

Séminaire de Radiothérapie Interne Vectorisée

14-16 mars 2022 - montpellier

Théranostique et rôle en RIV

Elif Hindié

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Université de Bordeaux*



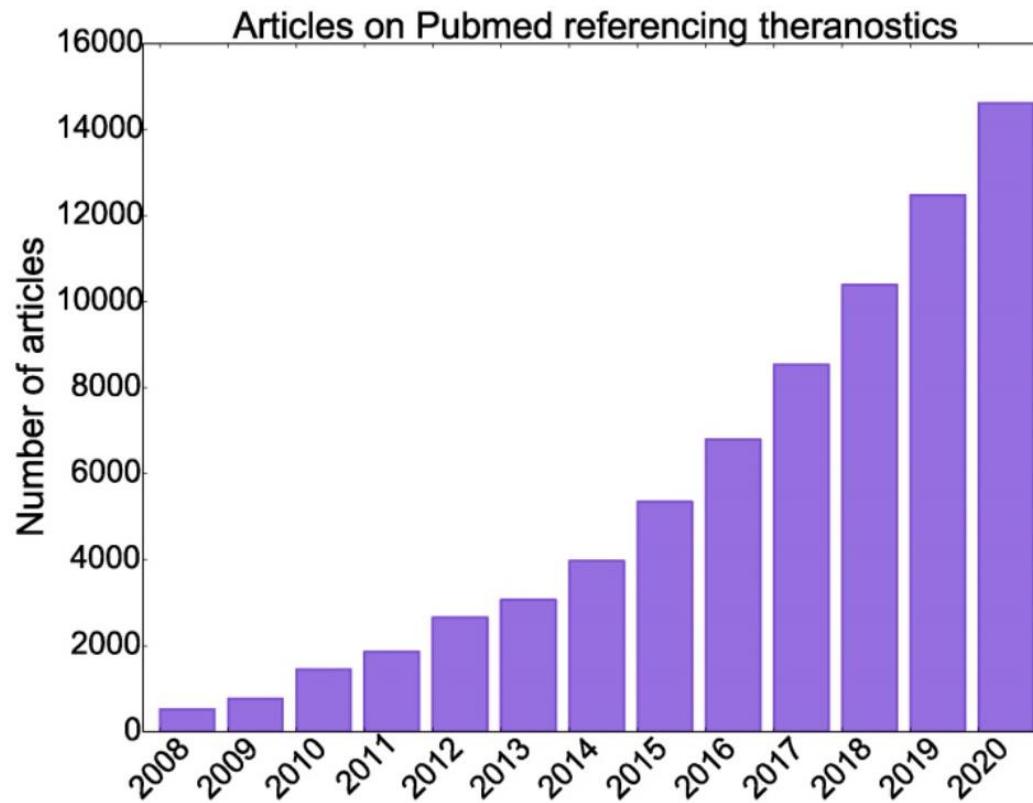
CENTRE
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de BORDEAUX

**30 IUF
ANS**
institut
universitaire
de France
1991 - 2021


Institut de Neurosciences Cognitives
et Intégratives d'Aquitaine

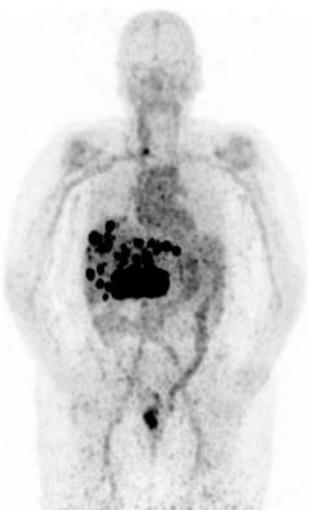
- Number of articles published on PubMed containing the words “theranostics” or “theragnostics” from 2006 to 2020.



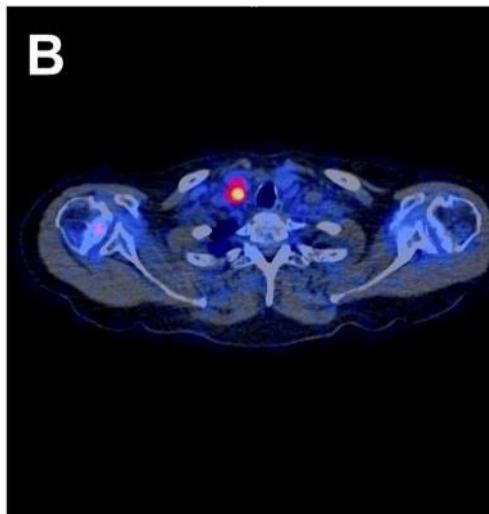
- The word "theranostics" is derived from the combination of the words "**therapeutics**" and "**diagnostics**"...
- It is now most commonly applied to the field of nuclear medicine where radioactive molecules are attached to gamma or positron emitters for SPECT or PET imaging, and to beta, alpha or Auger electrons for therapy.
- **Theranostics** is a personalised approach to treating cancer, using similar molecules for both imaging (diagnosis) and therapy...
- **Theranostics and theragnostics are interchangeable terms**... derived from the Greek words "thera" from "therapeia" meaning healing or to heal, e.g. therapy, and "gnostic" from Greek "gnos" meaning knowledge and to know, e.g. diagnostic...
- **Radiotheranostics (*radiotheragnostics*)** is a subspecialty of theranostics using similar pharmaceuticals for both imaging and therapy with radiation. The pharmaceutical or mechanism of localization/action remains the same with the radionuclide being interchangeable...

L'imagerie moléculaire peut également s'intégrer dans une démarche théranostique hors RIV

A



B



^{89}Zr -trastuzumab PET imaging in a patient with HER2-positive metastatic breast cancer imaged 4 d after injection.

[Theranostics Using Antibodies and Antibody-Related Therapeutics.](#)

Moek KL.

J Nucl Med. 2017; 58(Suppl 2):83S-90S.

Theranostic Targets

«pour la RIV»

- Somatostatin receptors (SSTRs) are theranostic targets in neuroendocrine tumors (NET). Somatostatin analogs bind to somatostatin receptor. When combined with diagnostic radionuclides are utilized for diagnosis. When combined with therapeutic radionuclides are effective in treating neuroendocrine tumors.
 - Prostate-specific membrane antigen (PSMA) is a molecular target for both imaging diagnostics and therapeutics, i.e., a theragnostics target.
-
- [Theragnostics in prostate cancer.](#)
Farolfi A, et al. Q J Nucl Med Mol Imaging. 2021; 65:333-41.
 - [Net theranostics.](#)
Ichikawa Y, et al. Cancer Sci. 2022 Mar 10.

Theragnostics before we found its name.

Modoni S, Frangos S, Iakovou I, Boero M, Mansi L.

Q J Nucl Med Mol Imaging. 2021; 65: 299-305.

- The birth of what we call today theragnostics can be traced in 1936, with the proposal of radioiodine, the first radiopharmaceutical approved in 1951 by FDA, in USA, as ^{131}I sodium iodide.
- Proposed in first eighties as $[^{131}\text{I}]$ Metaiodobenzylguanidine (MIBG), the theragnostic couple $^{123}\text{I}/^{131}\text{I}$ MIBG is still used in neural crest tumors.
- The "Theragnostics called with this name" can be dated to early 90's with the first proposal of the somatostatin model in neuroendocrine tumors with radio-chelates usable for diagnosis and therapy.
- Since then, many investigators are working on new theragnostics agents. The fast growth is stimulated by the interest of big pharma.
- Theragnostic concepts are the roots of nuclear medicine and new great goals are soon to be achieved in the direction of an increasing precision and tailored medicine.

Radiothérapie Interne Vectorisée par iode-131 du Cancer de la Thyroïde et de l'Hyperthyroïdie

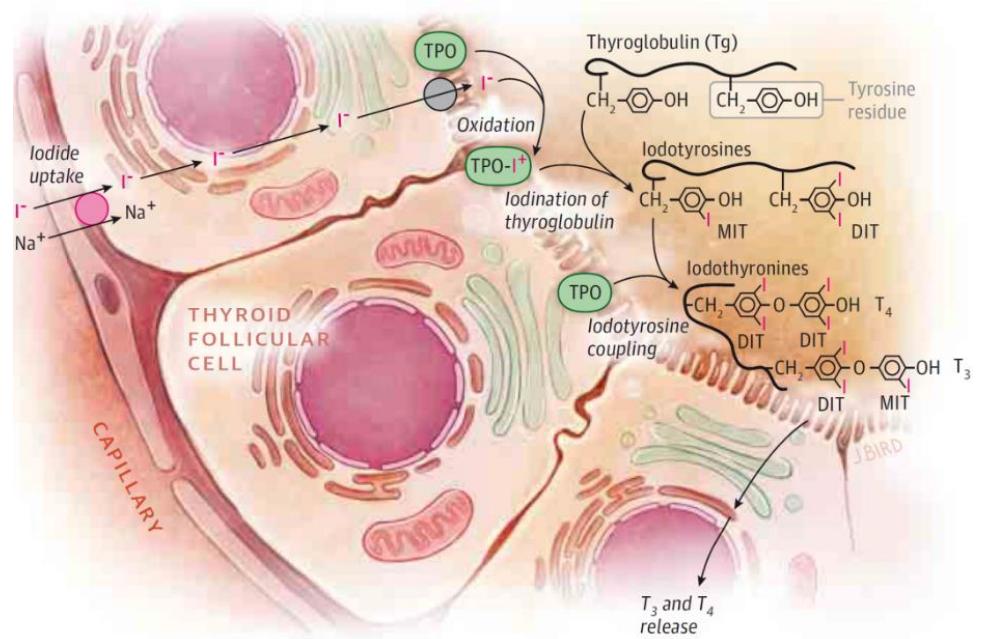
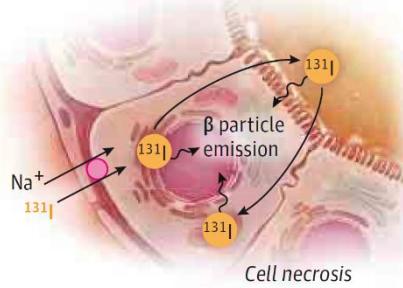
Thérapie ciblée mettant à profit l'expression au niveau des cellules thyroïdiennes normales et tumorales du NIS « sodium-iodide symporter »

[Cloning and characterization of the thyroid iodide transporter.](#)

Dai G, Levy O, Carrasco N.
Nature. 1996 Feb 1; 379:458-60.

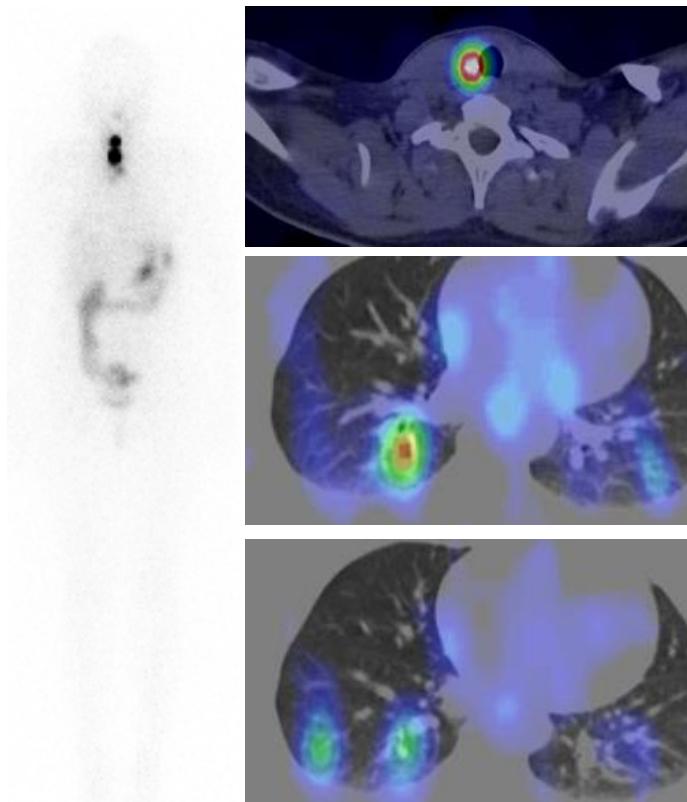
Burch HB, Cooper DS,
JAMA 2015; 314: 2544-54.

Radioactive iodine (RAI)



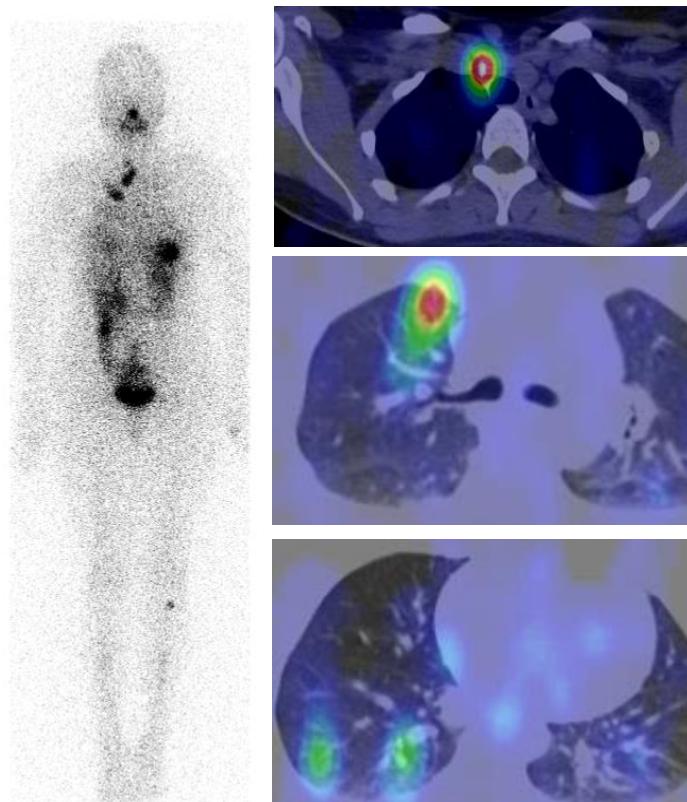
29-year-old woman: TNM 2017: pT3bN1b (CHU Bordeaux)

First ^{131}I treatment (3.7 GBq)
« post-surgery ablation »



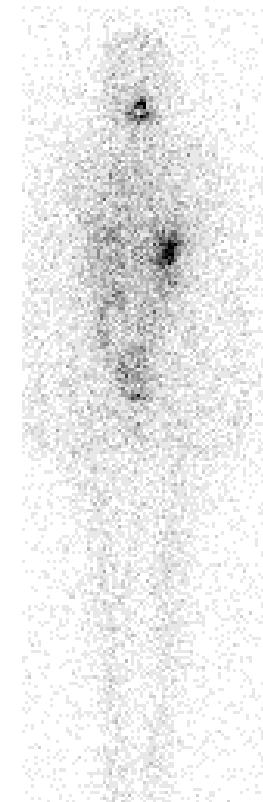
Tg (off T4) = 12.7 ng/mL

2nd ^{131}I treatment (3.7 GBq) for
LN and pulmonary metastases



Tg=9

3rd ^{131}I treatment
« negative WBS »

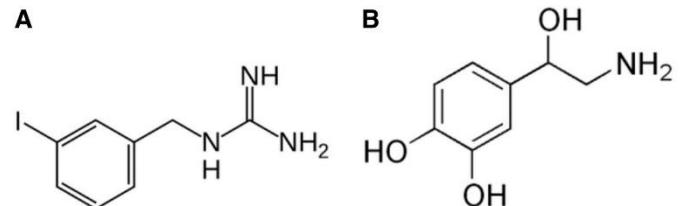


Tg=3.6

Imagerie et Traitement par Ciblage du Transporteur de la Noradrénaline

^{123}I / ^{131}I -MIBG

« Meta-iodo-benzyl-guanidine »



^{123}I -MIBG :

imagerie scintigraphique très utile dans la prise en charge du **neuroblastome**

^{131}I -MIBG :

Utilisée dans le traitement des **neuroblastomes** à haut-risque, en rechute ;
Egalement dans les **paragangliomes/phéochromocytomes** métastatiques

[Norepinephrine Transporter as a Target for Imaging and Therapy.](#)

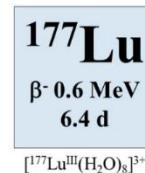
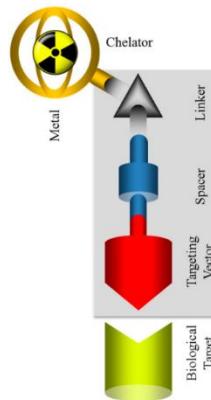
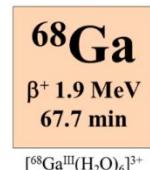
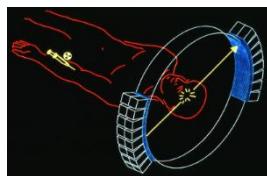
Pandit-Taskar N, Modak S.

J Nucl Med. 2017; 58(Suppl 2):39S-53S.

Théranostique

- Contraction de « Thérapie et Diagnostique »
- Médecine personnalisée : Traitement guidé par un biomarqueur
- En médecine nucléaire cela signifie *Imager et traiter* : La possibilité d'administrer une « radiothérapie interne vectorisée » sur la base d'une « imagerie moléculaire préalable »

68Ga: pour l'imagerie TEP
« Tomographie par Emission de Positons »



177Lu: pour la RIV
« Radiothérapie Interne
Vectorisée »

Rösch F, Herzog H, Qaim SM.
Pharmaceutics (Basel). 2017; 10(2).

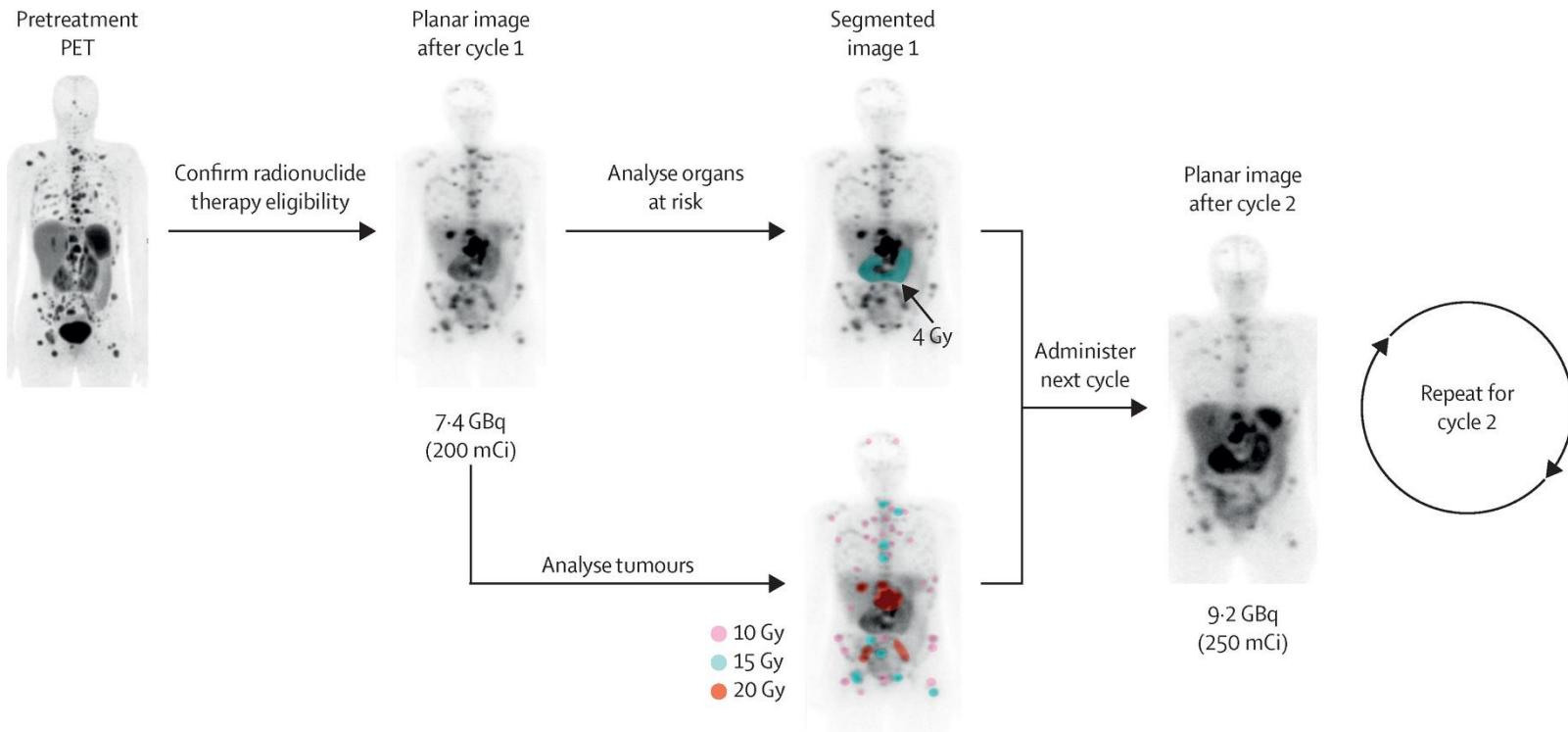
Molécule spécifique pour ciblage + Chélate + Radionucléide

- Theranostics allows us to “see what we treat and treat what we see”

Recent advances in theranostics and challenges for the future.
Turner JH. Br J Radiol. 2018; 91:20170893.

Dosimetry in radionuclide therapy: the clinical role of measuring radiation dose.

Lawhn-Heath C, et al. Lancet Oncol. 2022; 23:e75-e87.

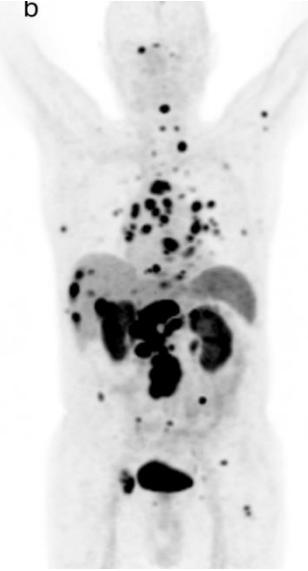


- Dosimetry after each cycle of 177Lu-Dotatacept radionuclide therapy for patients with neuroendocrine tumours

Evénement marquant-1 : Imagerie et Traitement des tumeurs neuroendocrines (TNE) par ciblage des Récepteurs de la Somatostatine

Imagerie

b



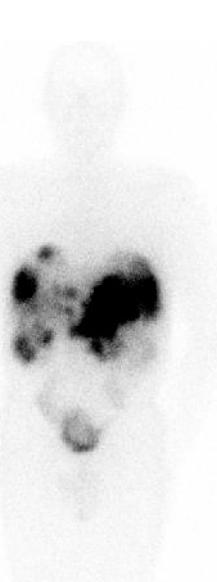
**68Ga-DOTATATE
TEP-TDM**

Traitement



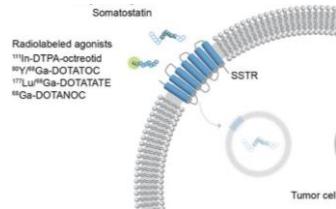
177Lu-DOTATATE
(Lutathera – AAA/Novartis)

(Scintigraphie post-administration
- γ 208 keV)



Octreoscan
111In-Pentétrotide

TNE-GEP : Surexpression des récepteurs de la somatostatine au niveau de la membrane des cellules tumorales.



Somatostatin
Radiolabeled agonists
 ^{111}In -DTPA-octreotide
 ^{111}In - ^{113}In -Ga-DOTATOC
 ^{177}Lu - ^{111}In -Ga-DOTATATE
 ^{68}Ga -DOTANOC
SSTR
Tumor cell

Evénement marquant-1 : Imagerie et Traitement des tumeurs neuroendocrines (TNE) par ciblage des Récepteurs de la Somatostatine

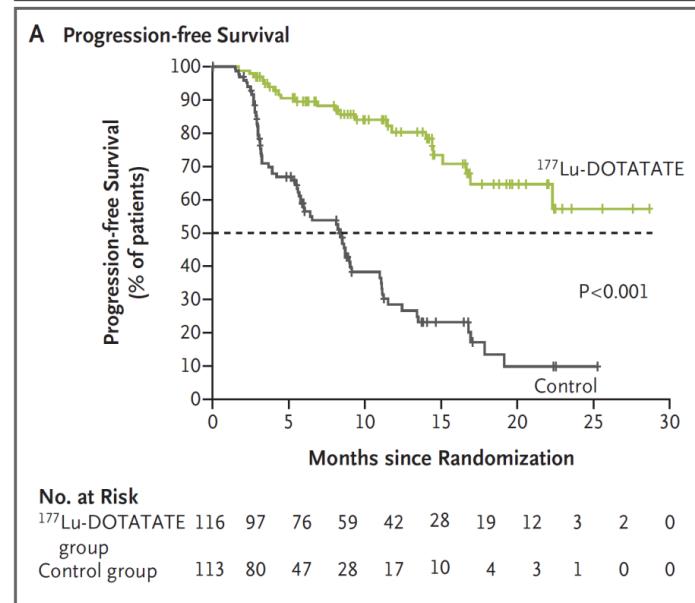
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

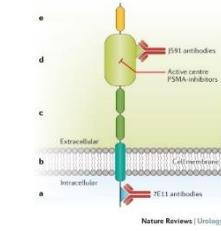
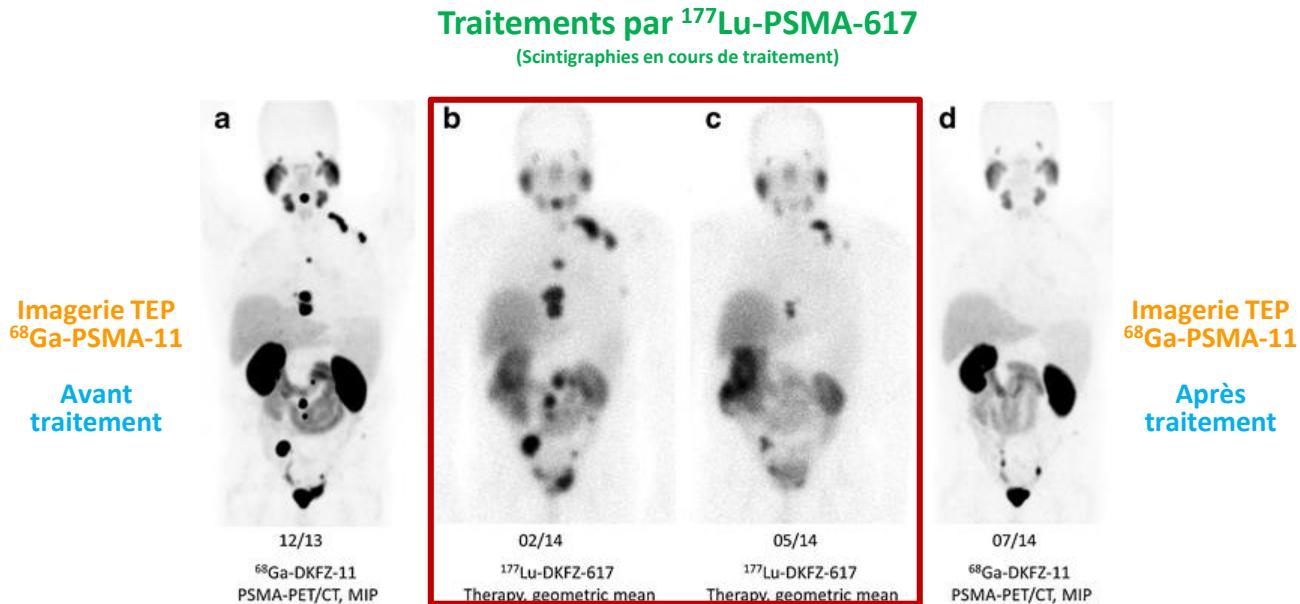
J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, 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*

N ENGL J MED 376;2 NEJM.ORG JANUARY 12, 2017



- Hazard ratio for disease progression or death with ^{177}Lu -Dotatate vs. control: 0.21 (95% CI, 0.13 to 0.33; $P < 0.001$)

Evénement marquant-2 : Imagerie et Traitement du Cancer de la Prostate Métastatique par ciblage du PSMA



PSMA : Prostate-specific Membrane Antigen
Surexprimée dans les cellules cancéreuses de la prostate.
Expression qui augmente dans les phases avancées de la maladie métastatique résistante à la castration

- Patient with metastatic Prostate Cancer**
- ^{68}Ga -PSMA PET/CT (a) demonstrates a tumour phenotype with strong PSMA expression.
 - The patient was treated with a cumulative activity of 7.4 GBq ^{177}Lu -DKFZ-617 (b, c).
 - Restaging with ^{68}Ga -PSMA PET/CT (d) reveals a striking radiological response.
 - PSA level decreased from 38.0 to 4.6 ng/ml.

[\$^{177}\text{Lu}\$ Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer.](#)
Kratochwil C, et al.
Eur J Nucl Med Mol Imaging. 2015 May; 42:987-8.

Evénement marquant-2 : Imagerie et Traitement du Cancer de la Prostate Métastatique par ciblage du PSMA

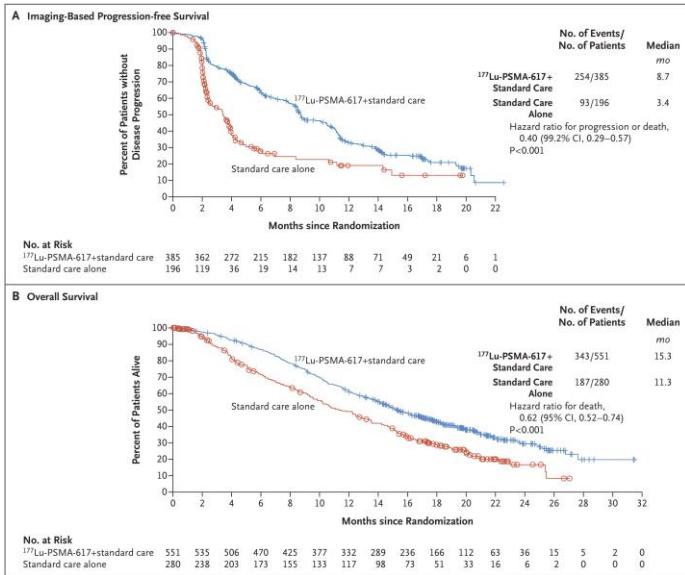
N ENGL J MED 385;12 NEJM.ORG SEPTEMBER 16, 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*



[¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt, Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Gumiński, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet*, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†

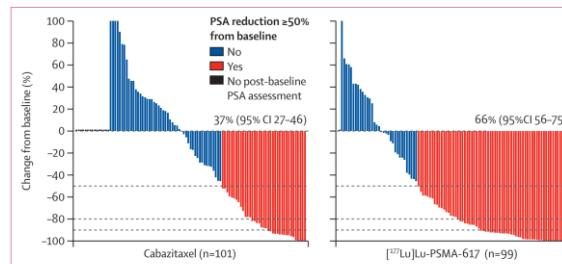


Figure 2: PSA response
PSA=prostate-specific antigen. ¹⁷⁷Lu=lutetium-177.

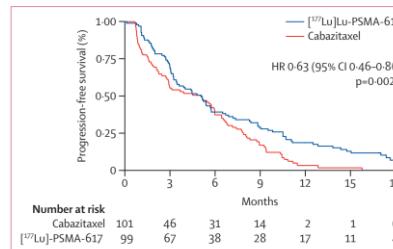


Figure 3: Radiographic or PSA progression-free survival
HR=hazard ratio. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. ¹⁷⁷Lu=lutetium-177.

	[¹⁷⁷ Lu]-PSMA-617 (n=98)	Cabazitaxel (n=85)		
Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	19 (19%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown.
¹⁷⁷Lu=Lutetium-177; PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Fibrile neutropenia.

Table 2: Adverse events

Radiotheranostics: a roadmap for future development.

Herrmann K, et al.

Lancet Oncol. 2020; 21:e146-e156.

	Ligand	Therapeutic isotope	Imaging isotope	Target	Manufacturer	Disease	Clinical trial phase or approval date
Iodine	None	¹³¹ I	¹²⁴ I, ¹³¹ I	Nal symporter	Curium, GE Healthcare	Thyroid cancer	NA
Dotatate (Lutathera)	Peptide	¹⁷⁷ Lu	⁶⁸ Ga, ¹¹¹ In	SS2R	Adacap (Novartis)	Neuroendocrine tumours	Approved, 2018
Satoreotide tetraoctetan	Peptide	¹⁷⁷ Lu	⁶⁸ Ga	SS2R	Ipsen	Neuroendocrine tumours, small-cell lung cancer, and breast cancer	Phase 1 and 2
PSMA-617	Small molecule	¹⁷⁷ Lu	⁶⁸ Ga, ¹⁸ F	PSMA	Adacap (Novartis)	Castration-resistant prostate cancer	Phase 3
Lexidronam (Quadramet)	None	¹⁵³ Sm	⁹⁹ Tc, ¹⁸ NaF	New bone formation	Lanthus	Bone metastases	Approved, 1997
Radium223 (Xofigo)	None	²²³ Ra	⁹⁹ Tc, ¹⁸ NaF	Calcimimetic	Bayer	Prostate cancer and bone metastases	Approved, 2013
Strontium89 (Metastron)	None	⁸⁹ Sr	¹⁸ NaF	New bone formation	GE Healthcare	Bone pain	Approved, 1993
Ibritumomab tiuxetan (Zevalin)	Antibody	⁹⁰ Y	None	CD20	Spectrum Pharmaceuticals	Relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma	Approved, 2002
Tositumomab (Bexxar)	Antibody	¹³¹ I	¹²⁴ I, ¹³¹ I	CD20	GlaxoSmithKline	Low-grade, transformed low-grade, or follicular large-cell lymphoma	Approved, 2003; withdrawn, 2014
Iobenguane (Azedra)	Antibody	¹³¹ I	¹²³ I, ¹²⁴ I	Norepinephrine transporter	Progenics	Pheochromocytoma and Paraganglioma	Approved, 2018
Apamistamab (Iomab-B)	Antibody	¹³¹ I	None	CD45	Actinium Pharmaceuticals	Bone marrow ablation	Phase 3
Lilotomab satetraxtetan (Betalutin)	Antibody	¹⁷⁷ Lu	None	CD37	Nordic Nanovector	Indolent non-Hodgkin lymphoma, follicular lymphoma, diffuse large B-cell lymphoma	Phase 1 and 2
Omburtamab	Antibody	¹³¹ I	None	CD276	Ymabs Therapeutics	Neuroblastoma, CNS metastases, and small-round-cell tumour	Phase 2 and 3
3BP-227	Small molecule	¹⁷⁷ Lu	¹⁷⁷ Lu	NTSR1	Ipsen	Pancreatic ductal adenocarcinoma, colorectal cancer, and gastric cancer	Phase 1
FAPI	Small molecule	⁹⁰ Y, ²³¹ Bi, or ²¹² Pb	⁶⁸ Ga, ¹⁸ F	FAP	Sofie Biosciences	Pancreatic ductal adenocarcinoma, colorectal cancer, and head and neck cancer	Compassionate use (Germany)
Pentixather	Peptide	¹⁷⁷ Lu or ⁹⁰ Y	⁶⁸ GA	CXCR-4	Pentixapharm	Multiple myeloma and lymphoma	Compassionate use
Glass microspheres	None	⁹⁰ Y	None	Tumour vessels (angiogenesis)	BTG (Boston Scientific)	Hepatocellular carcinoma	Approved, 2000
Resin microspheres	None	⁹⁰ Y	None	Tumour vessels (angiogenesis)	Sirtex	Hepatocellular carcinoma and liver metastases	Approved, 1998
Microspheres	None	¹⁶⁶ Ho	¹⁶⁶ Ho	Tumour vessels (angiogenesis)	Terumo	Hepatocellular carcinoma and liver metastases	Phase 2

The list shows common radiotheranostics, but is not comprehensive. The availability and development of radiotheranostics varies between countries. NA=not applicable. SSR2=somatostatin receptor type 2. PSMA=prostate-specific membrane antigen. NTSR1=neurotensin receptor type 1. FAPI=fibroblast-activated protein inhibitor. FAP=prolyl endopeptidase FAP. CXCR-4=C-X-C chemokine receptor type 4.

Table 1: Summary of radiotheranostics for cancer treatment

Limites de l'approche théranostique comme substitut à la dosimétrie

- Radiotheranostics implies that the same targeting vector is suitable to be labeled with two different radionuclides maintaining similar biological and chemical features, whereby one is used for therapy, the second for imaging purposes.
- This would be the case for iodine radionuclides/iodine-labelled radiotheranostics.
- TRT is now mostly performed with radiometal-based radiopharmaceuticals, notably lutetium-177 that has no diagnostic isotope match. Gallium-68 is the most widely used diagnostic surrogate,
- **Can the therapeutic radiation dose from ^{177}Lu be predicted from diagnostic imaging? We should consider several potential pitfalls linked to:**
 - Differences in the ligands used for diagnosis and therapy
 - Differences in injected masses of the ligand between diagnosis and therapy
 - Differences in coordination chemistry between ^{68}Ga and ^{177}Lu and implication for chelators
 - Above all, differences in physical half-life between ^{68}Ga and ^{177}Lu
 - etc...

Limites de l'approche théranostique comme substitut à la dosimétrie

Table 6. Correlation strength between ^{68}Ga PET and ^{177}Lu SPECT markers, using Spearman rank correlation analysis, when used to label different pharmaceuticals. AUC = area under the curve, D/A₀ = absorbed dose per injected activity

^{68}Ga PET Marker	^{177}Lu SPECT Marker	Tracer	Location	Correlation	Source
SUV _{mean}	Effective Dose	PSMA-617	Main Organs	Moderate ($r = 0.61, P < 0.001$)	Wang et al. [64]
SUV _{mean}	AUC	PSMA-617	Tumor Lesions	High ($r = 0.907, P < 0.001$)	Wang et al. [64]
SUV _{max}	AUC	PSMA-617	Tumor Lesions	High ($r = 0.915, P < 0.001$)	Wang et al. [64]
SUV _{mean}	D/A ₀	DOTATOC (^{68}Ga) & Octreotide (^{177}Lu)	Tumor Lesions	Moderate ($r = 0.72, P < 0.001$)	Ezziddin et al. [62]
SUV _{max}	D/A ₀	DOTATOC (^{68}Ga) & Octreotide (^{177}Lu)	Tumor Lesions	Moderate ($r = 0.71, P < 0.001$)	Ezziddin et al. [62]
SUV _{mean} (in lesions)	Dose	PSMA-11 (^{68}Ga) & PSMA-617 (^{177}Lu)	Whole Body	Moderate ($r = 0.62, P < 0.01$)	Violet et al. [38]
SUV _{max} (before therapy)	Maximum Voxel Dose	DOTATOC/DOTATATE	Tumor Lesions	Moderate ($r = 0.76, P = 0.02$)	Hänscheid et al. [63]
SUV _{max} (after therapy)	Maximum Voxel Dose	DOTATOC/DOTATAT	Tumor Lesions	High ($r = 0.99, P = 0.003$)	Hänscheid et al. [63]

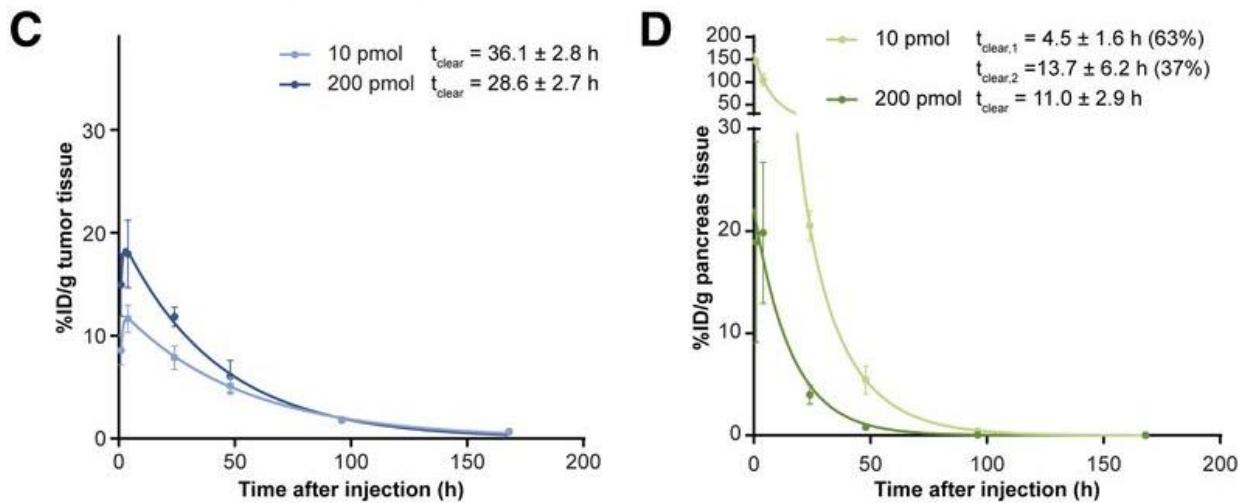
Implications of physics, chemistry and biology for dosimetry calculations using theranostic pairs.

Miller C, et al. Theranostics. 2022; 12: 232-59.

Our ability to develop multiple imaging tracers is a strength but also a weakness

- PET/CT with ^{68}Ga -labeled somatostatin analogs plays an important role in imaging neuroendocrine tumors (NET) and can identify patients who would potentially benefit from peptide receptor radionuclide therapy (PRRT) with ^{177}Lu -DOTA-TATE (Lutathera $^{\circledR}$).
- Two different diagnostic PET imaging molecules can be used :
 - ^{68}Ga -DOTA-TATE (NETSPOT $^{\circledR}$) in USA
 - ^{68}Ga -DOTA-TOC (SomaKit TOC $^{\circledR}$) in Europe
- What are the correspondence for patient selection with the Rotterdam scale previously established with the old tracer ^{111}In -octreotide?
- Cut-off for treatment decision that can be developed with one PET tracer (mean tumor SUV cut-off ; tumor-to-liver ratio, etc.) might not apply to the other tracer ; hampering international standardization.

The injected ligand mass have pharmacokinetic implications (differences in injected mass between the diagnostic and therapy procedure need to be considered).



- (C) Pharmacokinetic modeling of ^{177}Lu -NeoBOMB1 tumor uptake.
- (D) Pharmacokinetic modeling of ^{177}Lu -NeoBOMB1 pancreas uptake.

Differences in coordination chemistry/chelation do not allow to consistently find a match between the diagnostic and therapeutic ligand.

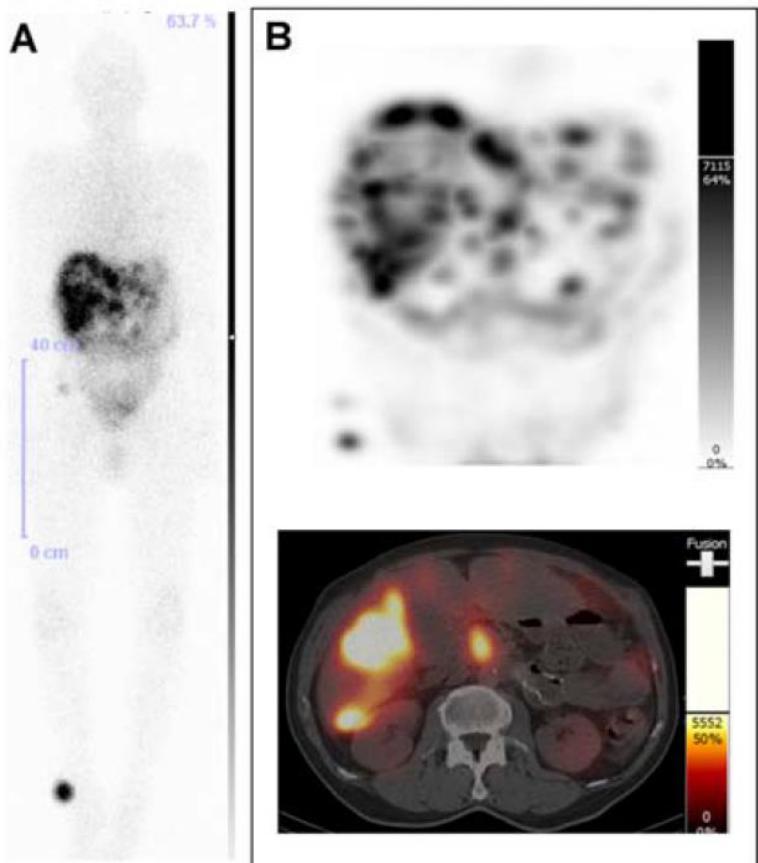
Few examples, among others:

- PSMA-11 could not be labelled with ^{177}Lu .
- There is currently no ^{68}Ga -labelled diagnostic counterpart to the novel NTR1 antagonist therapy agent ^{177}Lu -3BP-227.
- Different ligands are used for CXCR4 targeting :
 - imaging: ^{68}Ga -Pentixafor
 - therapy: ^{177}Lu -Pentixather

¹⁷⁷Lu-3BP-227 for neurotensin receptor 1-targeted therapy of metastatic pancreatic adenocarcinoma - first clinical results.

Baum RP, et al.

J Nucl Med. 2017 Oct 12.



¹⁷⁷Lu-3BP-227 scan of patient 1.

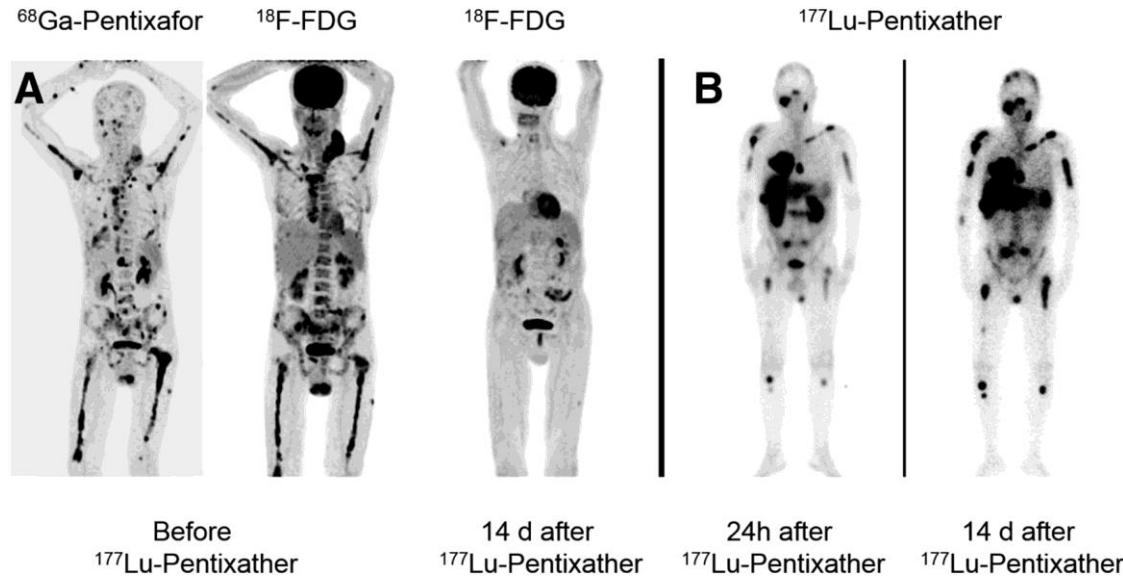
(A) Planar scintigraphy 24 h p.i.

(B) Upper panel: SPECT MIP 45 h p.i.

Lower panel: liver lesions and primary tumor, 45h p.i.

There is currently no ⁶⁸Ga-labelled imaging counterpart to the NTR1 antagonist ¹⁷⁷Lu-3BP-227 therapy agent.

Targeting CXCR4



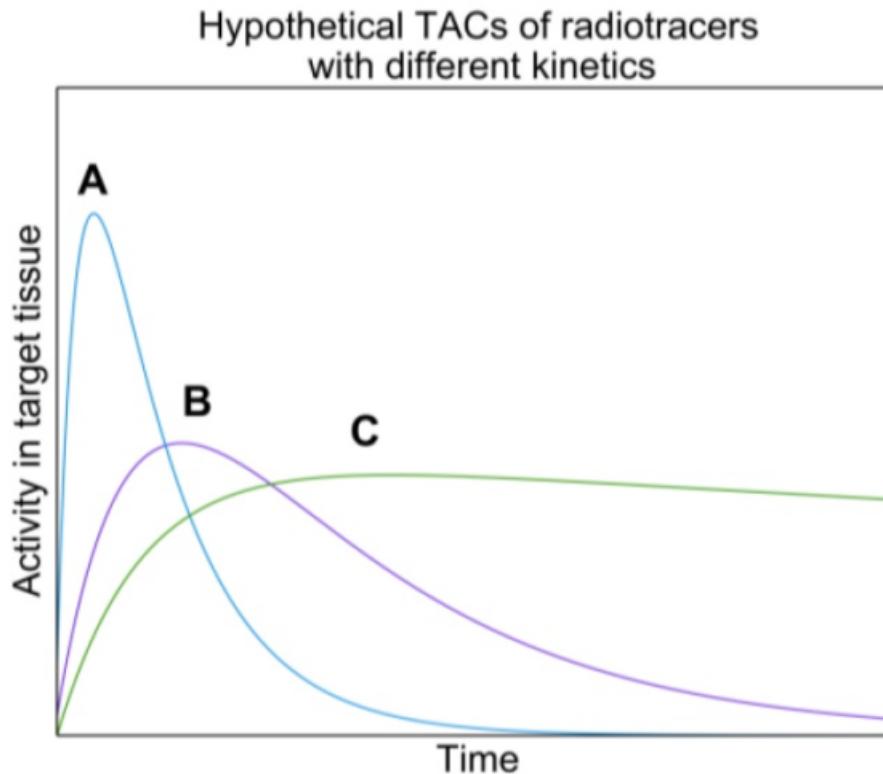
- (A) MIP images of ⁶⁸Ga-pentixafor indicate high CXCR4 expression in multiple intramedullary and extra-medullary, ¹⁸F-FDG–avid myeloma lesions. Corresponding ¹⁸F-FDG PET/CT image 2 wk after ⁹⁰Y-pentixather shows complete metabolic response.
- (B) Scintigraphic images of another patient at 24 h and 15 d after ¹⁷⁷Lu-pentixather injection.

- **¹⁷⁷Lu-pentixather displays excellent retention in tumor tissue**

[First-in-Human Experience of CXCR4-Directed Endoradiotherapy with
¹⁷⁷Lu- and ⁹⁰Y-Labeled Pentixather in Advanced-Stage Multiple Myeloma
with Extensive Intra- and Extramedullary Disease.](#)

Herrmann K. J Nucl Med. 2016; 57:248-51.

A short physical half-life of the diagnostic agent can severely hamper prediction of tumor radiation dose from the therapy agent.



[Implications of physics, chemistry and biology for dosimetry calculations using theranostic pairs.](#)
Miller C, et al. Theranostics. 2022; 12: 232-59.

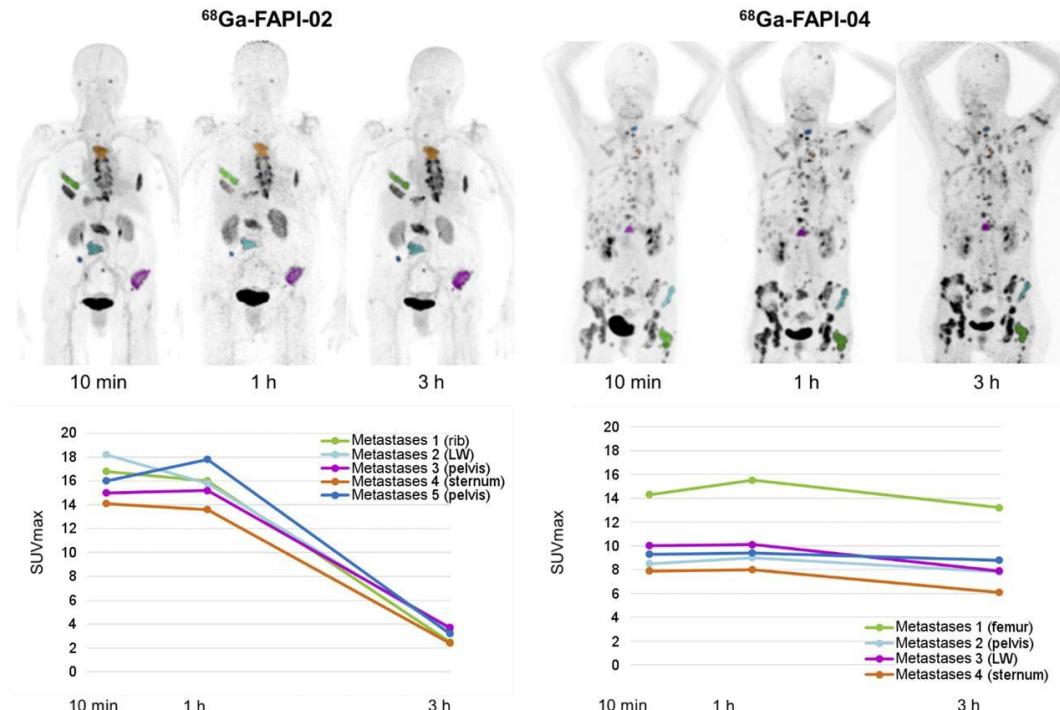
Bi-exponential TACs of hypothetical radiopharmaceuticals with varying uptake and washout kinetics in a tissue of interest.

- A: fast uptake and clearance,
- B: intermediate uptake and slow clearance,
- C: slow uptake and long retention.

The total number of disintegrations (i.e. TIAs) will be quite different for each of these curves resulting in different absorbed dose values.

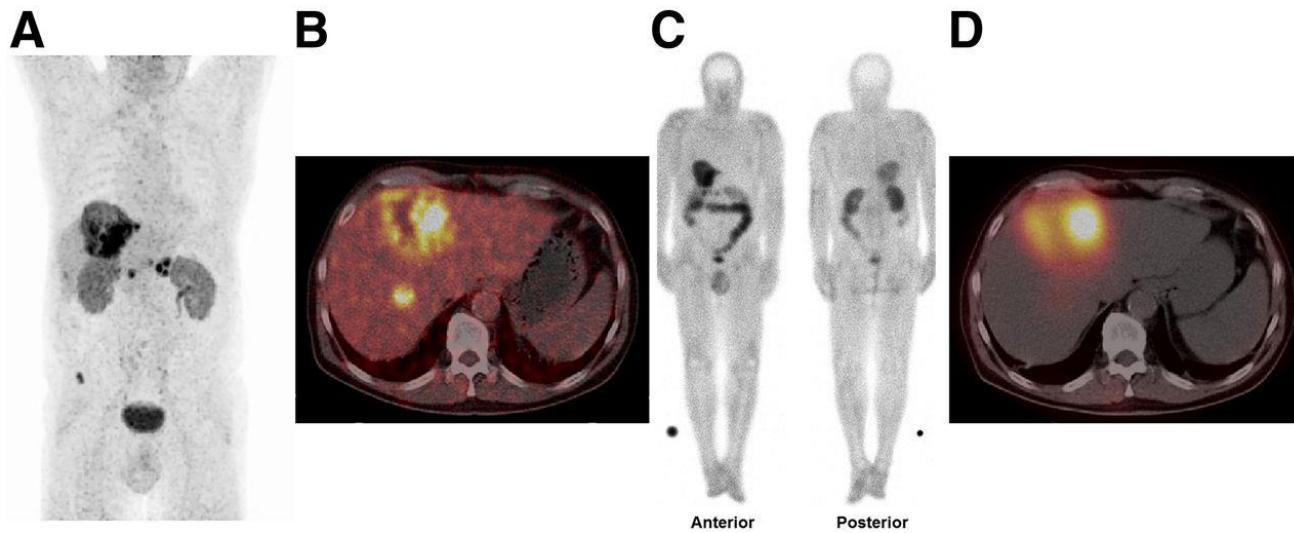
- Example: Targeting fibroblast activation protein (FAP) in cancer-associated fibroblasts (CAFs) has attracted significant attention for imaging, and potentially therapy. However, many FAP ligands display short retention in tumors and prediction with ^{68}Ga can be misleading

- ^{68}Ga -FAPI-2 and ^{68}Ga -FAPI-4 at different imaging time points in 2 patients with metastasized breast cancer.



Feasibility, Biodistribution, and Preliminary Dosimetry in Peptide-Targeted Radionuclide Therapy of Diverse Adenocarcinomas Using ^{177}Lu -FAP-2286: First-in-Humans Results.

Baum RP, et al. J Nucl Med. 2022 Mar; 63:415-423.



Patient with adenocarcinoma of pancreatic body, as well as hepatic, peripancreatic lymph node, and osseous metastases.

- High FAP expression on maximum-intensity-projection ^{68}Ga -FAP-2286 PET image (A) and transverse ^{68}Ga -FAP-2286 PET/CT image (B).
- Significant uptake and late retention of ^{177}Lu -FAP-2286 were noted in liver metastases on posttherapeutic whole-body scintigraphy in anterior and posterior views at 48 h after injection (C) and on transverse SPECT/CT image (D).

La RIV en quête du couple théranostique idéal

A la différence du ^{177}Lu , certains émetteurs β^- ont un isotope compagnon permettant l'imagerie diagnostique "Theranostic pairs" or "twins".

Trois de ces radionucléides : ^{47}Sc , ^{67}Cu , ^{161}Tb , ont une énergie β^- voisine du ^{177}Lu , une émission γ pour imagerie post-traitement, et 1 isotope pour l'imagerie diagnostique.

Comparison between Three Promising β -emitting Radionuclides, $(67)\text{Cu}$, $(47)\text{Sc}$ and $(161)\text{Tb}$,
with Emphasis on Doses Delivered to Minimal Residual Disease.

Champion C, Quinto MA, Morgat C, Zanotti-Fregonara P, Hindié E.
 Theranostics. 2016; 6:1611-8.

Table 1: Radionuclide characteristics (see also Figure 1 for electron emission spectra).

Radionuclide	^{67}Cu	^{47}Sc	^{161}Tb
Half-life (day)	2.576	3.349	6.906
Type of Decay (%)	β^- (100 %)	β^- (100 %)	β^- (100 %)
β particles mean energy (keV)	135.9	161.9	154.3
Daughter	$^{67}\text{Zinc}$ (stable)	$^{47}\text{Titanium}$ (stable)	$^{161}\text{Dysprosium}$ (stable)
CE emission (energy per decay in keV)	13.74	0.48	39.28
CE energy range (keV) *	81.6 – 184.5	154.4 – 158.9	3.3 – 98.3
Auger and Coster-Kronig electrons (energy per decay in keV)	0.75	0.01	8.94
Auger and Coster-Kronig electrons energy range (keV) *	0.057 – 9.4	0.027 – 4.8	0.018 – 50.9
Total electron energy per decay (average in keV)	150.4	162.4	202.5
γ radiation useful for imaging (Energy in keV and % abundance)	184.6 (49.6%); 91.3 (7.6%); 93.3 (3%)	159.4 (68.3%)	74.6 (10.2%)
Photons X and γ (total energy per decay in keV)	114.9	108.9	36.35
Energy per decay in keV (photons + electrons)	265.3	271.3	238.9
Percentage of energy emitted as photons	43.3 %	40.1 %	15.2 %

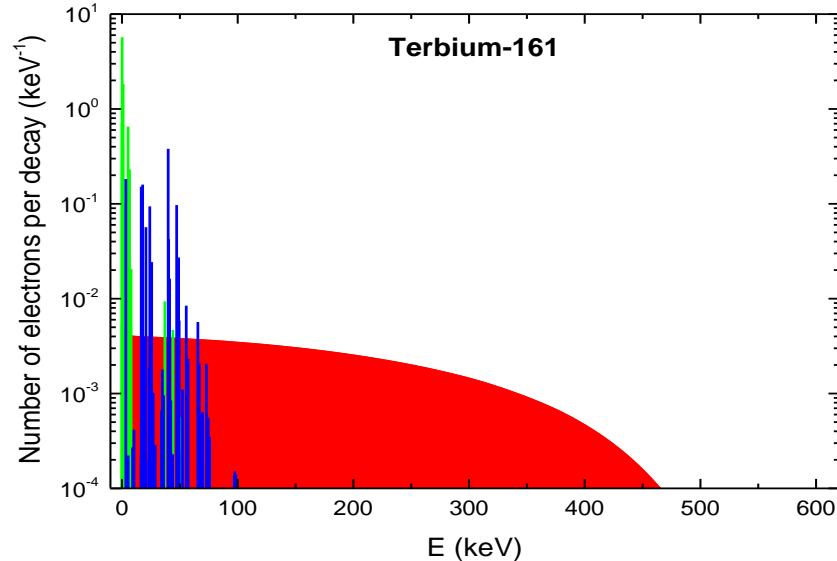
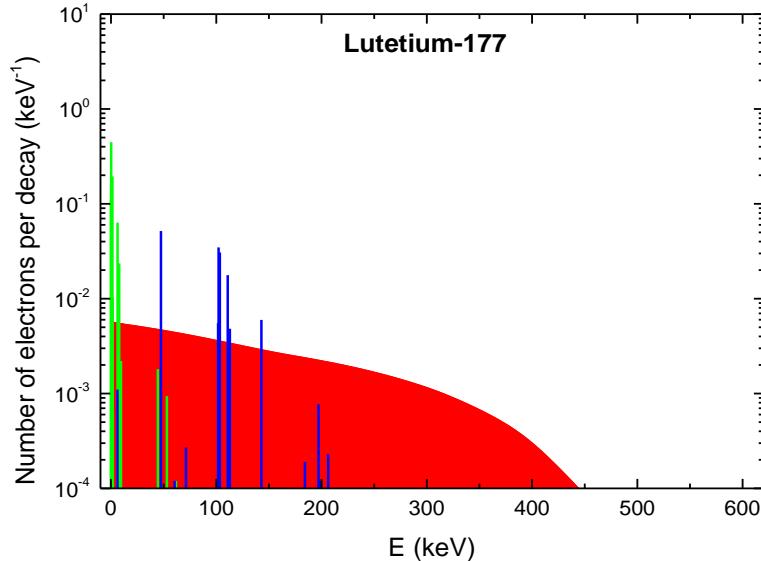
Table 2: Physical characteristics of the diagnostic radionuclides ^{64}Cu , ^{43}Sc , ^{44}Sc , ^{152}Tb and ^{155}Tb .

Radionuclide	^{64}Cu	^{43}Sc	^{44}Sc	^{152}Tb	^{155}Tb
Half-life	12.7 h	3.89 h	3.97 h	17.5 h	5.32 days
Type of Decay	EC, β^+ , β^- β^+ (17.6%), β^- (38.5%)	EC, β^+ β^+ (88.1%)	EC, β^+ β^+ (94.3 %)	EC, β^+ β^+ (20.3%)	EC (100%)
Mean energy of β particles (keV)	β^+ : 278 β^- : 191	β^+ : 476	β^+ : 632	β^+ : 1140	-
Main γ emissions ($\geq 5\%$)	-	372.9 keV (22.5%)	1157 keV (99.9%)	271.1 keV (9.5%) 344.3 keV (63.5%) 586.3 keV (9.2%) 778.9 keV (5.5%)	86.6 keV (32.0 %) 105.3 keV (25.1%) 180.1 keV (7.5%) 262.3 keV (5.3%)
X and γ emission (total energy per decay in keV) §	~ 8	~ 85	~ 1177	~ 1146	~ 176

Terbium-161 as an alternative to lutetium-177

Nuclide	^{161}Tb	^{177}Lu
Half-life (day)	6.91	6.65
Type of Decay (%)	β^- (100 %)	β^- (100 %)
β particles mean energy (keV)	154	133
Conversion electrons (total energy per decay in keV)	39.3	13.5
Auger electrons (total energy per decay in keV)	8.9	1.1
γ radiation for imaging (Energy in keV and abundance)	75 (10%)	208 (11%) ; 113 (6%)
Percentage of energy emitted as photons	15 %	19 %

- ^{161}Tb associates the advantages of a medium-energy β^- emission spectrum and those of conversion and Auger electrons.



Terbium-161 as an alternative to lutetium-177

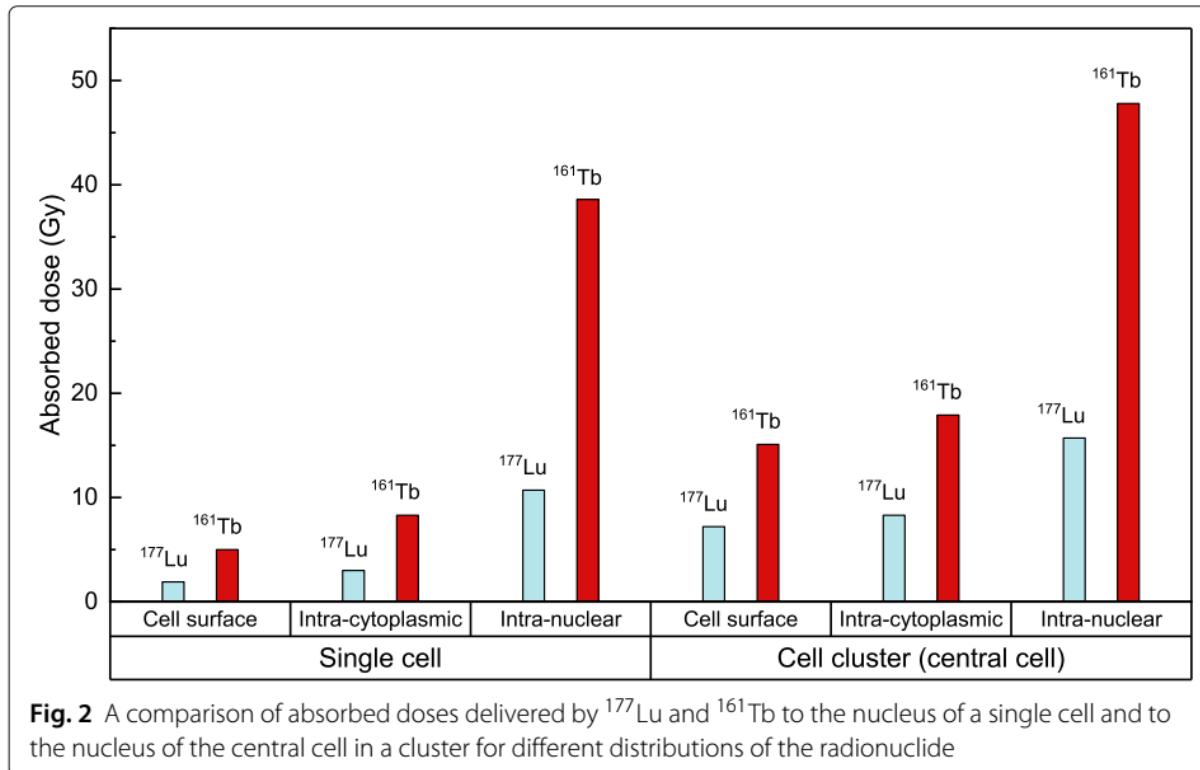
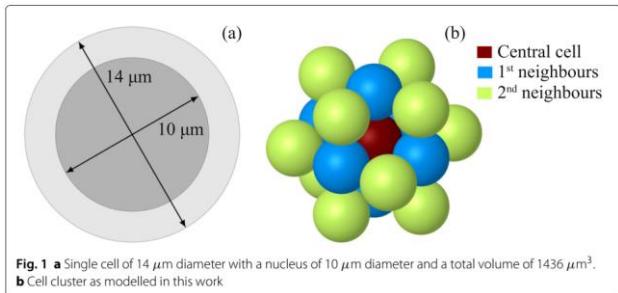
- Terbium-161 is a radiolanthanide with similar chemical properties to lutetium-177
- It can be produced in high activities and in quality suitable for future clinical applications
 - Gracheva N, et al. [Production and characterization of no-carrier-added \$^{161}\text{Tb}\$ as an alternative to the clinically-applied \$^{177}\text{Lu}\$ for radionuclide therapy.](#) EJNMMI Radiopharm Chem. 2019; 4: 12.
- Preclinical, in vitro and in vivo, studies suggest that the β^- and Auger emitter ^{161}Tb is superior to ^{177}Lu
 - Müller C, et al. [Direct in vitro and in vivo comparison of \(\$^{161}\text{Tb}\$ \) and \(\$^{177}\text{Lu}\$ \) using a tumour-targeting folate conjugate.](#) Eur J Nucl Med Mol Imaging. 2014;41:476-85.
 - Grünberg J, et al. [Anti-L1CAM radioimmunotherapy is more effective with the radiolanthanide terbium-161 compared to lutetium-177 in an ovarian cancer model.](#) Eur J Nucl Med Mol Imaging. 2014; 41:1907-15.
 - Müller C, et al. [Terbium-161 for PSMA-targeted radionuclide therapy of prostate cancer.](#) Eur J Nucl Med Mol Imaging. 2019; 46:1919-30.
- Monte Carlo analysis of dose deposits shows superiority of ^{161}Tb over ^{177}Lu , (also over ^{90}Y and ^{111}In)

Table 4: Absorbed dose from ^{67}Cu , ^{47}Sc , and ^{161}Tb assuming a uniform concentration of the radionuclide. Data for ^{177}Lu are shown for comparison.

Sphere diameter (μm)	Absorbed dose for 1 decay per μm^3 (Gy)				Absorbed dose for 1 MeV released per μm^3 (Gy)				Absorbed dose ratio "Efficacy ratio" (with ^{177}Lu as reference) §			
	^{177}Lu	^{67}Cu	^{47}Sc	^{161}Tb	^{177}Lu	^{67}Cu	^{47}Sc	^{161}Tb	^{177}Lu	^{67}Cu	^{47}Sc	^{161}Tb
5,000	21.6	22.1	24.2	29.3	145	147	149	146	1	1.01	1.03	1.01
2,000	19.0	19.6	19.8	26.0	128	130	122	129	1	1.02	0.95	1.01
1,000	15.4	16.1	14.5	21.7	104	107	89.6	108	1	1.03	0.86	1.04
500	11.1	11.6	9.19	16.6	74.8	77.1	56.7	82.7	1	1.03	0.76	1.11
200	6.18	6.37	4.39	11.6	41.8	42.4	27.2	57.6	1	1.01	0.65	1.38
100	3.63	3.61	2.39	8.95	24.5	24.1	14.8	44.5	1	0.98	0.60	1.82
50	2.08	1.93	1.28	6.67	14.1	12.9	7.89	33.3	1	0.91	0.56	2.36
20	0.98	0.89	0.54	4.06	6.61	5.91	3.35	20.2	1	0.89	0.51	3.06
10	0.58	0.51	0.28	2.83	3.92	3.42	1.74	14.1	1	0.87	0.44	3.60

Comparison between Three Promising β -emitting Radionuclides, ^{67}Cu , ^{47}Sc and ^{161}Tb , with Emphasis on Doses Delivered to Minimal Residual Disease

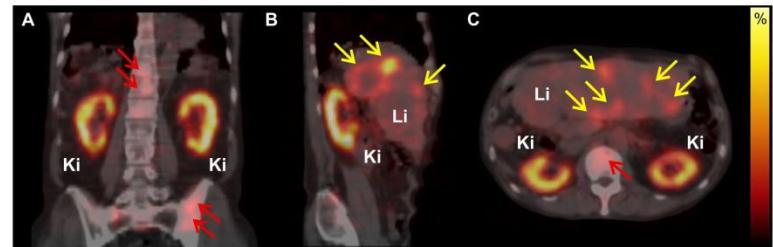
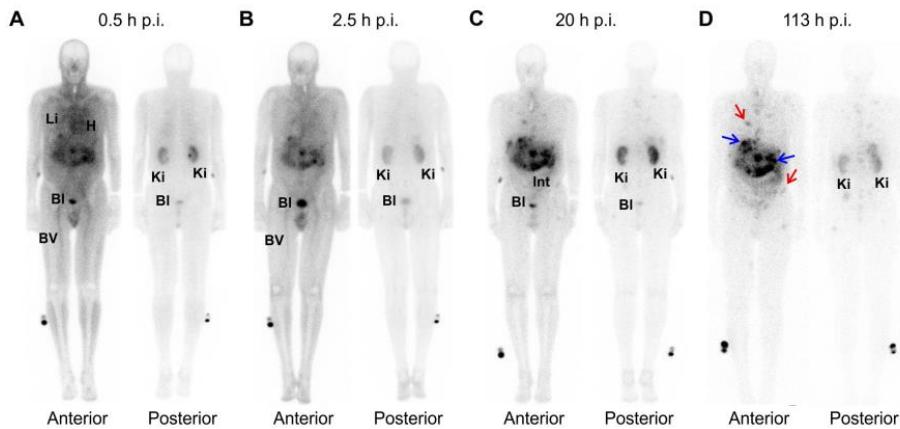
- **^{161}Tb delivers higher absorbed doses, and should be a better candidate than ^{177}Lu for targeting single tumor cells and micrometastases, whatever the subcellular distribution is.**



[First-in-Human Application of Terbium-161: A Feasibility Study Using \$^{161}\text{Tb}\$ -DOTATOC.](#)

Baum RP, et al.

J Nucl Med. 2021; 62:1391-7.



SPECT/CT images obtained at 19 h after injection of ^{161}Tb -DOTATOC in a patient with metastatic pancreatic neuroendocrine tumor.

- images show uptake of ^{161}Tb -DOTATOC in bilobar hepatic metastases (yellow arrows), as well as multiple osteoblastic skeletal metastases in the vertebral column and the pelvis (red arrows).
- Physiological uptake of ^{161}Tb -DOTATOC is seen in both kidneys (Ki), as well as in the liver (Li)

Whole-body images at different time points after injection of ^{161}Tb -DOTATOC.

- Early blood-pool activity was noticed in the heart (H) and blood vessels (BV) up to 2.5 h p.i..
- Physiological uptake observed in the soft tissues, liver (Li), both kidneys (Ki), and the urinary bladder (BI).
- Pathological accumulation of ^{161}Tb -DOTATOC in bilobar liver (blue arrows) and multifocal osseous metastases (red arrows).

Addressing micrometastases and minimal residual disease «MRD»

- Recurrence is a major threat in solid and hematological malignancies
- Diverse treatments are used as «adjuvant therapy» in high risk patients to eradicate occult micrometastases (*not seen on imaging; < 1-2mm*), or as « consolidation » for MRD after 1st-line treatment:
 - Chemotherapy
 - Naked antibodies
 - Antibody-drug-conjugates
 - Tyrosine kinase inhibitors
 - Immunotherapies
 - „„
- Why not TRT ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

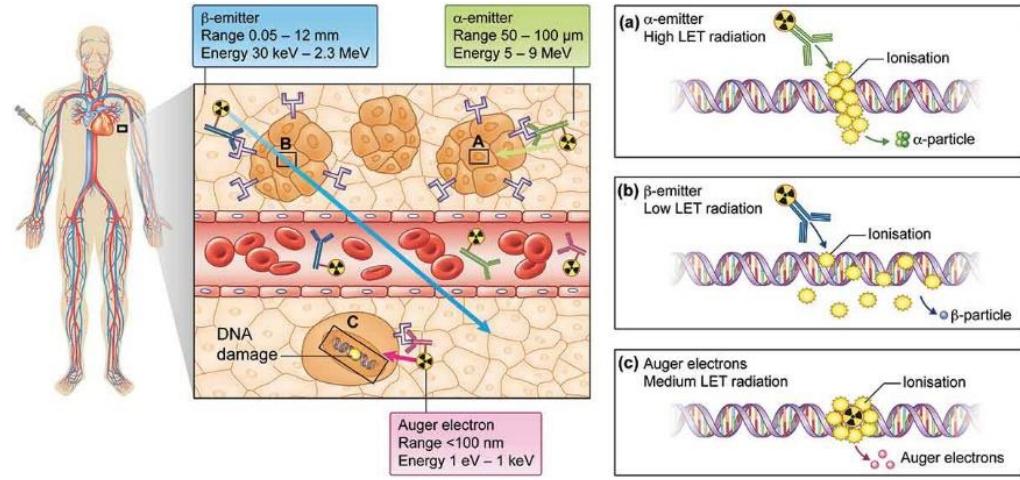
Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

TRT of micrometastasis: Specific needs in the choice of the radionuclides and targets

Table 1. Radioisotopes used in RIT.

Isotope	Half-life (T _{1/2})	Maximum energy (keV)	Maximum range (μm)	Emission type
β⁻-emitters (LET: 0.2 keV/μm)				
⁹⁰ Y	2.67 d	2280.0	11,300	β ⁻
¹³¹ I	8.02 d	606.31	2300	β ⁻ , γ
¹⁷⁷ Lu	6.65 d	498.3	1800	β ⁻ , γ
⁶⁷ Cu	61.83 h	577.0	2100	β ⁻ , γ
¹⁸⁶ Re	3.72 d	1069.5	4800	β ⁻ , γ
¹⁸⁸ Re	17.01 h	2120.4	10,400	β ⁻ , γ
Auger emitters (LET: 4–26 keV/μm)				
¹¹¹ In	2.80 d	26	17	Auger, γ
⁶⁷ Ga	3.26 d	9.6	3	Auger, β ⁻ , γ
^{195m} Pt	4.02 d	64	76	Auger
¹²⁵ I	59.41 d	31.7	20	Auger, γ
α-emitters (LET: 50–230 keV/μm)				
²¹³ Bi	45.59 min	8400	90	α, β ⁻ , γ
²¹² Bi	60.54 min	7800	100	α, β ⁻ , γ
²¹¹ At	7.21 h	7500	80	α, EC
²¹² Pb ^a	10.64 h	7800	100	α, β ⁻ , γ
²²⁵ Ac	9.92 d	8400	90	α, β ⁻ , γ
²²⁷ Th	18.7 d	7400	70	α, β ⁻ , γ



Martins CD. Expert Opin Drug Deliv. 2017

The characteristic decay of the radionuclide will generate radiation with different energies and ranges in tissue.

- **β⁻-emitters** keV-MeV energies and mm-cm range in tissue ('crossfire' toxicity).

Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides.

O'Donoghue JA, Bardiès M, Wheldon TE. J Nucl Med. 1995; 36:1902-9.

- **α-emitters** with MeV energies, produce densely ionizing high-LET radiation.
- **Auger-emitters** intense energy deposition over a short range.

For Auger electrons: We need to consider subcellular location; impact on DNA but also mitochondriae, cell membrane,...

Cell membrane is a more sensitive target than cytoplasm to dense ionization produced by auger electrons.

Pouget JP, et al. Radiat Res. 2008; 170: 192-200.

Localized Irradiation of Cell Membrane by Auger Electrons Is Cytotoxic Through Oxidative Stress-Mediated Nontargeted Effects.

Paillas S, et al. Antioxid Redox Signal. 2016; 25: 467-84.

En RIV, la corrélation entre "imagerie + dosimétrie" et réponse tumorale/PFS/OS peut être complexe (et différente de la radiothérapie externe).

Aussi, concernant la toxicité aux tissus sains

Corrélation en RIV entre doses aux tissus sains et toxicité

- **L'imagerie avec dosimétrie** peut permettre d'évaluer la dose aux organes cibles (ex, reins) et de moduler ainsi le nombre de traitements administrés.
- **Nuances :**
 - Seuils de toxicité différents de ceux de la radiothérapie externe,
 - Les seuils sont spécifiques à un radiopharmaceutique donné (dépendent de sa distribution microscopique, mais aussi du profil de dépôts d'énergie vis-à-vis des structures sensibles) :
 - ^{90}Y -DOTATOC et ^{177}Lu -DOTATE n'ont pas le même seuil de toxicité rénale.
 - ^{225}Ac -PSMA et ^{177}Lu -PSMA n'ont pas la même toxicité salivaire (probablement même à dose égale).
 - Les facteurs de risque individuels doivent être pris en compte.

Corrélation en RIV entre doses aux lésions tumorales et réponse tumorale/PFS/OS

- Certaines études trouvent une corrélation
 - Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using ^{177}Lu -DOTATATE. Ilan E, et al. J Nucl Med. 2015; 56:177-82.
 - Prospective observational study of ^{177}Lu -DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. Garske-Román U. Eur J Nucl Med Mol Imaging. 2018; 45:970-88.
 - Dosimetry of ^{177}Lu -PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes. Violet J, et al. J Nucl Med. 2019; 60:517-23.
- D'autres non
- Hormis les facteurs confondants classiques en RIV (Ex: distribution de dose et hétérogénéité à l'échelle macroscopique / microscopique) ; plusieurs facteurs compliquent l'analyse en comparaison avec la radiothérapie externe :
 - **Multiplicité des sites métastatiques avec des réponses différentes en fonction des sites**
 - **Hétérogénéité de captation**
 - **Les cibles que l'on adressent sont elles-mêmes des facteurs pronostiques.**

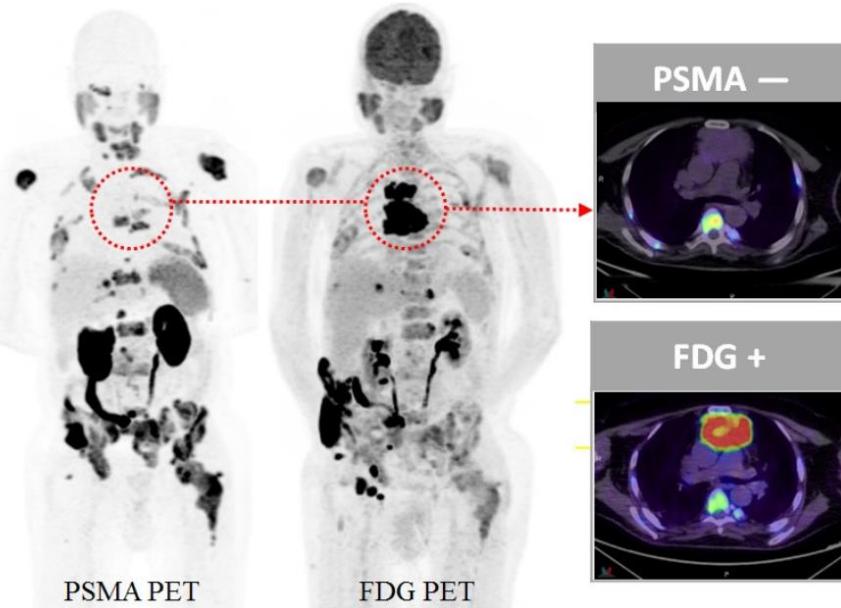
Nomograms to predict outcomes after (177)Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study.

Gafita A, et al. Lancet Oncol. 2021; 22:1115-25.

	Definition	Estimate HR or OR (95% CI)	p value
Overall survival			
Time since diagnosis	Continuous, years	0.92 (0.89–0.95)	<0.0001
Chemotherapy status	Previous chemotherapy vs no chemotherapy	1.53 (1.01–2.37)	0.044
Baseline haemoglobin	Continuous, g/dL	0.85 (0.77–0.95)	0.0035
Number of metastases	≥20 vs <20	1.66 (1.12–2.44)	0.0031
Tumour SUV _{mean}	Continuous, no unit	0.94 (0.90–0.98)	0.0078
Bone involvement	M1b vs no M1b	1.10 (0.57–2.13)	0.77
Liver involvement	Liver metastases vs no liver metastases	2.11 (1.38–3.23)	<0.0001
PSA-progression-free survival			
Time since diagnosis	Continuous, years	0.94 (0.92–0.97)	0.00012
Chemotherapy status	Previous chemotherapy vs no chemotherapy	1.55 (1.03–2.34)	0.028
Tumour SUV _{mean}	Continuous, no unit	0.92 (0.88–0.96)	0.00052
Pelvic nodal involvement	N1 vs N0	0.70 (0.51–0.97)	0.035
Bone involvement	M1b vs no M1b	1.93 (1.07–3.52)	0.032
Liver involvement	Liver metastases vs no liver metastases	2.59 (1.69–3.95)	<0.0001
PSA decline ≥50%			
Chemotherapy status	Previous chemotherapy vs no chemotherapy	0.32 (0.13–0.77)	0.012
Tumour SUV _{mean}	Continuous, no unit	2.88 (1.80–4.62)	<0.0001
Pelvic nodal involvement	N1 vs N0	1.87 (0.96–3.62)	0.062
Liver involvement	Liver metastases vs no liver metastases	0.29 (0.11–0.81)	0.018
Estimates are hazard ratios for the overall survival and PSA-progression-free survival analyses, and odds ratios for the PSA decline of 50% or greater analysis. HR=hazard ratio. OR=odds ratio. SUV=standardised uptake value. PSA=prostate-specific antigen.			
Table 2: Multivariate analysis of predictors selected by LASSO regression procedure in the development cohort			

Hétérogénéité métastatique

- La « dose lésionelle minimale » chez un patient, lésion avec la moindre captation, est probablement un facteur pronostique plus important que la dose moyenne ou maximale,
- Attentions aux métastases invisibles... Importance parfois d'une imagerie associée (18F-FDG ou autre).

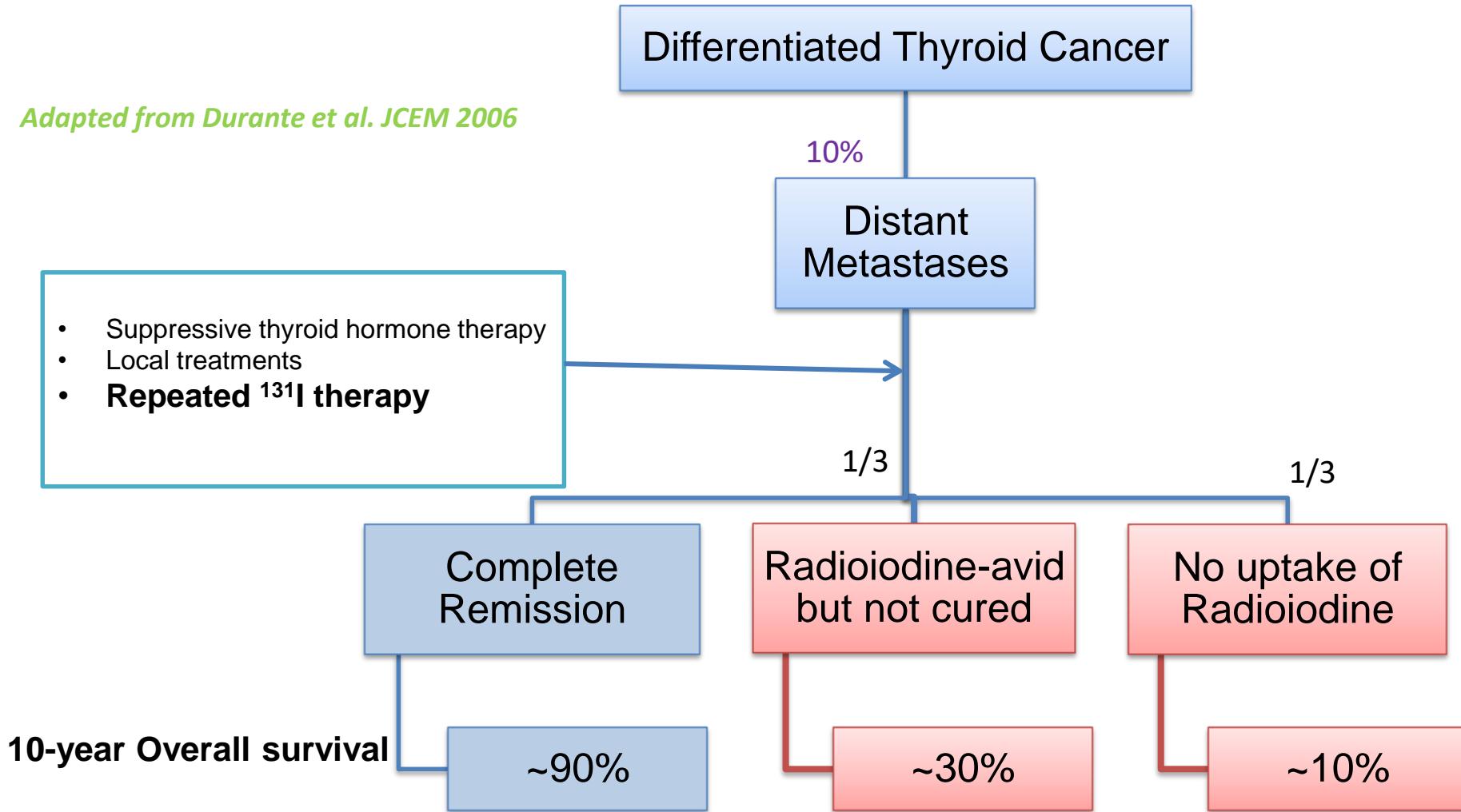


Patient has high PSMA uptake in osseous disease
but a site of anterior mediastinal nodal disease
with high FDG but absent PSMA uptake.

(Hofman-Lancet Oncology 2018).

En RIV, les cibles que l'on adressent sont elles-mêmes des facteurs pronostiques

Adapted from Durante et al. JCEM 2006



En RIV, les cibles que l'on adressent sont elles-mêmes des facteurs pronostiques

« Un facteur confondant pour la corrélation entre dose et réponse »
Importance des études initiales avec escalade de l'activité injectée pour bien démontrer l'effet « Dose absorbée »

[Indium-111-pentetreotide scintigraphy and somatostatin receptor subtype 2 expression: new prognostic factors for malignant well-differentiated endocrine tumors.](#)

Asnacios A, Courbon F, Rochaix P, et al.
J Clin Oncol. 2008; 26:963-70.

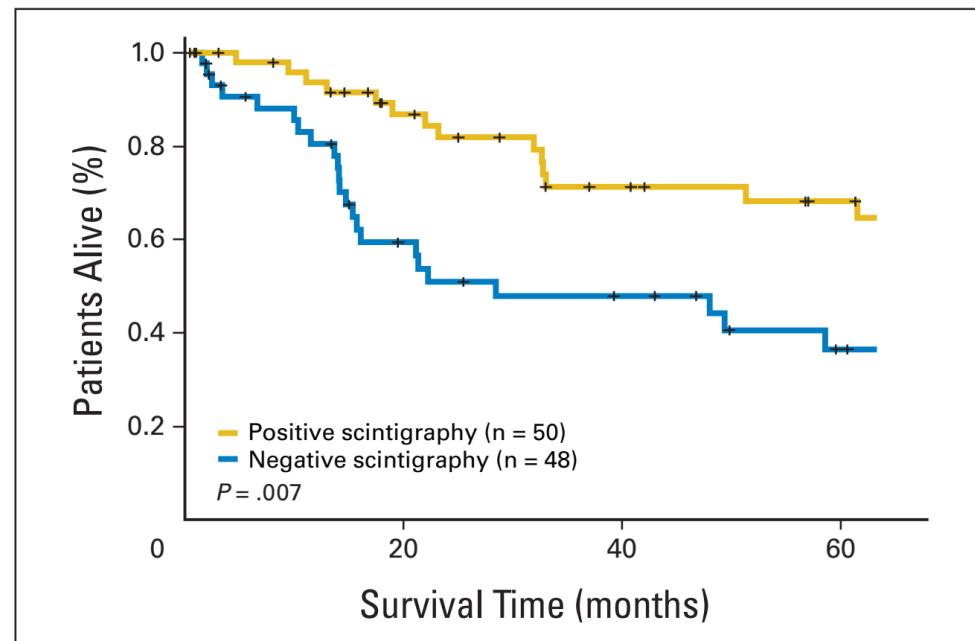


Fig 2. Survival analysis of the two groups of patients with well-differentiated endocrine carcinoma using Kaplan-Meier method.

Merci pour votre attention