOME MESSAGE

For patients who show tumor progression after first-line treatment with SSAs, the selection of second-line therapy may be difficult due to the lack of an absolute standard.

The sequence SSAs followed by PRRT upon progression has become a common/standard approach in G1-G2 SI-NEN patients

The ongoing clinical trial could change our attitude.

New horizon of radiopharmaceuticals will increase number of patients eligible for PRRT

THANK YOU

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