



dal 1846



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Ministero della Salute



Italiadomani
PIANO NAZIONALE
DI RIPRESA E RESILIENZA

**MIRAGE: tumori neuroendocrini,
uno sguardo al futuro**

Sabato 3 ottobre 2026

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**Università
degli Studi
di Ferrara**



SERVIZIO SANITARIO REGIONALE
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Innovazioni In Terapia - Terapia Medico Nucleare

Teranostica NET con SSA radiomarcanti



^{68}Ga

PET imaging

^{90}Y e ^{177}Lu

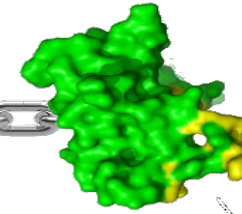
RLT

Radionuclide

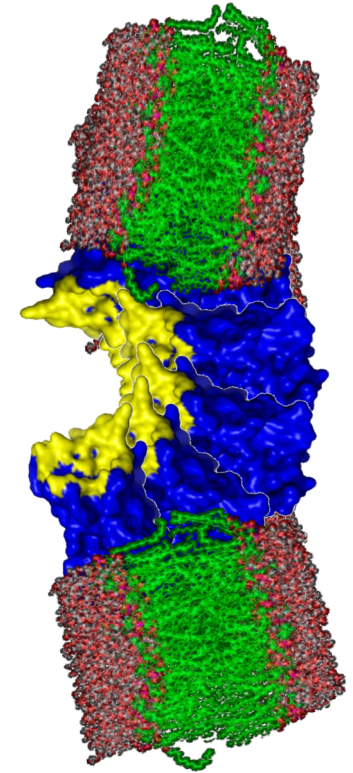


LINKER

Sistema
chelante
(DOTA)



Peptide
sintetico
(TOC)

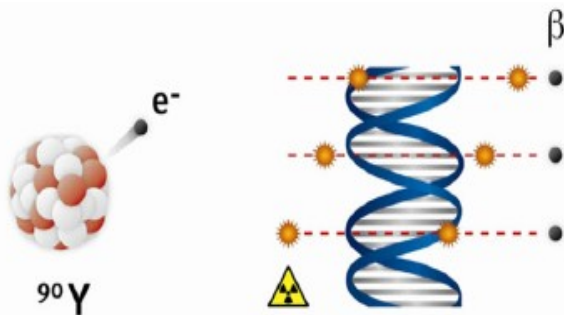


Recettore della
somatostatina

EFFETTORE

VETTORE

TOC $\rightarrow$ SSTR 2, 5
TATE $\rightarrow$ SSTR 2
NOC $\rightarrow$ SSTR
2,3,5



Pre-NETTER Era		
1994	First RLT with high-dose ¹¹¹ In-octreotide	PAST and PRESENT
1996	First RLT with ⁹⁰ Y-octreotide	
2000	First RLT with ¹⁷⁷ Lu-Octreotate	
NETTER Era		
2012	Phase III registration trial of ¹⁷⁷ Lu-Octreotate: NETTER-1	PRESENT and SHORT-TERM FUTURE
2017	Publication of the results of NETTER-1 trial	
2019	Availability on the drug market of ¹⁷⁷ Lu-Oxodotreotide (Lutathera®)	
2019	Phase III registration trial of ¹⁷⁷ Lu-Octreotate: NETTER-2	
2021	Publication of the final results of NETTER-1 trial	
2024	Publication of the results of NETTER-2 trial	
Post-NETTER Era		
Ongoing trials		SHORT-TERM FUTURE

Ere della PRRT

 **Lutathera®**

 **RADIOFARMACI
FUTURI**

N Engl J Med 2017;376:125-35.

DOI: 10.1056/NEJMoa1607427

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu -Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregini, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

SSTR+ metastatic, inoperable, or locally advanced midgut GEP-NETs that had progressed during SSA treatment N=229

Stratification Factors

- SSTR uptake: grade 2, 3, or 4
- Time receiving constant dose of octreotide: ≤ 6 months vs > 6 months

Select Inclusion Criteria

- Well-differentiated grade 1/2 tumors
- Ki-67 index $\leq 20\%$
- Karnofsky PS ≥ 60

1:1

**LUTATHERA*
+ 30 mg
octreotide LAR†**

(n=116)

**60 mg
octreotide LAR‡**

(n=113)

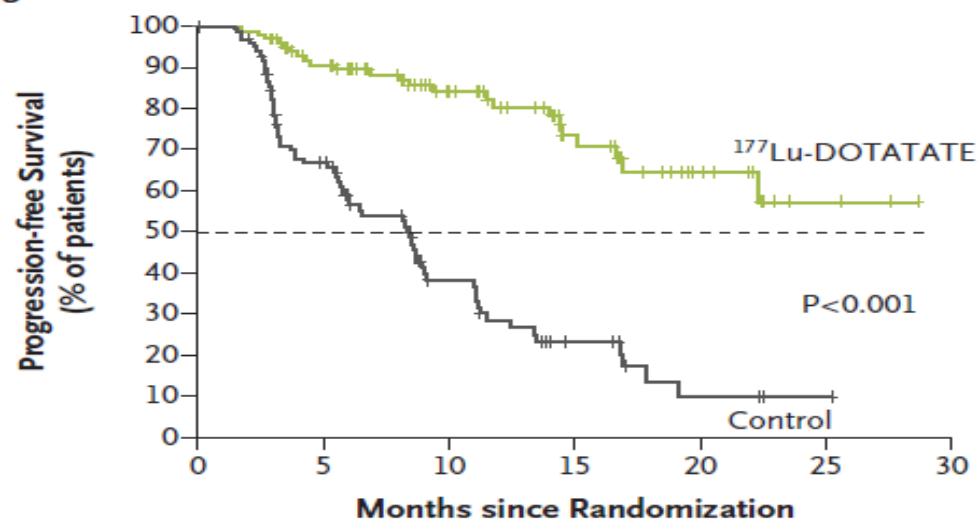
Primary end point^{1,2}:

PFS (independent central review by radiologists unaware of the treatment according to RECIST v1.1), defined as the time from randomization to documented disease progression or death from any cause

Secondary end points^{1,2}:

ORR, OS, DOR, safety

A Progression-free Survival



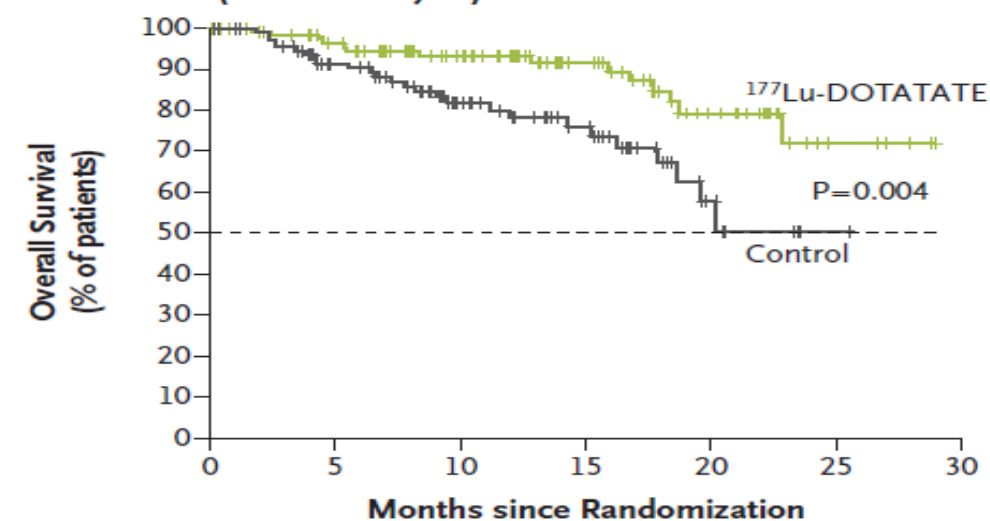
No. at Risk

¹⁷⁷ Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

	¹⁷⁷ Lu-DOTATATE	Control
Events (PD and Ex)	n=23	n=68
20m-DFS	65.2%	10.8%
median PFS	NR	8.4 m

79% lower risk of event in ¹⁷⁷Lu-DOTATOC group

B Overall Survival (Interim Analysis)



No. at Risk

¹⁷⁷ Lu-DOTATATE group	116	108	96	79	64	47	31	21	8	3	0
Control group	113	103	83	64	41	32	17	5	1	0	0

	¹⁷⁷ Lu-DOTATATE	Control
Events (Ex)	n=14	n=26
20m-OS	~ 80%	~ 55%
median PFS	NR	NR

60% lower risk of event in ¹⁷⁷Lu-DOTATOC group

¹⁷⁷Lu-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



Lancet Oncol 2021

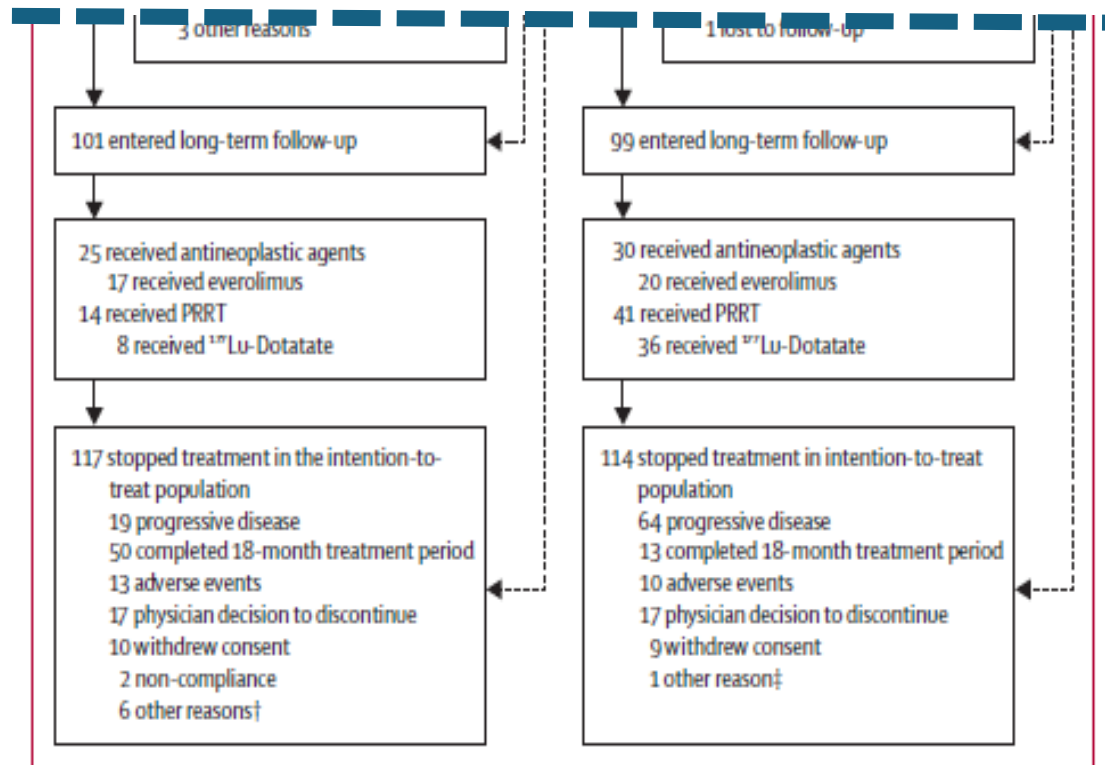
Published Online

November 15, 2021

[https://doi.org/10.1016/](https://doi.org/10.1016/S1470-2045(21)00572-6)

S1470-2045(21)00572-6

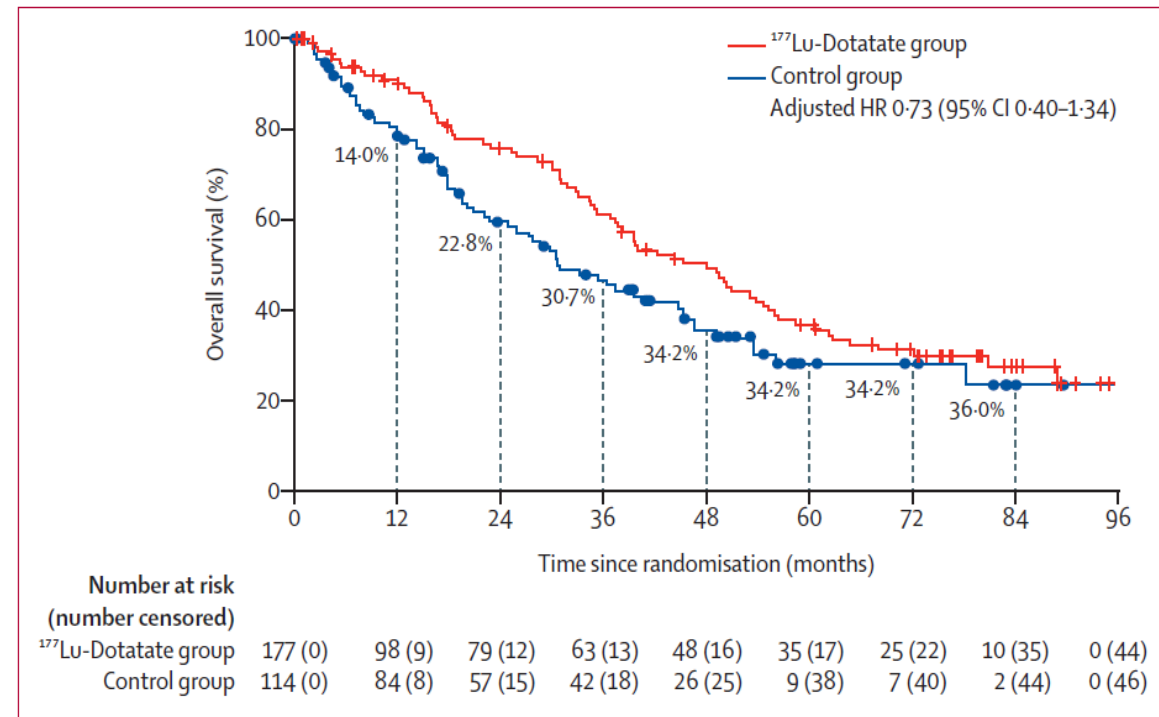
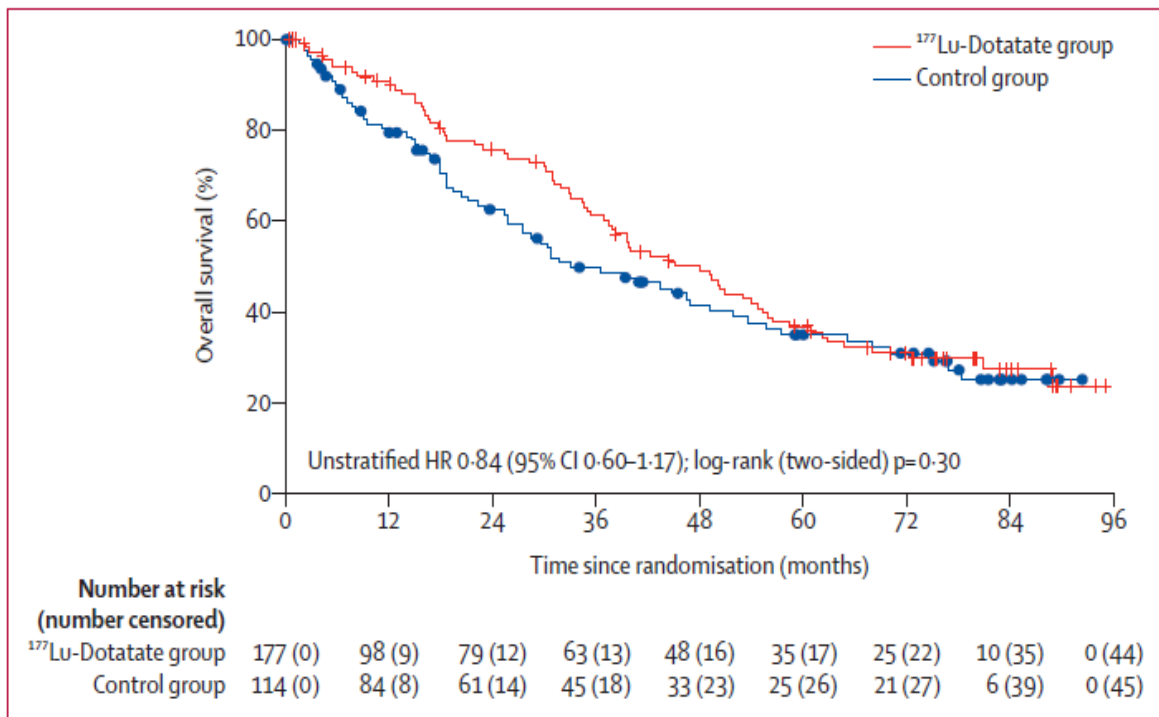
Jonathan R Strosberg, Martyn E Caplin, Pamela L Kunz, Philippe B Ruszniewski, Lisa Bodei, Andrew Hendifar, Erik Mittra, Edward M Wolin, James C Yao, Marianne E Pavel, Enrique Grande, Eric Van Cutsem, Ettore Seregni, Hugo Duarte, Gernot Gericke, Amy Bartalotta, Maurizio F Mariani, Arnaud Demange, Sakir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



2021

- 5 years cutoff data: **Jan 18, 2021**
- Alternative cutoff of 158 deaths: **NR**
- n=41 pts (of control 36%) group had documented

	177Lu-DOTATATE	Control
long-term analysis	n=117	n=114
exitus	n=73 (62%)	n=69 (61%)
median follow-up	76.3 m	76.5 m

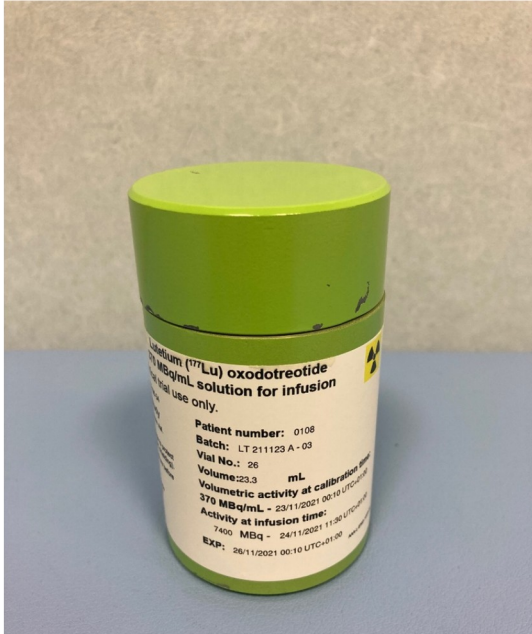


	177Lu-DOTATATE	Control
long-term analysis	n=117	n=114
median OS	48.0 m	36.3 m
Δ in median OS	11.7 m	

In a sensitivity analysis using the **rank-preserving structural failure time method**, which adjusted survival of those patients in the control group who crossed over to PRRT (36%), the **adjusted median OS was 30.9 m in the control group**.

significantly improve median overall survival versus high-dose long-acting octreotide. Despite final overall survival not reaching statistical significance, the 11.7 month difference in median overall survival with ¹⁷⁷Lu-Dotatate treatment versus high-dose long-acting octreotide alone might be considered clinically relevant. No new safety signals were reported during long-term follow-up.

Registrazione e commercializzazione di ^{177}Lu -oxodotreotide



1° dose in Italia:
29 aprile 2019
INT (Milano)

Indicazioni terapeutiche: ^{177}Lu -oxodotreotide (approvato da FDA e EMA) è indicato in pazienti adulti per il trattamento di tumori neuroendocrini gastroenteropancreatici (GEP-NET) ben differenziati (G1 e G2), in progressione ad analogo freddo, non asportabili o metastatici, positivi ai recettori per la somatostatina.

Posologia: consiste in **4 infusioni di ^{177}Lu -DOTATATE da 7.4 GBq** ciascuna [dose cumulativa ➔ 29.6 GBq]. L'intervallo consigliato tra una somministrazione e la successiva è di 8 settimane, estensibile fino a 16 settimane in caso di tossicità modificante la dose (DMT).

**Non è previsto un eventuale
ritrattamento dopo i 4 cicli**

Innovazione in PRRT

Cosa può essere ancora migliorato?

La selezione del paziente

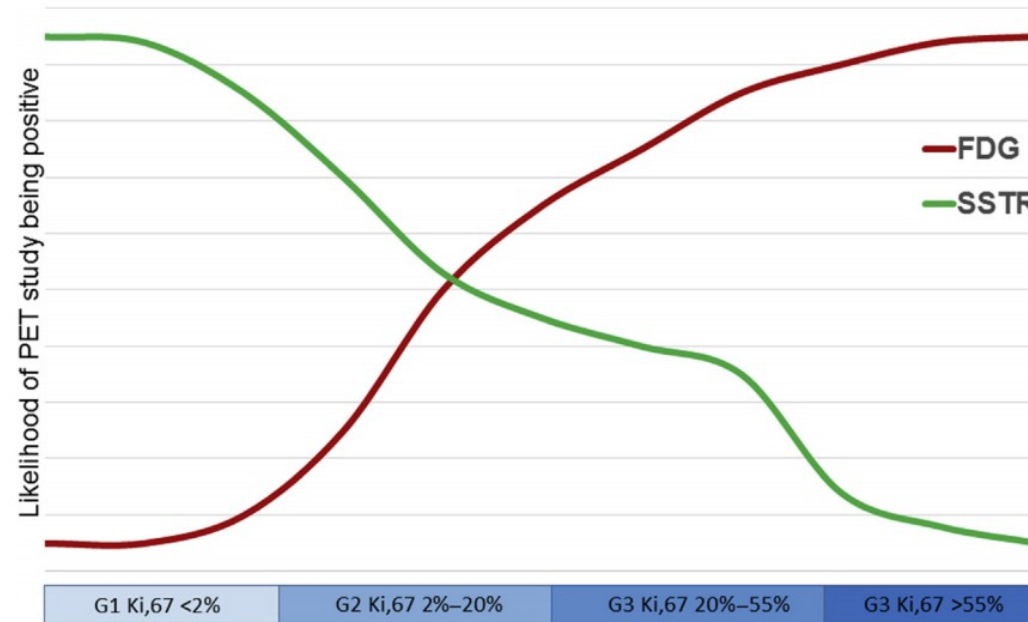


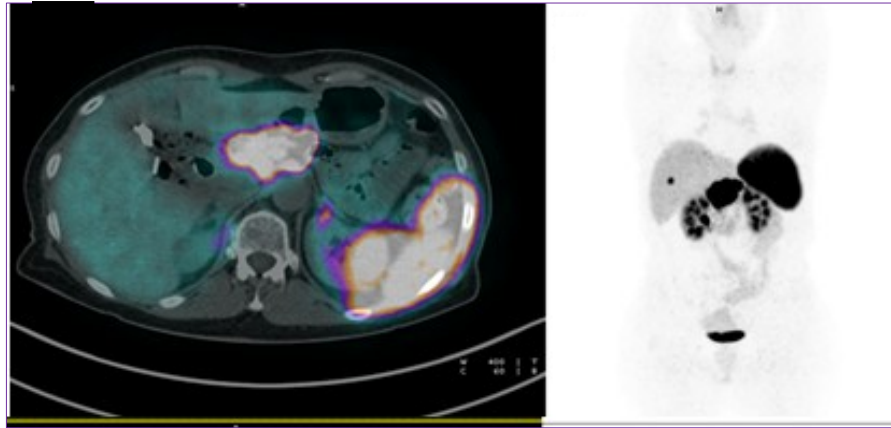
Fig. 3. Likelihood of positive SSTR and FDG PET/CT depending on proliferative rate in patients with neuroendocrine tumors. Most but not all patients with indolent well-differentiated tumors have SSTR-positive FDG-negative disease, whereas patients with aggressive poorly differentiated carcinomas have SSTR-negative FDG-positive disease. Patients in the middle of the spectrum have both SSTR- and FDG positivity. Patients under the green line are potential candidates for peptide receptor radionuclide therapy.

Pattison et al. Role of fluorodeoxyglucose PET/computed tomography in targeted radionuclide therapy for endocrine malignancies. PET Clin. 2015

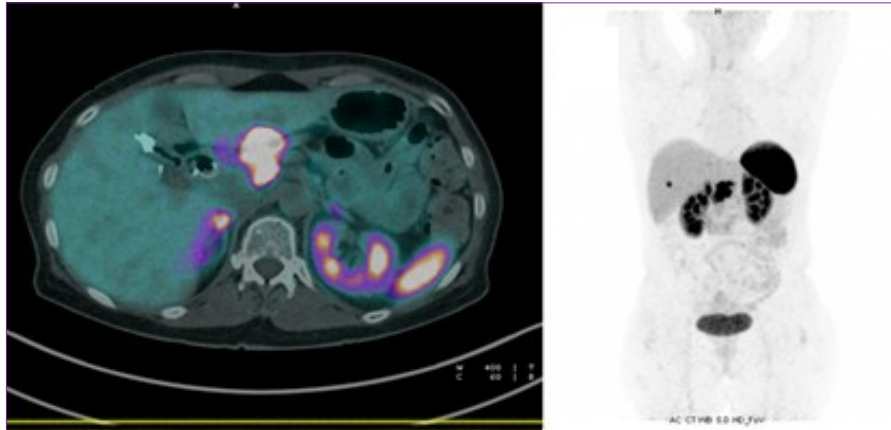
Fenomeno FLIP-FLOP

La personalizzazione del trattamento

PET/CT con ^{68}Ga -DOTATOC



Pre-PRRT

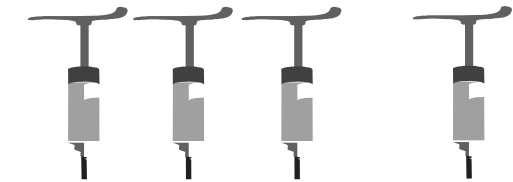
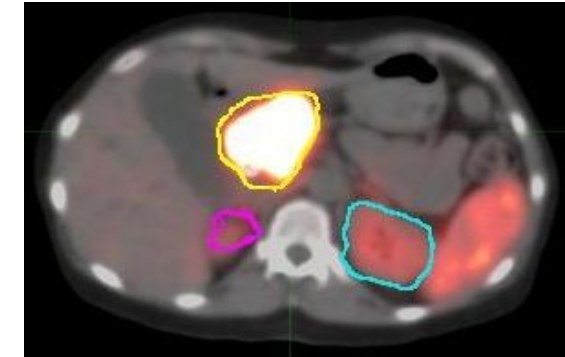


Post-PRRT

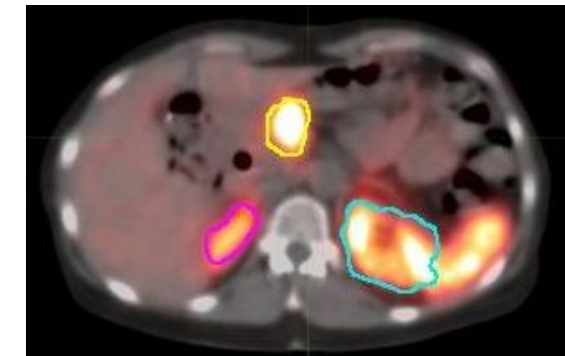
PRRT con ^{177}Lu -DOTATOC/TATE



Somministrazione EV



Iperfrazionata (n cicli)



DOSIMETRIA!

Applicazioni AI in dosimetria

Image enhancement & noise reduction

**SPECT/CT
dosimetriche
sono time
consuming!**

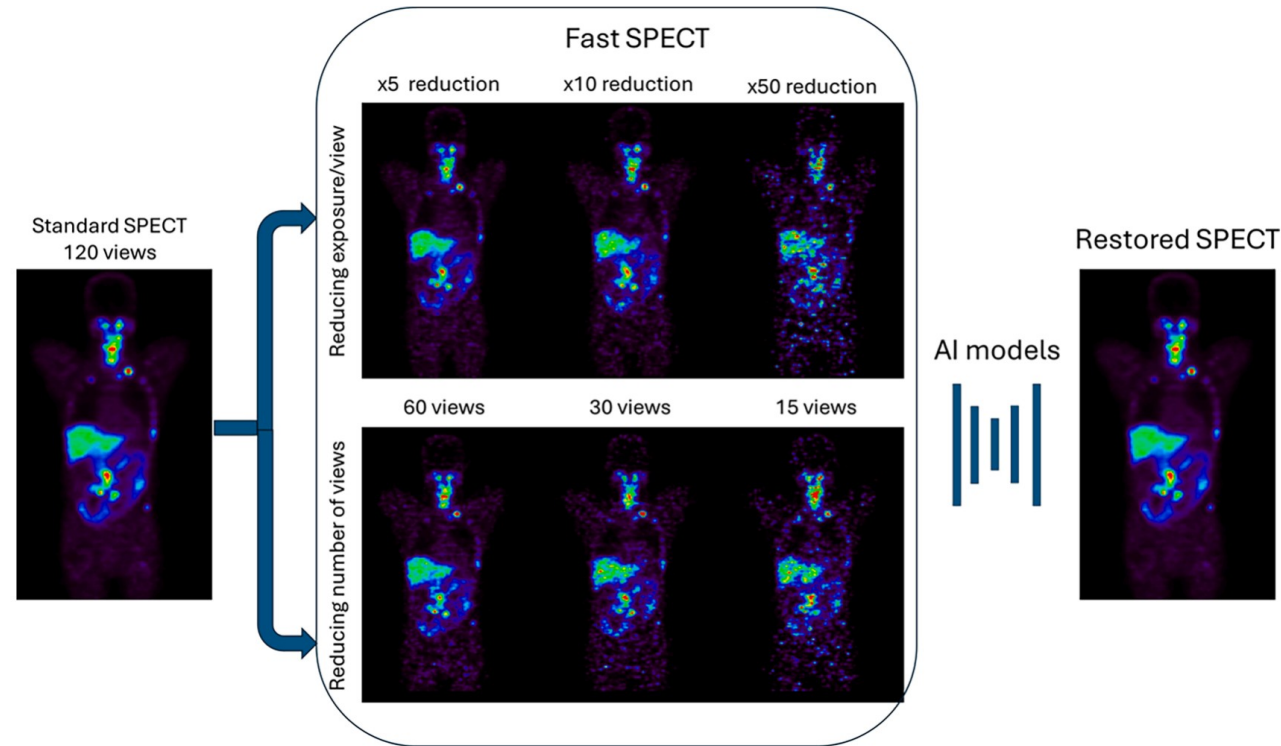
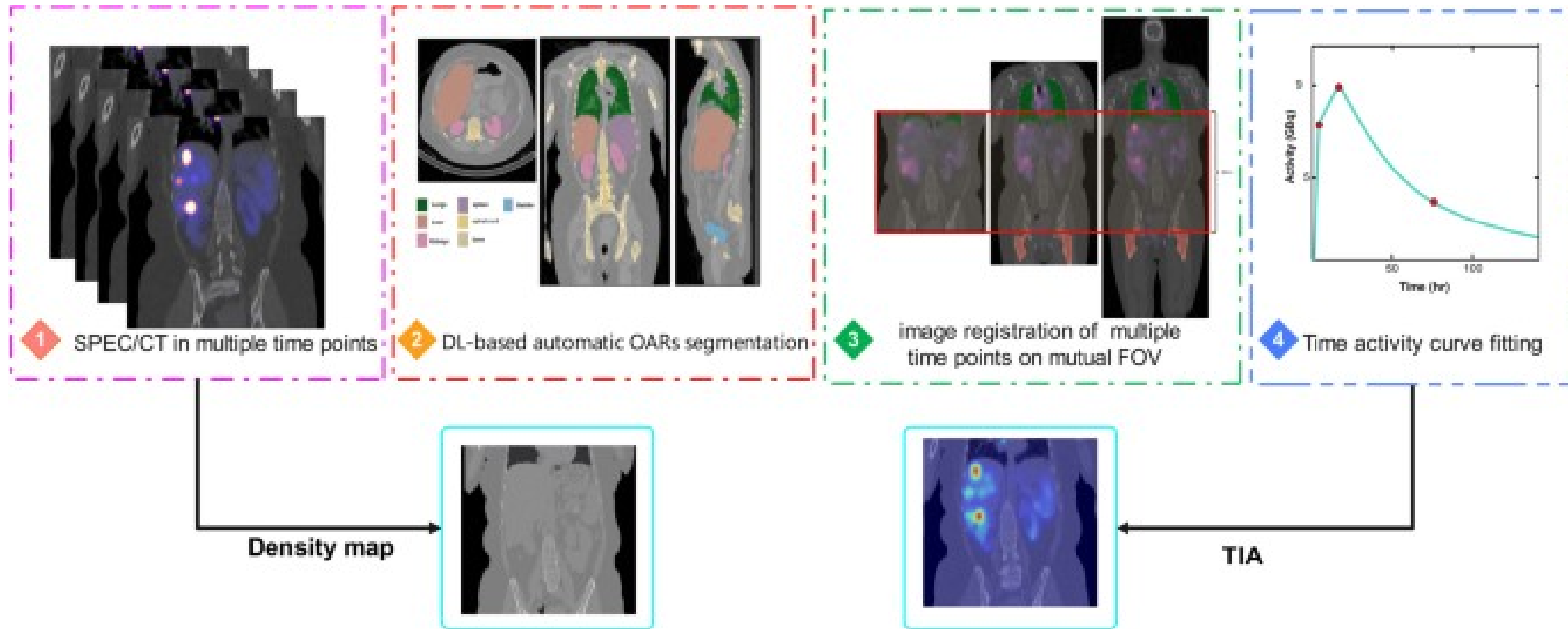
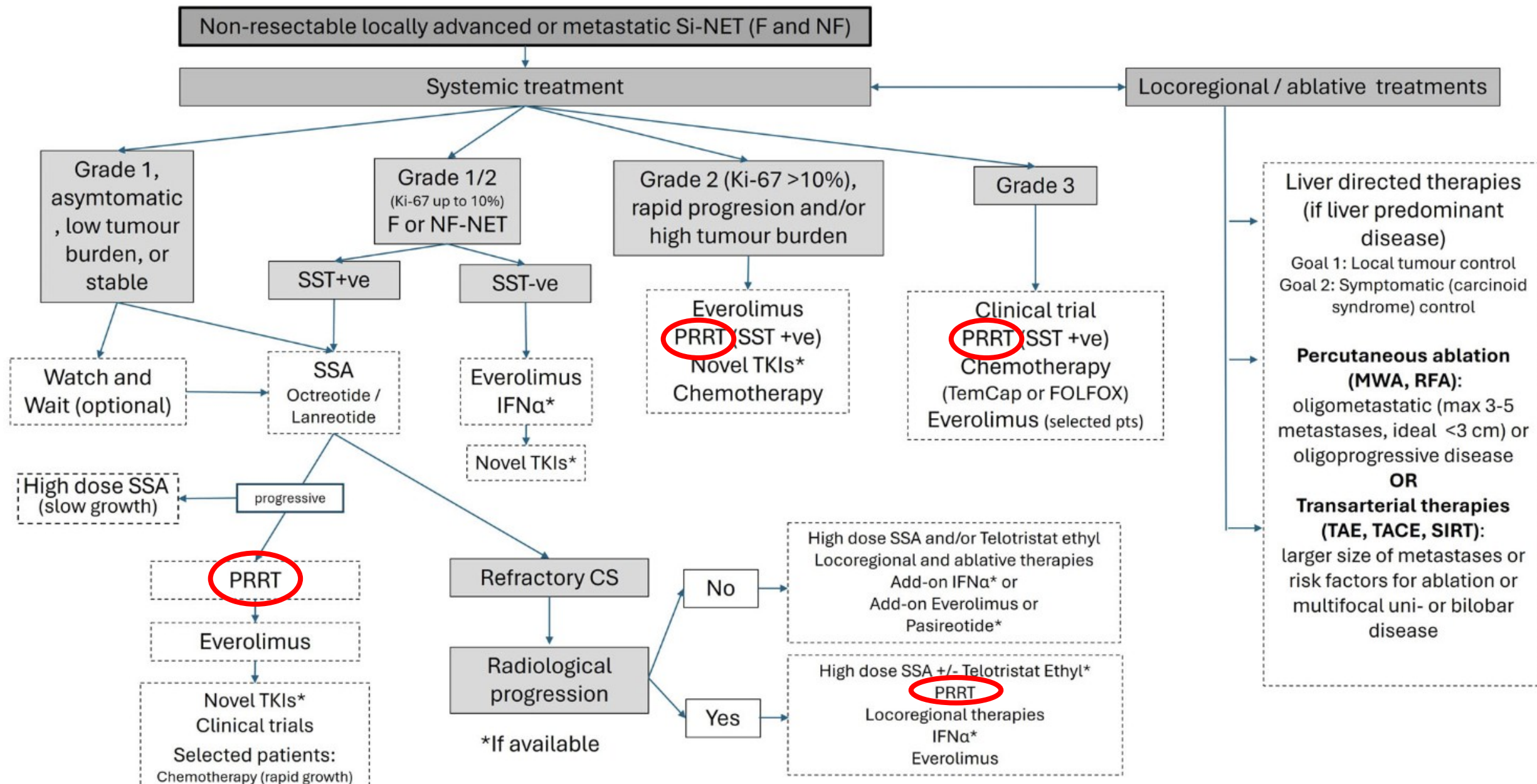


Fig. 5. Examples of shortened protocols for fast SPECT acquisitions and impact on image quality, showing degradation for both reduction of exposure per view and reducing number of total views. Also shown is schematic representation of AI models to restore SPECT quality.

Applicazioni AI in dosimetria

Stima della dose e predizione della TAC

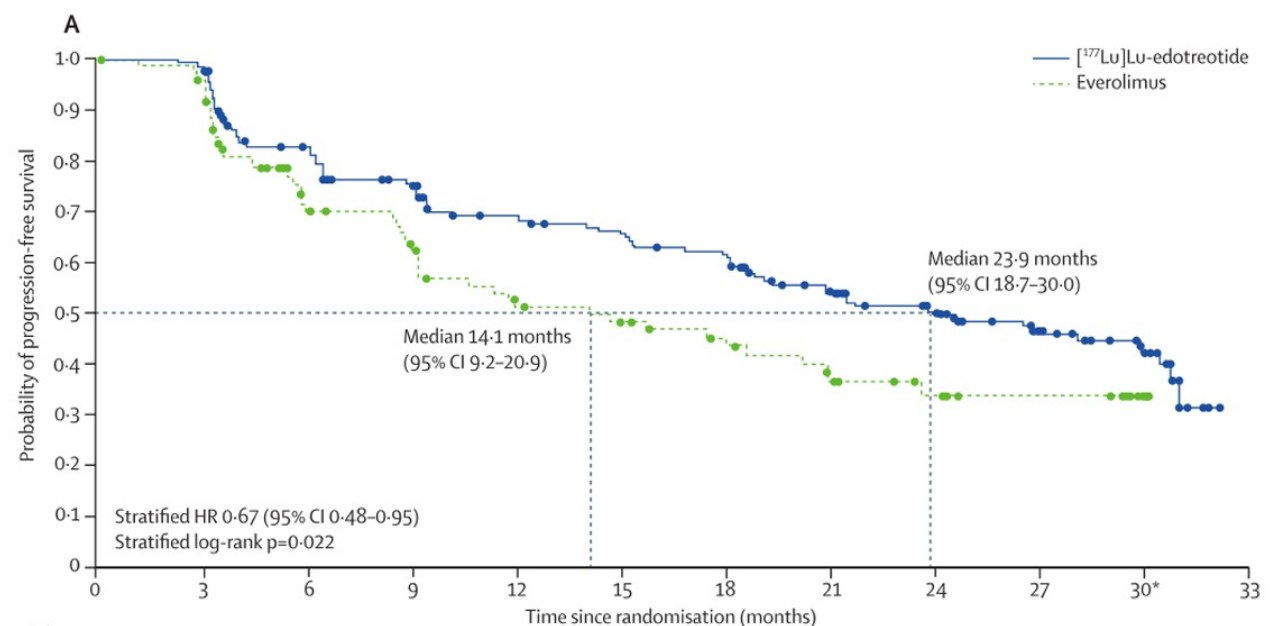




[¹⁷⁷Lu]Lu-edotreotide versus everolimus for gastroenteropancreatic neuroendocrine tumours (COMPETE): a phase 3, multicentre, randomised, open-label, superiority trial



Thomas Walter, Henning Jann, Catherine Ansquer, Emmanuel Deshayes, Rocio Garcia-Carbonero, Alexandre Teulé, Richard P Baum, Hein J Verberne, Jarosław B Ćwikła, Rajaventhana Srirajaskanthan, Louis de Mestier, Chiara M Grana, Andreas Buck, Dieter Hörsch, Marianne Pavel, Lawrence O Dierckx, Michael Michael, Jonathan Strosberg, Attila Kollár, Paula Jimenez-Fonseca, Anja Rinke, Maribel del Olmo-García, Anthime Flaus, Jorge Hernando, Andreas Kluge, Monika Breuninger, Serhii Melnyk, Konstantin Zhernosekov, Jaume Capdevila, for the COMPETE Investigator Team*



Number at risk (censored)	0	3	6	9	12	15	18	21	24	27	30*	33
[¹⁷⁷ Lu]Lu-edotreotide	207 (0)	195 (7)	157 (15)	138 (20)	120 (28)	112 (30)	104 (31)	83 (40)	68 (49)	51 (62)	31 (79)	0 (106)
Everolimus	102 (0)	91 (7)	58 (18)	48 (22)	36 (25)	32 (27)	27 (30)	20 (32)	14 (37)	11 (40)	2 (49)	0 (51)

Clinical and Translational Imaging
<https://doi.org/10.1007/s40336-026-00797-1>

CORRESPONDENCE

From clinical practice to the COMPETE trial: PRRT confirms superiority over everolimus

Elena Zanetti¹ · Luca Urso^{1,2} · Mirco Bartolomei²

Received: 15 July 2026 / Accepted: 23 August 2026
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In conclusion, in a landscape where a growing number of systemic options are becoming available, COMPETE provides the first randomized evidence directly supporting PRRT over everolimus. As clinical practice continues to evolve toward earlier and more individualized use of PRRT, the COMPETE trial places yet another brick on the path forward.

Anticipare la RLT

Endocrine
<https://doi.org/10.1007/s12020-022-03170-0>

MINI REVIEW

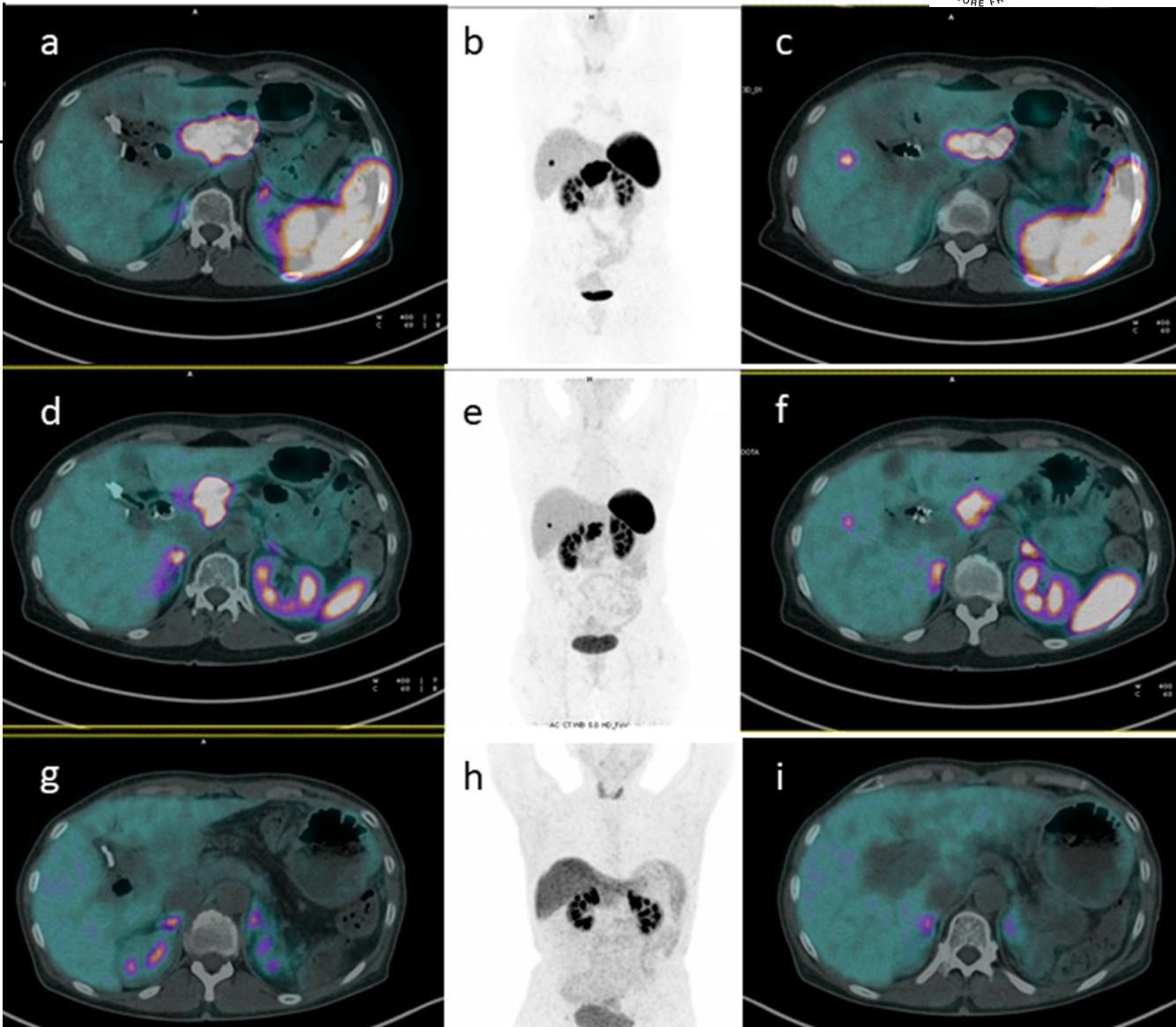
Radioligand therapy (RLT) as neoadjuvant treatment for inoperable pancreatic neuroendocrine tumors: a literature review

Luca Urso^{1,2} · Alberto Nieri¹ · Ilaria Rambaldi¹ · Angelo Castello³ · Licia Uccelli^{1,2} · Corrado Cittanti^{1,2} · Stefano Panareo⁴ · Irene Gagliardi⁵ · Maria Rosaria Ambrosio⁵ · Maria Chiara Zatelli⁵ · Mirco Bartolomei¹

Table 1 Literature review of neoadjuvant RLT in PanNETs

Study	Year	Patients treated	Radionuclide used	Outcome	Toxicity
Kaemmerer et al. [21]	2009	1	⁹⁰ Y-DOTATOC (2 cycles)	CR after surgery	Only mild transient hematologic toxicity
Stoeltzing et al. [34]	2010	1	⁹⁰ Y-DOTATOC (2 cycles)	CR after 1 year from surgery	Not reported
Ezzidin et al. [22]	2012	1	¹⁷⁷ Lu-DOTATATE (3 cycles)	Inoperable PAN-NET became eligible for surgery achieving a complete local remission for 22 months	Minor transient leukopenia (Grade 1)
Barber et al. [28]	2012	5 (4)	¹⁷⁷ Lu-DOTATATE (1–4 cycles)	3 scintigraphic PR; 4 radiological PR and 1SD. 1 patient affected by PanNET became eligible for surgery with a reduction in Ki67 from 10–15% to 5%.	Not reported
Van Vliet et al. [23]	2015	29	¹⁷⁷ Lu-DOTATATE (3–4 cycles)	9/29 patients became amenable for surgery and had an increase in PFS vs. control group (69 vs. 49 months)	No patients showed delayed toxicity
Partelli et al. [16]	2018	23	¹⁷⁷ Lu/90Y-DOTATATE (20/3 pt.)	• No pancreatic fistula development in RLT patients. • Longer PFS in RLT patients with R0 resection.	Only 1 patient had hematologic toxicity and stopped RLT
Da Silva et al. [24]	2018	1	¹⁷⁷ Lu-DOTATATE	Patient became eligible for surgery and was tumor-free after 3-year follow up	No RLT-induced toxicity reported
Zanata et al. [25]	2021	1	⁹⁰ Y-DOTATOC	Patient became eligible for surgery and was tumor-free after 108 months follow up. Disease downstaging from stage IV to stage I.	Not reported
Parghane et al. [26]	2021	57 (32)	¹⁷⁷ Lu-DOTATATE	6/32 PanNETs became resectable after RLT. Primary tumors and liver metastasis decreased in size.	Not reported
Opalinska et al. [27]	2021	9 (6)	¹⁷⁷ Lu/90Y-DOTATATE	Median primary tumor size decreased by 1.6 cm after RLT, with no differences between Pan-NETs and other GEP-NETs. 4/9 patients became resectable after RLT and in 2 a radical surgery was achieved. Liver metastases became undetectable in 2 patients.	No myelotoxicity or nephrotoxicity found
Minczeles et al. [29]	2022	49	¹⁷⁷ Lu-DOTATATE	Patients with neoadjuvant RLT followed by surgery had a longer PFS and OS than those who performed only RLT. A downstaging was found in the 38% of patients with baseline tumor-vessel involvement	47% of patients had transient hematologic toxicity. G3 liver toxicity was found in 1 patient

Treated patients: the number within brackets indicates the number of PanNETs among the cohort of patients treated with RLT.
CR complete response, PanNET pancreatic neuroendocrine tumors, PFS progression free survival, PR partial response, RLT radioligand therapy, SD stable disease.



Neoadjuvant ^{177}Lu -DOTATATE for non-functioning pancreatic neuroendocrine tumours (NEOLUPANET): multicentre phase II study

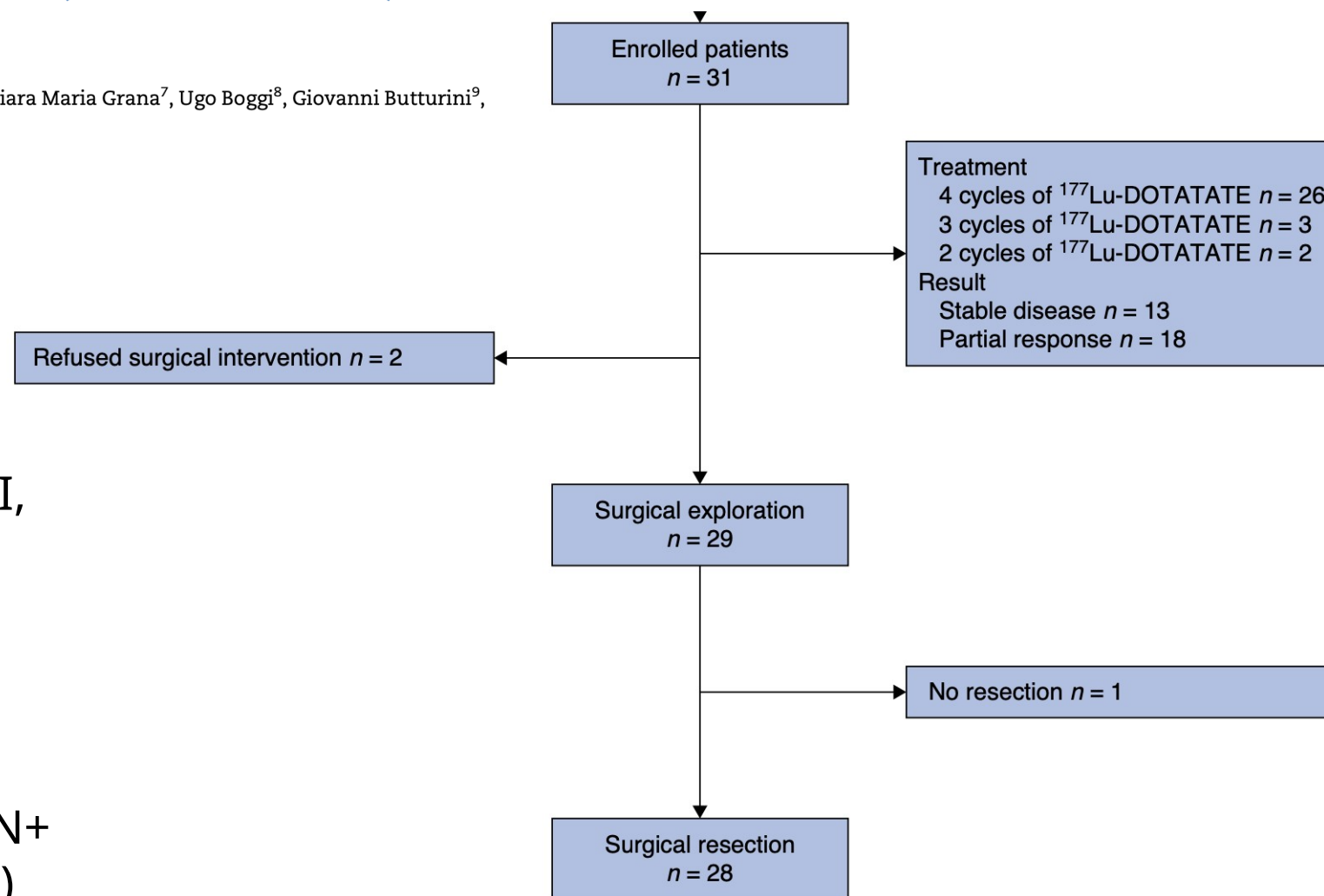
Stefano Partelli^{1,2}, Luca Landoni³, Mirco Bartolomei⁴, Alessandro Zerbi^{5,6}, Chiara Maria Grana⁷, Ugo Boggi⁸, Giovanni Butturini⁹, Riccardo Casadei^{10,11}, Roberto Salvia³ and Massimo Falconi^{1,2,*}

Prospective, multicenter, phase II,
single arm study

Enrolled Pan-NET:

- Resectable
- Potentially resectable (high T grade, vascular involvement, N+ disease, liver oligometastases)

<https://doi.org/10.1093/bjs/znae178>

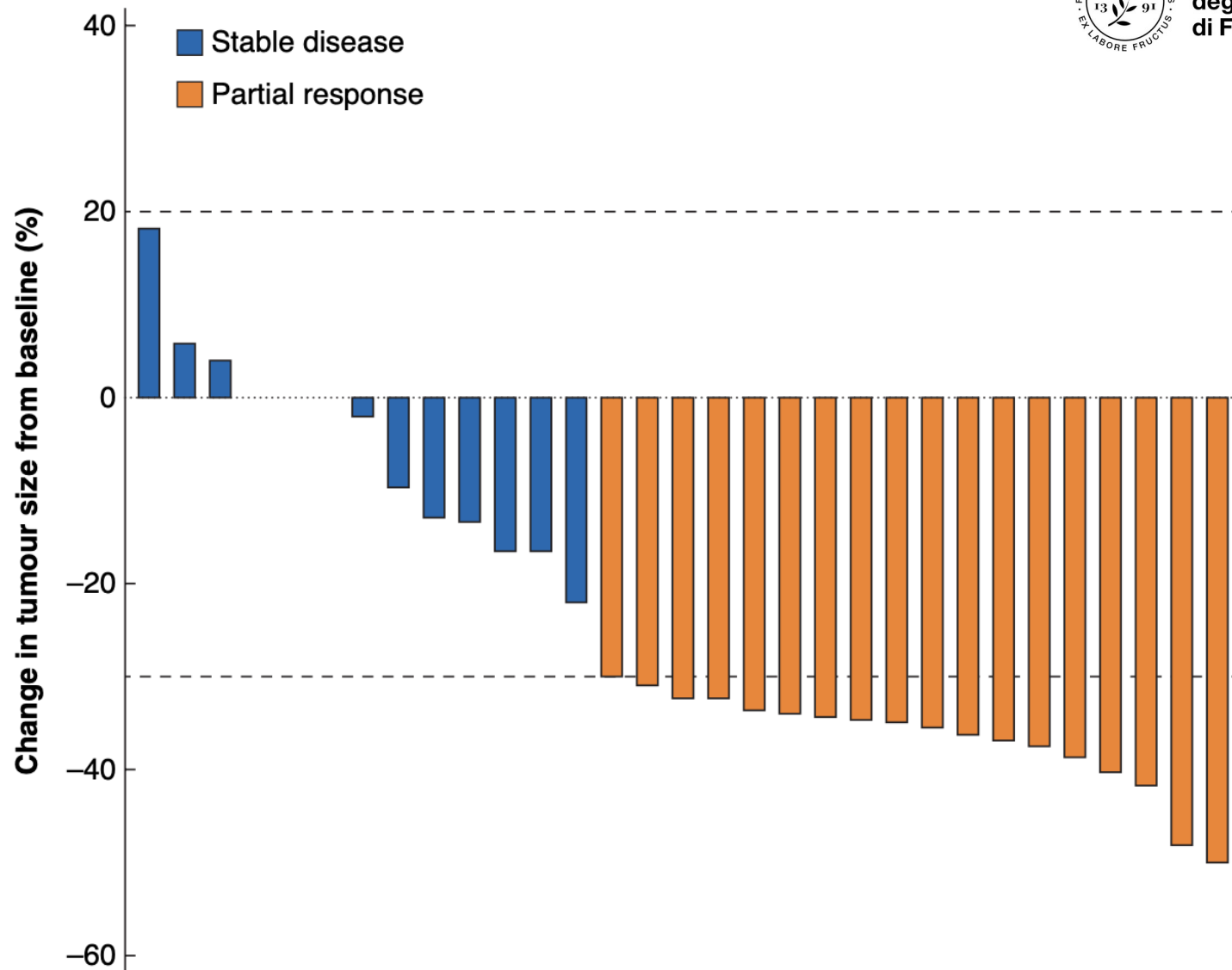


This prospective study has shown that neoadjuvant ^{177}Lu -DOTATATE is **safe and effective** for patients with resectable or potentially resectable NF-PanNETs at high risk of disease recurrence.

^{177}Lu -DOTATATE **did not reduce the rate of postoperative complications** as suggested by previous retrospective studies.

PR was observed in 60% of patients which is significantly higher than what is reported in the literature:

- NETTER-1: 18%
- Other literature: 25-35%



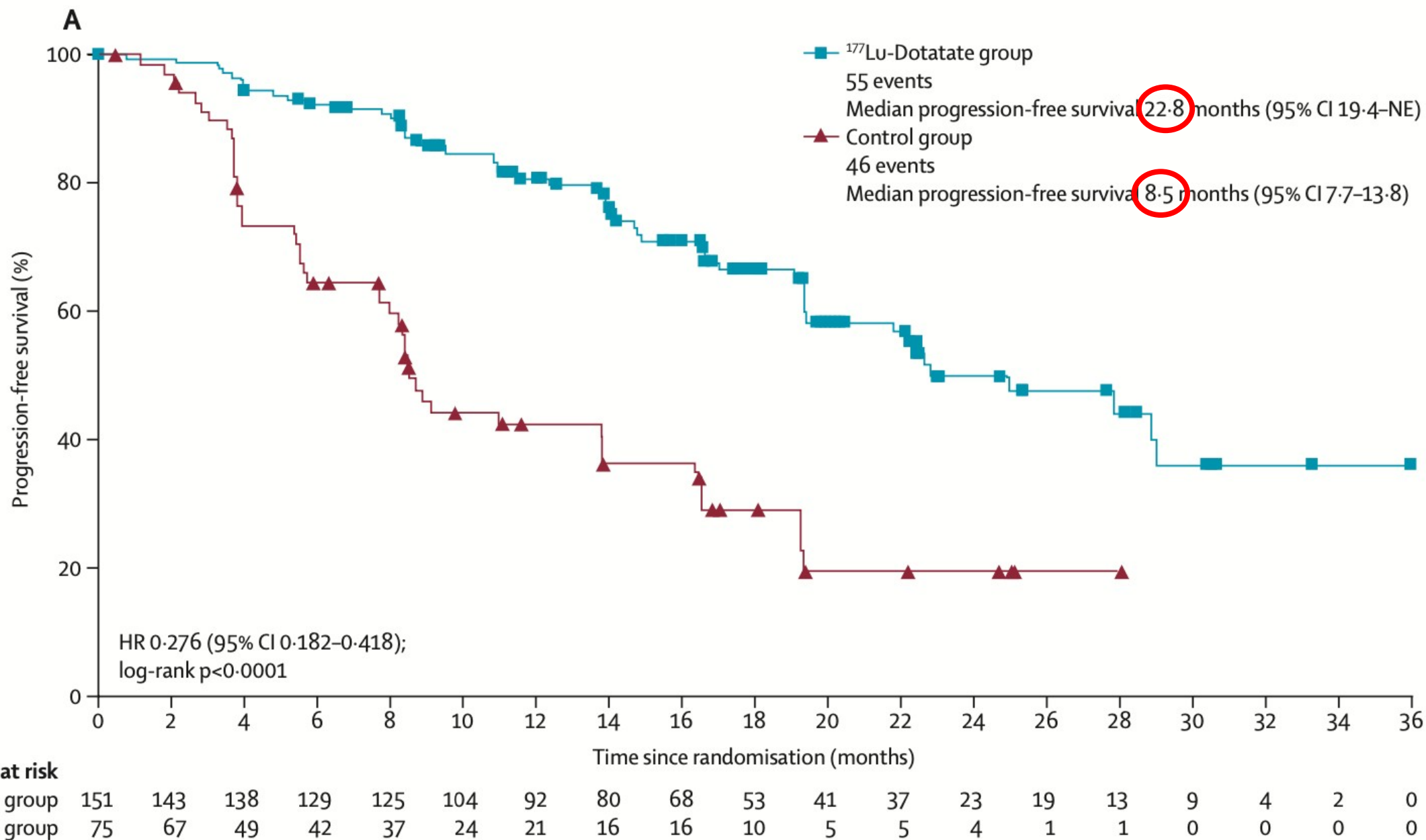
Dal Netter-1 al Netter-2

NETTER-1 (previous study)

- ^{177}Lu -DOTATATE plus 30 mg octreotide LAR provided a significant PFS increase in patients with progressive midgut carcinoid tumors compared to 60 mg octreotide LAR.
- Adult patient population included 34.5% of patients with G2 NET (65.5% G1), G3 NETs were excluded.
- Only patients progressive on SSAs were eligible (2nd line), SSA-naïve patients were excluded.

NETTER-2 (current study)

- Focuses on **high proliferation rate GEP-NET (G2 and G3 - $10 \leq \text{KI-67} \leq 55$)**.
- **Open to adolescents** aged ≥ 15 years and >40 kg body weight
- ^{177}Lu -DOTATATE is given as **1st line treatment** (**SSA-naïve** patients are eligible, as well as patients previously treated **with SSAs in the absence of progression**) and compared to treatment with high dose (60 mg) octreotide LAR.



L'accesso alla PRRT

Clinical and Translational Imaging
<https://doi.org/10.1007/s40336-024-00636-1>

COMMENT

Considerations on the preliminary results of the NETTER-2 trial: is the glass half full or half empty?

Mirco Bartolomei¹ · Alberto Nieri¹ · Licia Uccelli^{1,2} · Luca Urso^{1,2}



All NENs and RLT with [177Lu]Lu-Dotatate (in Italy)		Older diagnosis 2 nd or 3 th ... line <i>metastasized or locally advanced, inoperable, in progression to SSAs</i>	Age ≥ 18 years	Age ≥ 15 years	Recent diagnosis 1 st line <i>metastasized or locally advanced, inoperable, naïve for SSAs</i>	Re-treatment
GEP NENs	G1	NETTER-1			NETTER-3	NA
	G2 < 10%					
	G2 ≥ 10%			NETTER-2		
	G2 ≤ 20%					
	G3 ≤ 55%					
	G3 > 55%	Minor benefit				
Non-GEP NENs	Lung Thymus	NA	NA	NA	NA	NA
	Paraganglioma Pheochromocytoma Neuroblastoma	NA	NA	NA	NA	NA
	Meningioma Thyroid-derived Other	NA	NA	NA	NA	NA
	CUP	NA	NA	NA	NA	NA

22 anni,
Paraganglioma
laterocervicale destro,
Ki-67 5%



pharmaceutics



Università
degli Studi
di Ferrara

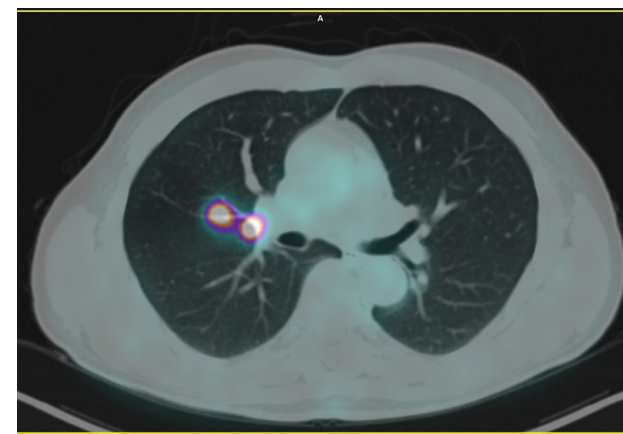
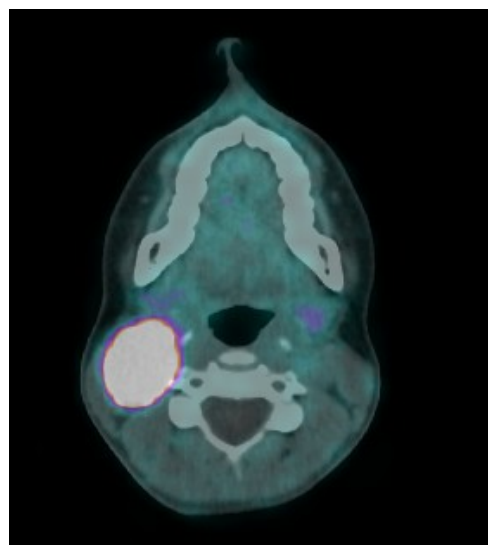
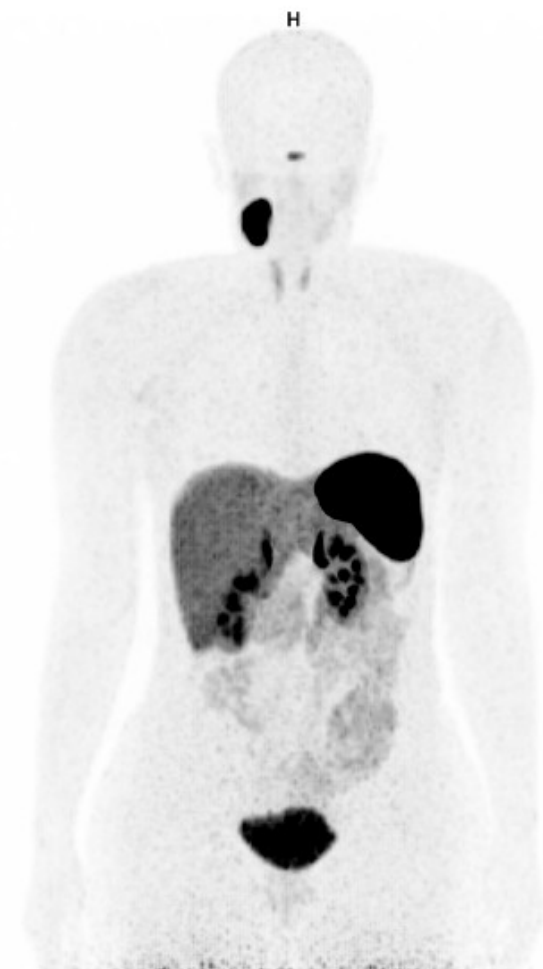
56 anni, carcinoide
polmonare atipico,
Ki-67 5%

Review

Lutathera[®] Orphans: State of the Art and Future Application of Radioligand Therapy with ¹⁷⁷Lu-DOTATATE

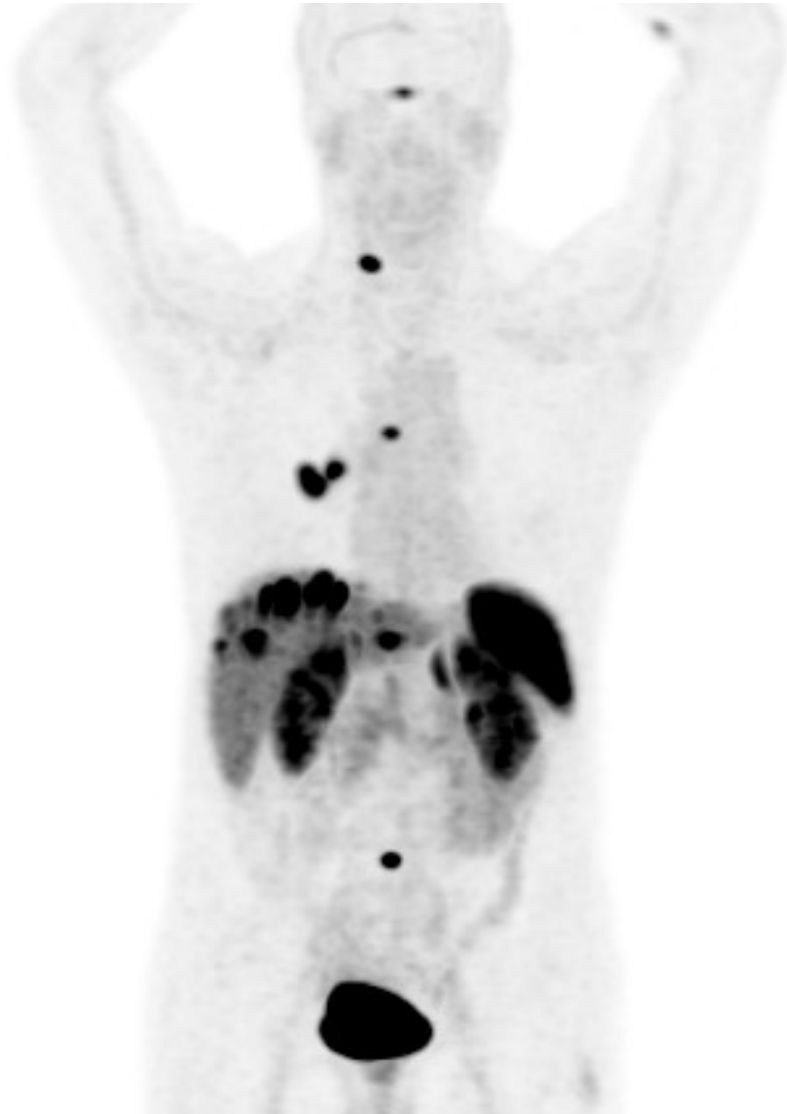
Luca Urso ^{1,2}, Alberto Nieri ³, Licia Uccelli ^{1,3,*}, Angelo Castello ⁴, Paolo Artioli ⁵, Corrado Cittanti ^{1,3}, Maria Cristina Marzola ², Luigia Florimonte ⁴, Massimo Castellani ⁴, Sergio Bissoli ⁵, Francesca Porto ¹, Alessandra Boschi ⁶, Laura Evangelista ⁷ and Mirco Bartolomei ³

**La terapia con radioligandi dei
tumori orfani di RLT è un
unmet clinical need!!**



Carcinoide polmonare atipico metastatico, Ki67 = 5%

**Pre
RLT**



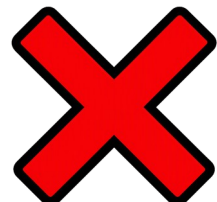
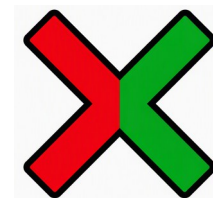
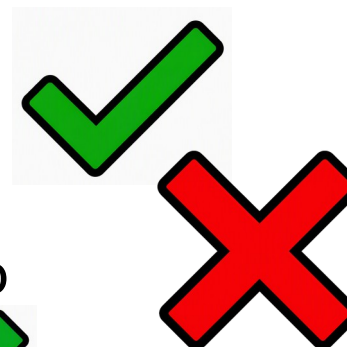
**Post
RLT**



Take Home Messages



- PRRT: terapia consolidata nei GEP-NET
- ~~Innovazione~~ Miglioramento:
 - Migliore selezione del paziente
 - Personalizzazione del trattamento
 - Miglioramento del timing
 - Accesso





CARCINOMA PROSTATICO

dalla diagnosi alla terapia, un percorso multidisciplinare

Ferrara, 9 ottobre 2026

