ESMO ADVANCED COURSE ON

Individualising the therapeutic approach in patients with NENs: Peptide Receptor Radionuclide Therapy (PRRT)

Name: Prakash Manoharan

Date: 14 June 2019

DISCLOSURES

Consulting or Advisory Role | Therasphere, AAA, AML

Speakers' Bureau | PrimeOncology, Therasphere, AAA, Jansen

Acknowledgements

- **The Christie**
- **Nuclear Medicine/ CMPE department**
- **Department of Radiology**
- **ENETs NET team**

Why, what and when: Factors that dictate NEN management and imaging

1. Grade
2. Primary
3. Liver only
4. Functional
5. Progressive
6. Therapy options: PRRT?

Management led by specialist NEN MDT

Molecular Imaging

"Molecular imaging is aimed at the exploitation of specific molecules as the source of image contrast"
Weissleder R. *Radiology.* 1999;212(3):609-614.

Aims:

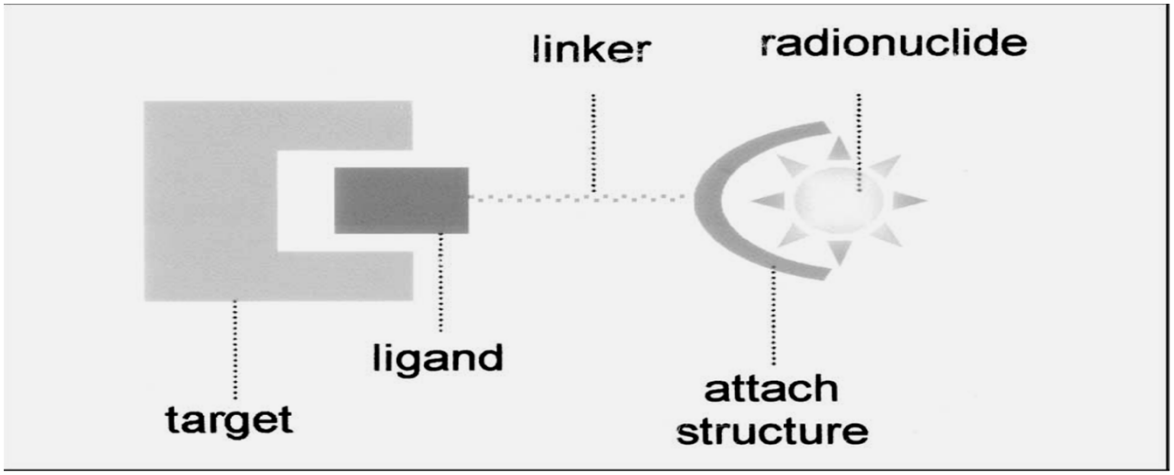
- Earlier detection and characterization of disease ("molecular signature" prior to irreversible damage)
- Understanding of underlying biology
- Selection of specific treatment option for targeted therapy
- Concept of THERANOSTICS nuclear medicine/molecular imaging ideally set for this dual role

Theranostics- **Therapy and Diagnostics**

- *Theranostics* publishes innovative research articles reflecting the fields of *in vitro* diagnostics and prognostics, *in vivo* molecular imaging, molecular therapeutics, image-guided therapy, biosensors, system biology and translational medicine, personalized medicine and a broad spectrum of biomedical research that can be applied to future theranostic applications.

Radionuclide Tracer

Key aspect of nuclear medicine imaging- labelled radiotracers

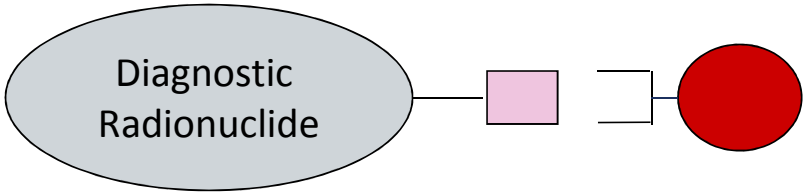


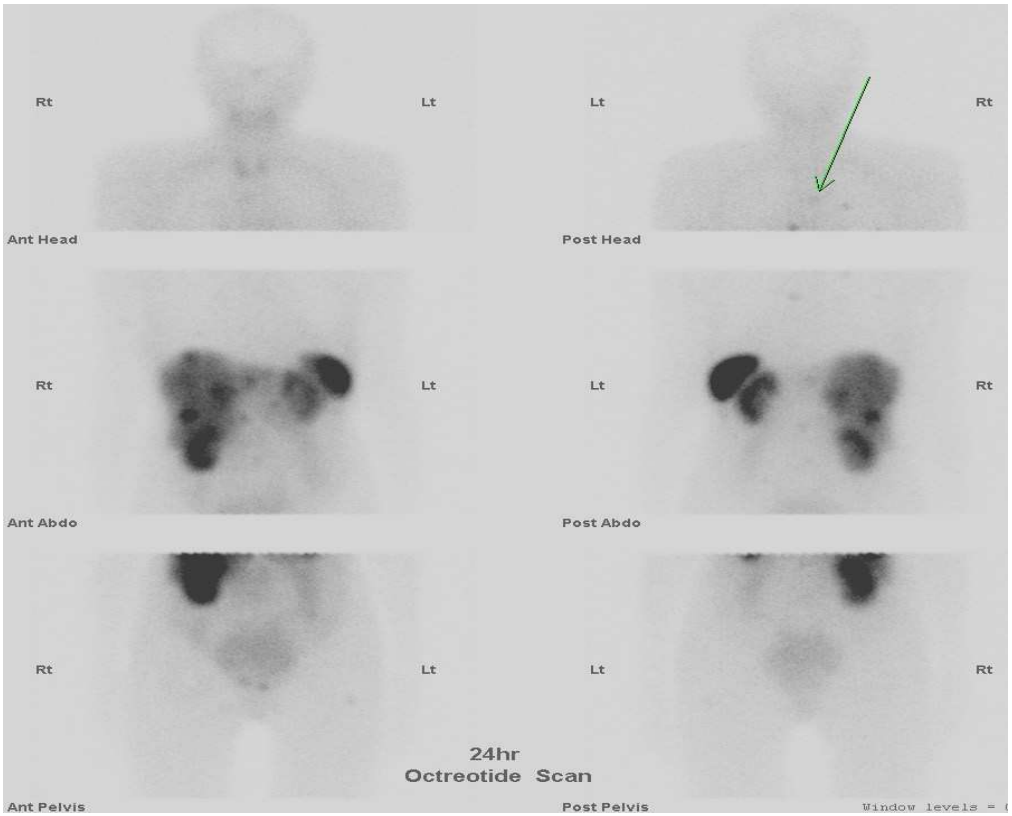
Somatostatin receptor	Octreotide	DOTA	68Ga/177Lu/90Y

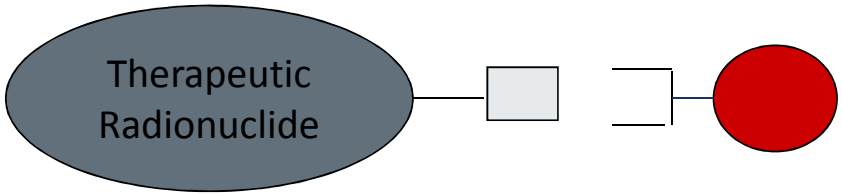
Octreotide is a somatostatin analogue

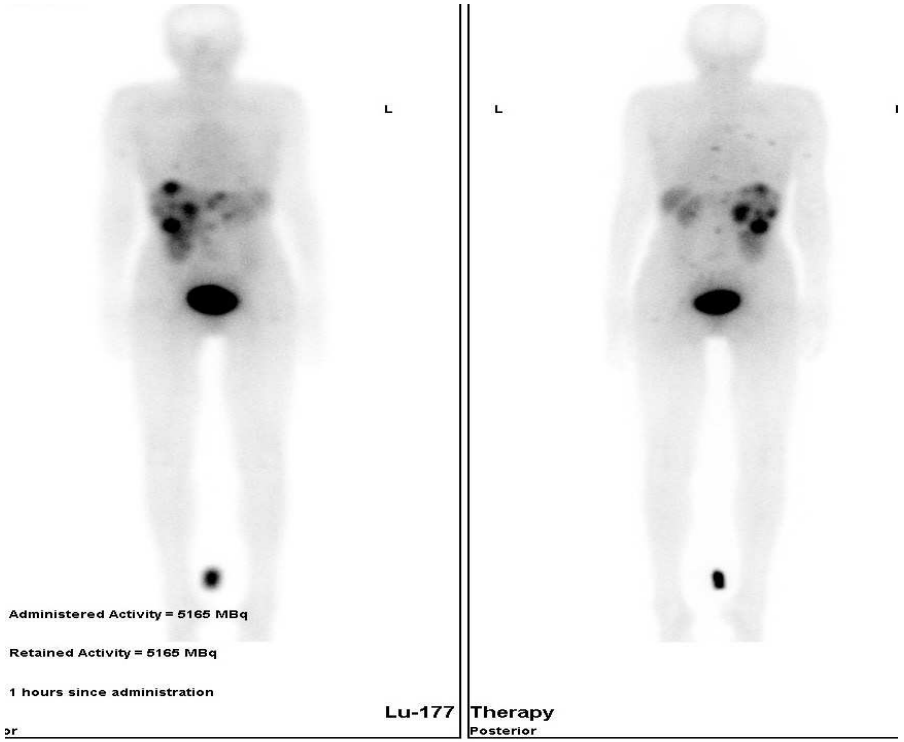
If we can see it, we can treat it!

Principles of Nuclear imaging and therapy (Theranostics)









The Role of ^{68}Ga-DOTATATE PET in Patients with Neuroendocrine Tumors and Negative or Equivocal Findings on ^{111}In-DTPA-Octreotide Scintigraphy

Rajaventhan Srirajaskanthan[1], Irfan Kayani[2], Anne Marie Quigley[3], Jade Soh[1], Martyn E. Caplin[1], and Jamshed Bomanji[2]

[1]Neuroendocrine Tumour Unit, Royal Free Hospital, London, U.K.; [2]Nuclear Medicine Department, University College Hospital, London, U.K.; and [3]Nuclear Medicine Department, Royal Free Hospital, London, U.K.

Results:

- **^{68}Ga-PET imaging changed management in *36 patients (70.6%),* who were subsequently deemed suitable for peptide receptor–targeted therapy**

Conclusion:

- **In patients with negative or equivocal ^{111}In-DTPA-octreotide findings, ^{68}Ga-DOTATATE PET identifies additional lesions and may alter management in most cases**

Srirajaskanthan R, et al. *J Nucl Med.* 2010;51(6):875-882.

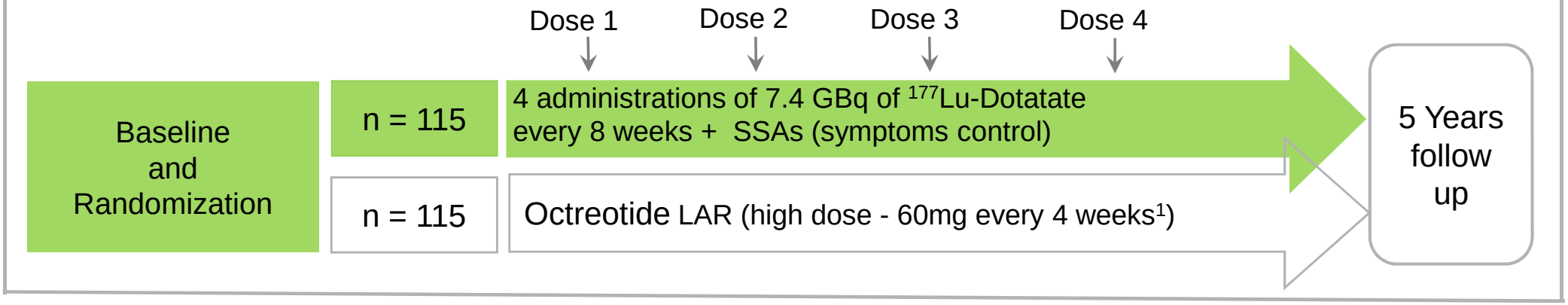
PRRT – What is the evidence?

NETTER -1 Study Objectives and Design

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments

Progression free survival (RECIST criteria) every 12 weeks



[1] FDA and EMA recommendation

Progression-Free Survival

N = 229 (ITT)

Number of events: 91

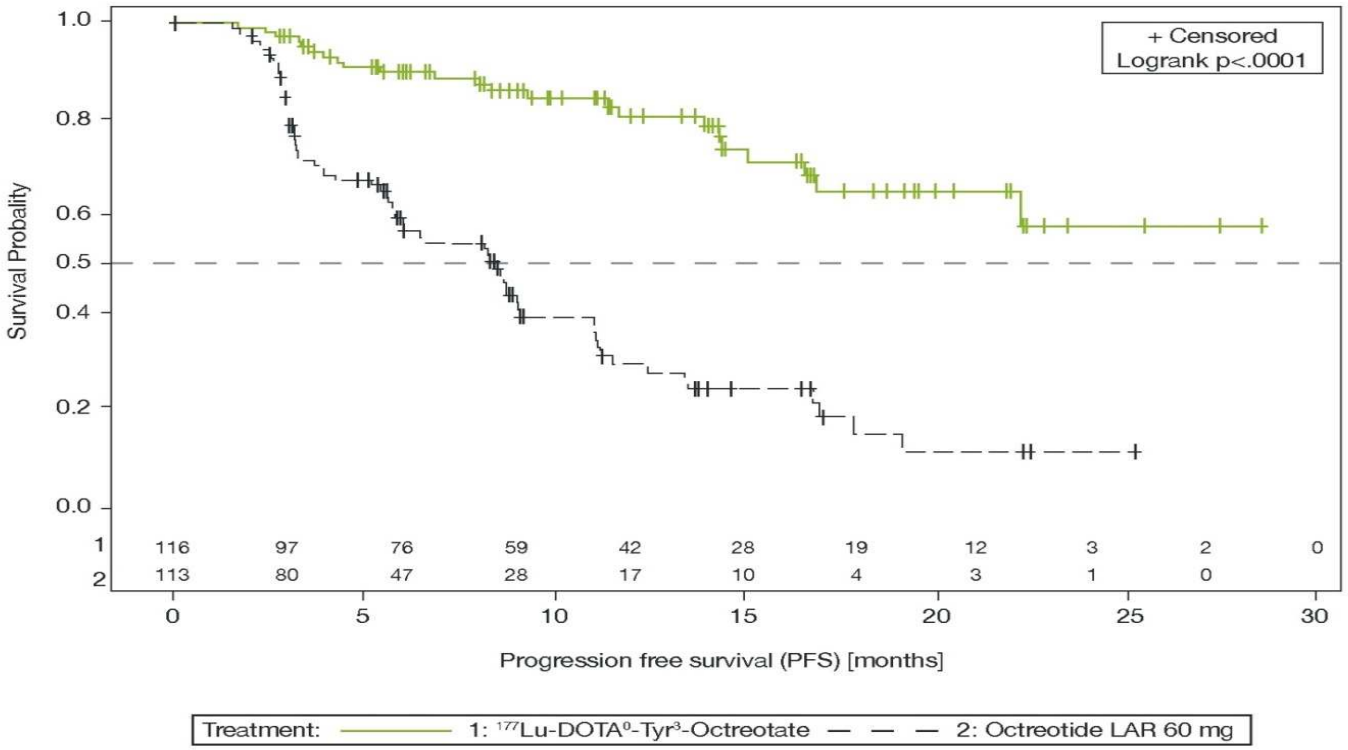
^{177}Lu-Dotatate: 23

Oct 60 mg LAR: 68

Hazard ratio: **0.21**
[0.13 – 0.33]
p < 0.0001

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm ≈ 40 months



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

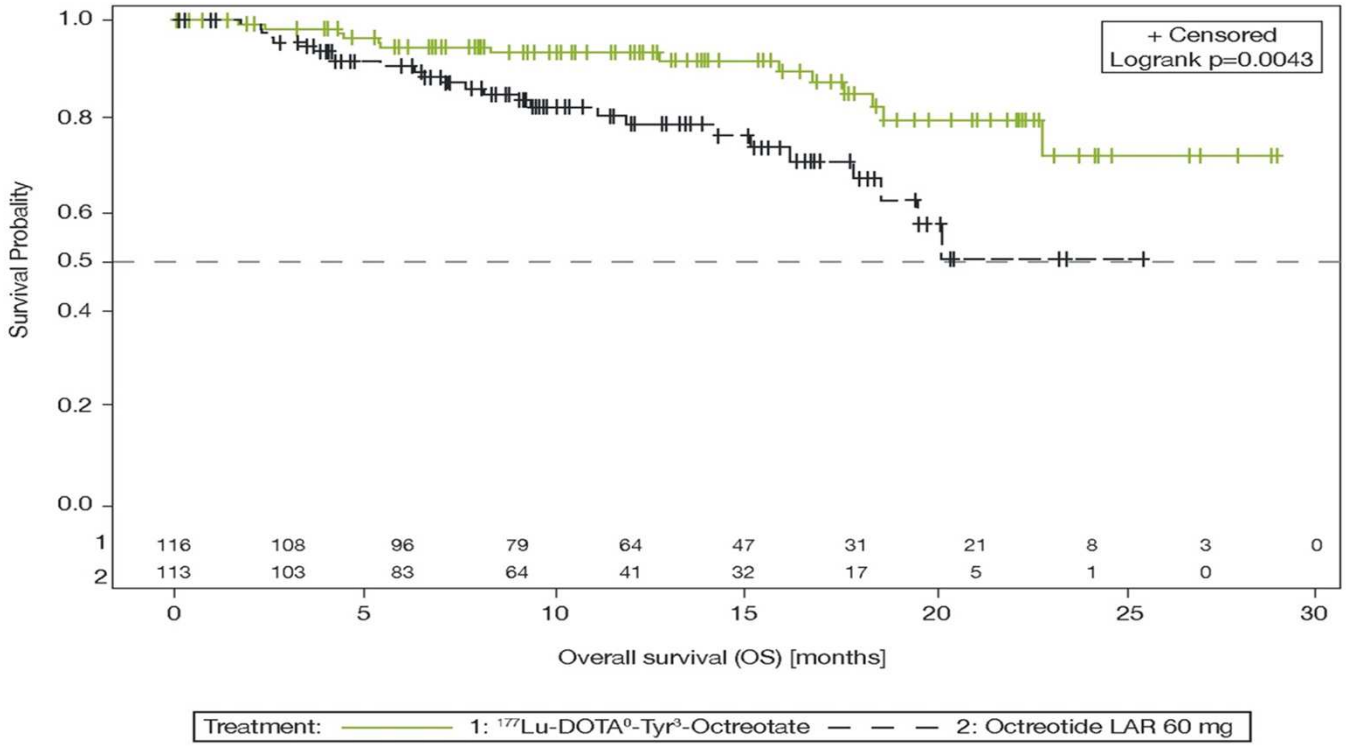
Overall Survival (interim analysis)

N = 229 (ITT)
Number of deaths: 40

^{177}Lu-Dotatate: 14

Oct 60 mg LAR: 26

Hazard ratio: **0.398**
[0.21 – 0.77]
P = 0.0043



All cases independently reviewed for eligibility (SAP)

Prespecified interim analysis significance level p<0.000085

NETTER-1: Effects of quality of life

VOLUME 36 · NUMBER 25 · SEPTEMBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With ^{177}Lu-Dotatate in the Phase III NETTER-1 Trial

Jonathan Strosberg, Edward Wolin, Beth Chasen, Matthew Kulke, David Bushnell, Martyn Caplin, Richard P. Baum, Pamela Kunz, Timothy Hobday, Andrew Hendifar, Kjell Oberg, Maribel Lopera Sierra, Thomas Thevenet, Ines Margalet, Philippe Ruszniewski, and Eric Krenning, on behalf of the NETTER-1 Study Group

Results

TTD was significantly longer in the ^{177}Lu-Dotatate arm (n = 117) versus the control arm (n = 114) for the following domains: global health status (hazard ratio [HR], 0.406), physical functioning (HR, 0.518), role functioning (HR, 0.580), fatigue (HR, 0.621), pain (HR, 0.566), diarrhea (HR, 0.473), disease-related worries (HR, 0.572), and body image (HR, 0.425). Differences in median TTD were clinically significant in several domains: 28.8 months versus 6.1 months for global health status, and 25.2 months versus 11.5 months for physical functioning.

Conclusion

This analysis from the NETTER-1 phase III study demonstrates that, in addition to improving progression-free survival, ^{177}Lu-Dotatate provides a significant QoL benefit for patients with progressive midgut NETs compared with high-dose octreotide.

J Clin Oncol 36:2578-2584.

NETTER-1

- Compelling evidence for PRRT in NET grade 1 and 2 patients
- RCT evidence based and fulfils the Theranostic principles

How does PRRT work?

A form of ‘hybrid’ therapeutics

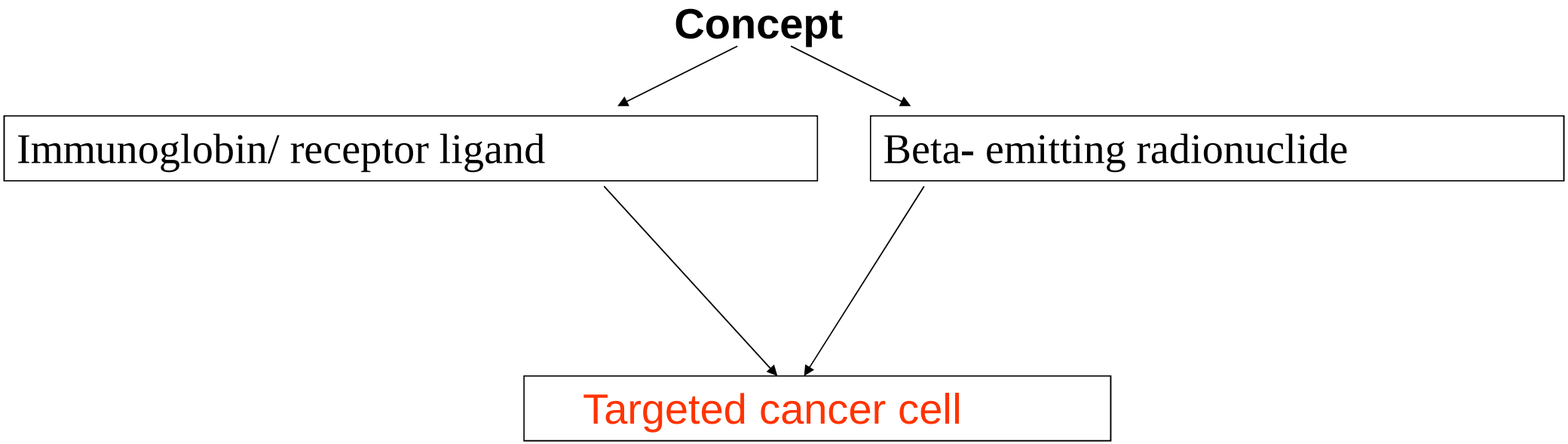
Partly ‘pharmaceutical’ principles- IV injection of tracer in suitable patients based on a biomarker test utilising a specific diagnostic test

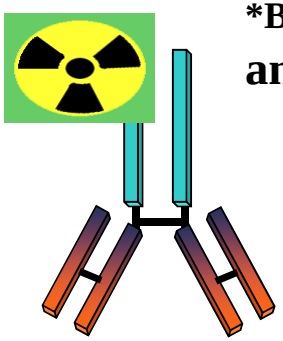
Partly ‘radiotherapy’ principles- hence the complexity of the technique

Hence why it has been poorly developed thus far

Radio-immunotherapy & Radionuclide therapy

First steps in the realisation of targeted ‘magic bullet’ and synergistic radiation cancer therapy





***BEXXAR:Radioisotope iodine 131 linked to a chimeric monoclonal antibody against CD20 antigen**

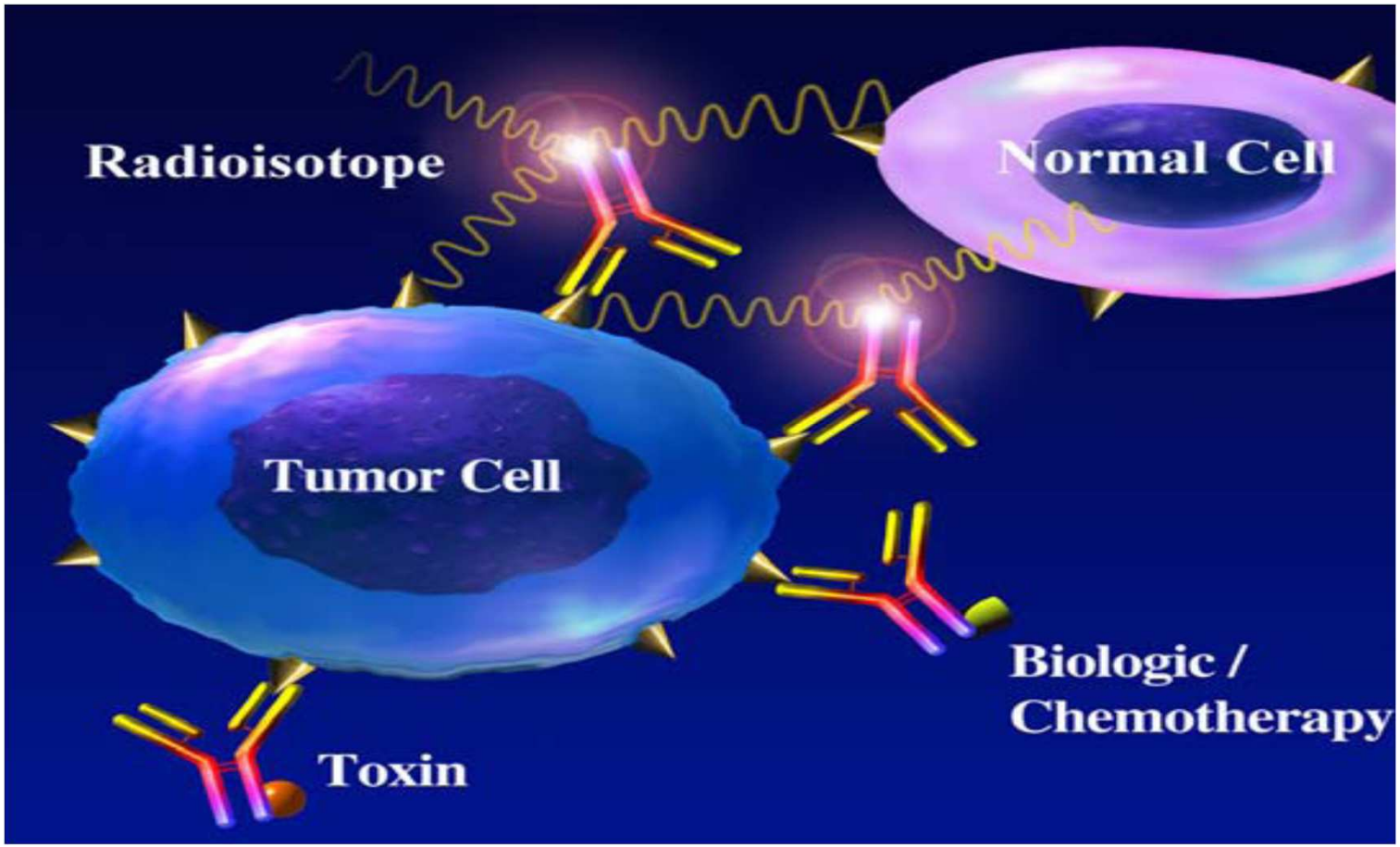


Table of therapeutic agents

Agent	β(MeV)	mm	γ	Other
Indium-111	NON		YES	Auger
Iodine-131	**0.2**	**0.45**	YES	
Yttrium-90	**0.94**	**4.2**	NON	
Lutetium-177	**0.15**	**0.27**	YES	

Indications for PRRT in GEP NEN

As per NICE guidance 2018 Lutetium (177Lu) oxodotreotide (Lutathera, AAA, referred to as lutetium) is indicated for:

- ‘Unresectable’ or metastatic
- Progressive- symptomatic, morphological
- Well-differentiated (G1 and G2)
- Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults'.

Suitable Patients

- Tumour uptake on the SSTR PET-CT scan should be at least as high as normal liver uptake. Comparable uptake with other somatostatin receptor imaging modalities may apply, but direct correlations are not available.
- The patient should have inoperable disease.
- Life expectancy at least 3–6 months.
- Tumour differentiation grade 1 or 2.
- Tumour proliferation rate, with a Ki-67/mitotic index<20%.

Patient relative contraindications (case by case assessment of patients)

- The following parameters are relative contra-indications (as modified from the NETTER-1 study) apart from pregnancy or breast feeding (unless discontinued) which are an absolute contraindication:
- :Eastern Cooperative Oncology Group (ECOG) performance status 3
- Severe myelosuppression (as indicated by any of the following):
  - Hb <5 mmol/L,
  - WBC <2 x10 ^{9} /L,
  - Neutrophills <1.5x10 ^{9} /L,
  - RBC <3x10 ^{9} /L,
  - Platelets <75x10 ^{9}/L

Patient relative contraindications (case by case assessment of patients)

- Severe liver or renal failure (as indicated by any of the following):
  - eGFR <50,
  - bilirubin > 3 x upper limit of normal,
  - albumin <30 g/L and prothrombin time increased.
- Severe cardiac impairment.
- Unstable patient condition, not allowing isolation therapy.
- Previous myelotoxic chemotherapy or extended external bean irradiation fields to the bone marrow (pelvis, spine). In doubtful cases of haematological compromise a bone marrow biopsy might be indicated.
- Persisting depressed platelets values following prior PRRT cycles can impede the timing and dosing of subsequent cycles.

Things to be aware of

- Clinical assessment by medical oncology/endocrinology team
- Pre-treatment diagnostic imaging must be within **4-12** weeks of start of therapy.
- Check the medication of the patient for drugs which may interfere with the uptake and/or retention of somatostatin analogues (lots of possible interactions).
- For patients receiving **long acting somatostatin analogue** formulations treatment should be scheduled at the nadir of the pharmacological activity, usually at day 21-28 following the previous injection. Patients should be switched to short acting formulations up to 1 day before PRRT if symptom control is required.

How PRRT is done

- Infusion of amino acid solutions that contain lysine and arginine is essential to reduce kidney radiation absorbed dose. A solution of 2.5% lysine, 2.5% arginine in 1 litre saline (or commercial alternative) can be infused in 4 hours, **starting 30 min before the administration of the radiopharmaceutical.**
-
- Before beginning the amino acid infusion, appropriate measures against nausea and vomiting should be undertaken by administering an antiemetic (e.g. 5-HT3 antagonist, such as granisetron or odansetron) and/or a corticosteroid (e.g. dexamethasone). Further antiemetics may be administered PRN.
-
- Nutrition and fluid intake should be similar to the pre-treatment tracer study. Adequate hydration must be ensured.
- Encourage bladder emptying hourly for the first 12 hours. If patient cooperation with fluid intake or kidney function is an issue, an overnight infusion of IV saline can be administered.
- A resuscitation cart as well as a trained emergency team must be available.

What dose and utility of ‘Dosimetry’?

- Controversial
- NETTER-1 did not perform routine dosimetry on all patients
- Currently the recommended dose of Lu177 DOTATATE is 7.4 GBq x 4 doses 8-10 weeks apart

Post PRRT follow up/toxicity

- All patients receive whole body planar imaging at 24 hours post therapy

- Blood test monitoring every two weeks (until the next PRRT cycle, or for 12 weeks following the final cycle) and NET clinic follow up 6 weeks following treatment will be organised by the nuclear medicine team
- .
- Follow up scans should be performed at **mid cycle** (after **2** cycles) and **12** weeks post final therapy.

- Long term clinical and blood parameter follow up to assess delayed renal toxicity and /or myelosuppression.

Repeat Cases to emphasise the principles of Theranostics

Case 1- 60 yr male

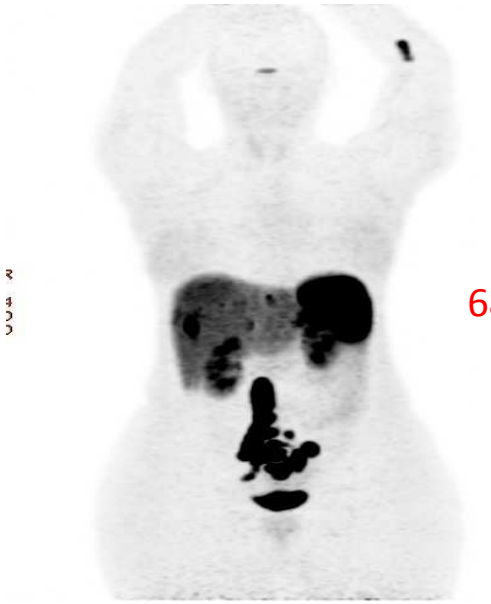
1. Grade	? Grade 1
2. Primary	SB
3. Liver only	Not involved
4. Functional	No
5. Progressive	No
6. PRRT?	? Future

Theranostic option of choice= Radical curative surgery

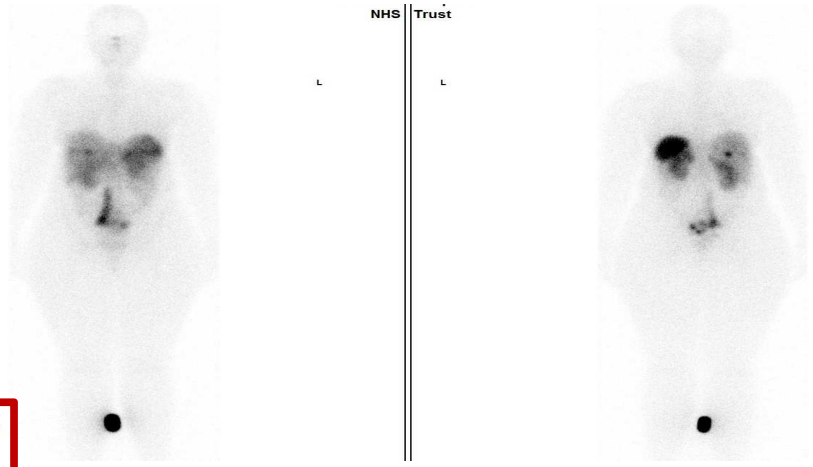
Case 2- 46 yr female

1. Grade	Grade 2
2. Primary	CUP/SB
3. Liver only	No
4. Functional	Yes
5. Progressive	Yes
6. PRRT?	??

Theranostic option of choice= PRRT



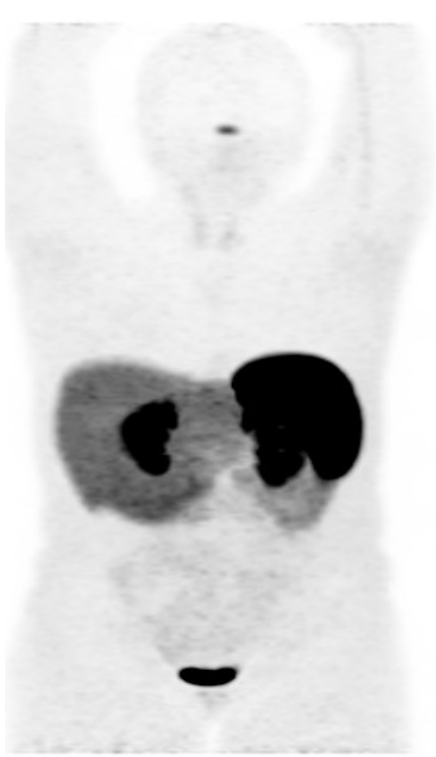
68Ga DOTATOC



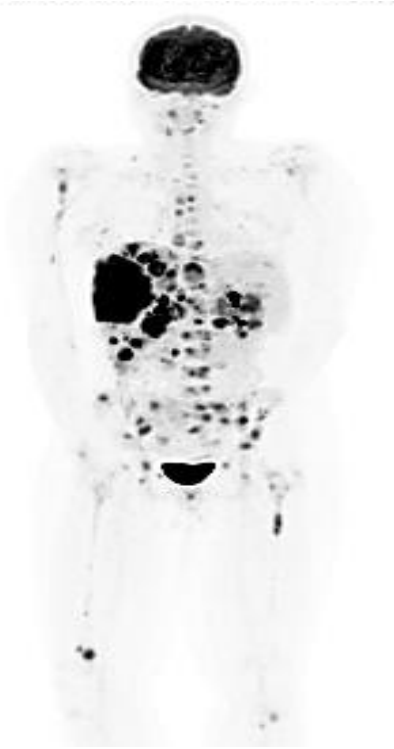
177Lu DOTATATE

Case 3- 15 yr female

1. Grade	Grade 3a
2. Primary	CUP
3. Liver only	No
4. Functional	No
5. Progressive	Yes
6. PRRT?	??



68Ga DOTATOC



18 FDG

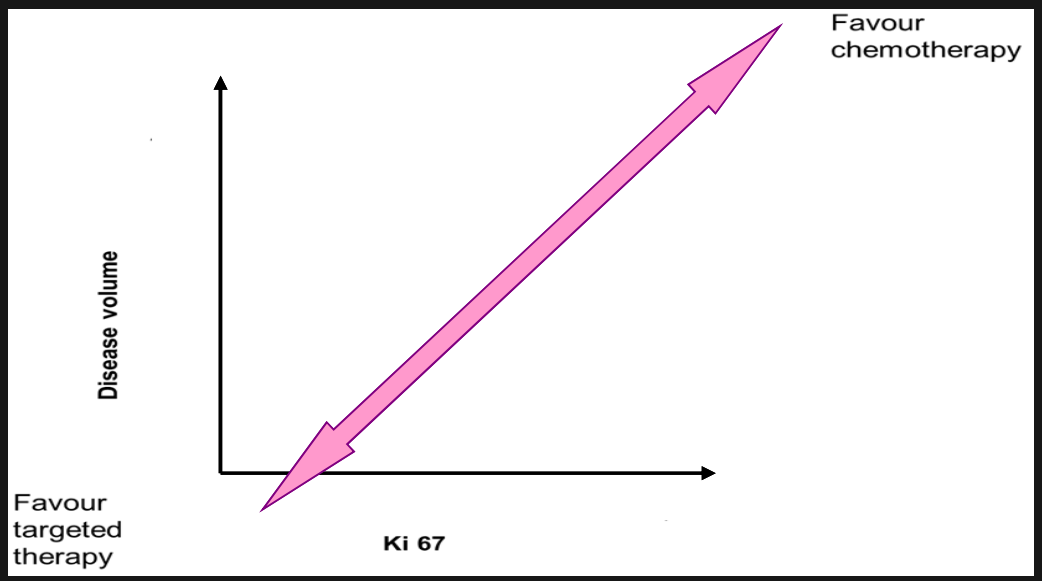
Theranostic option of choice= Chemotherapy (cis-etop)

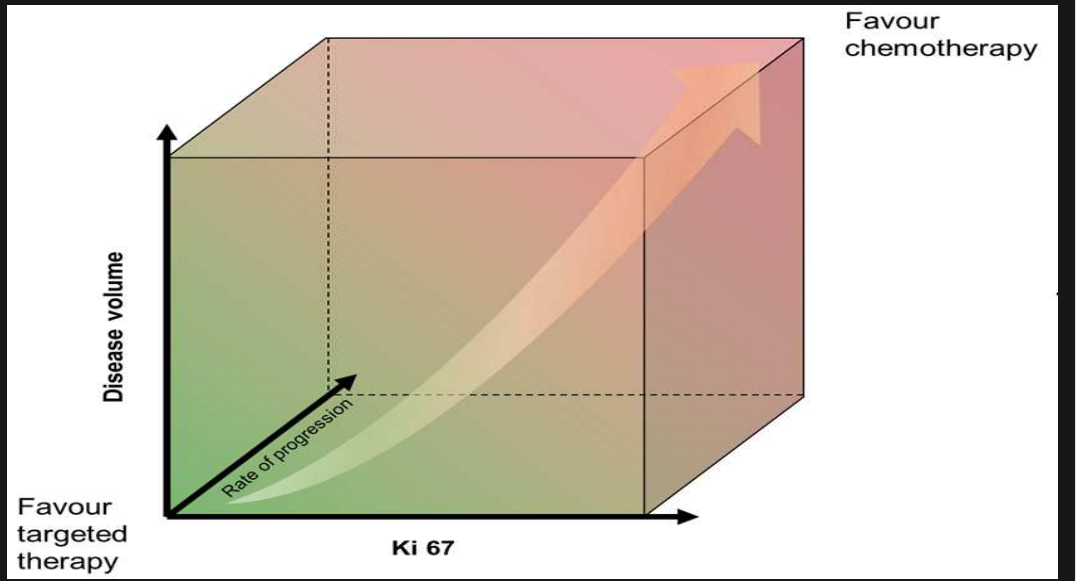
Current status of Ga68 DOTA SSTR imaging and PRRT in England

- Ga68 DOTA SSTR PET CT will be commissioned in NC2 PET CT wave
- PRRT for NET approved by NICE in 2018
- Utility is based on NETTER-1
- Only progressive GEP NET grades 1 and 2
- No second treatments
- Treatment centres are in the process of being commissioned
- 2 significant developments underpinned by clinical trials and licensed Theranostic tracers

Future

Concept of “mitotically-active” disease- where do the tracers fit?





Lamarca *et al* The Journal of Oncopathology 2014; 2(1):15-25

Principles to aid decision-making

- Concept of “mitotically-active” disease
- Patients usually live long enough to **receive multiple therapies**
- Need to identify sub-groups of patients (through research) who benefit most from each therapy
- **One-size does not fit all**

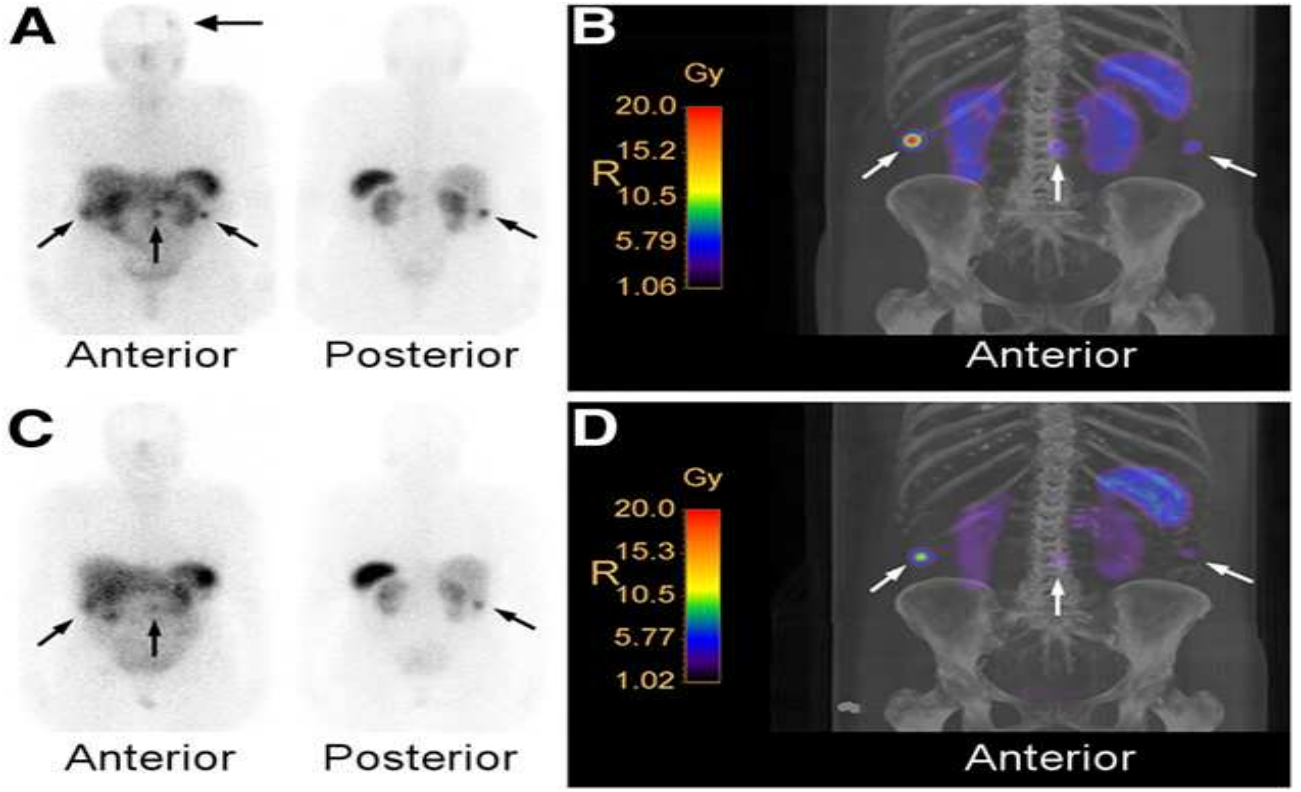
Future: PRRT for G3/Combination/ NEN Theranostic driven treatment

- Future clinical trials
- Lots of exciting opportunities

Somatostatin receptors part of G protein sub group- **Antagonist tracers**

ANTAGONIST

AGONIST



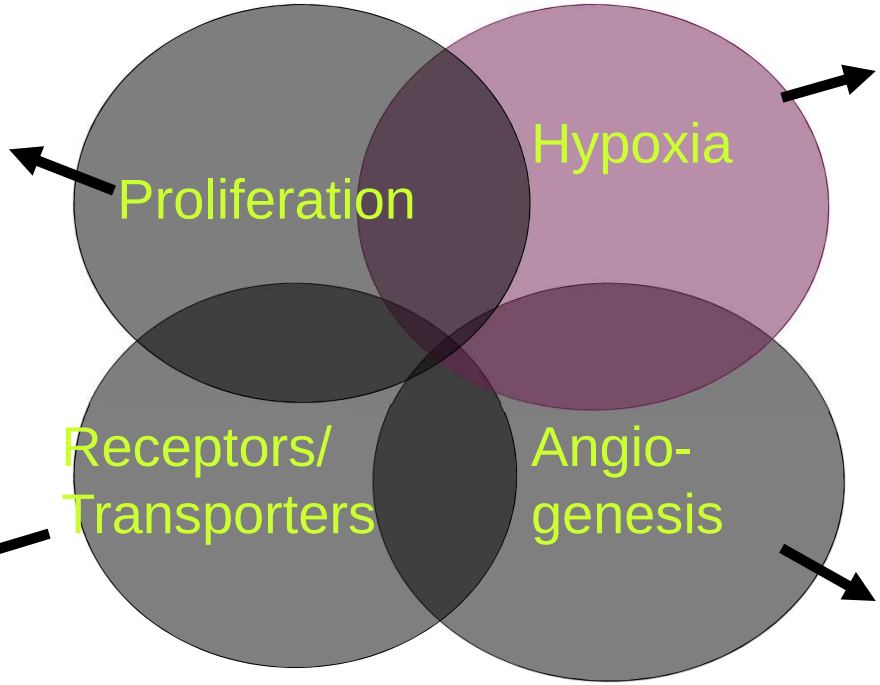
Somatostatin Receptor Antagonists for Imaging and Therapy
Melpomeni Fani et al. J Nucl Med 2017; 58:61S–66S

Summary

- Theranostic utilises molecular imaging as a biomarker signal to manage patients
- Specialist pathology / imaging assessment guides the entire management pathway- G1, G2, G3a/b
- Molecular Imaging then guides targeted decision making
- NEN therapy choices especially PRRT is driven by Threanostic principles
- PRRT is a complex therapy to deliver and a joint collaborative team approach is strongly advocated

Individualisation of Tumour Therapy: inc Chemo, PBT, MRI Linac, 3T MRI,PET CT

Conventional anti-proliferative chemotherapies



Hypoxia-directed therapies
(EPO, carbogen, HBO, chemotherapy with NLCQ1,TPZ)
Targeting hypoxic fraction (IMRT)

Somatostatin DOTA
SIRT

Anti-angiogenic therapy
(i.e. Avastin, Cu-chelators)

In summary: it is getting more complex but more exciting!

Thank You
The Era of Molecular Imaging and Therapy