PRRT: Indian Experience

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IAEA-RCA Project RAS6071/9002/01
Mid-term Review and Educational Meeting on Radionuclide Therapies
Tata Memorial Centre, Mumbai, INDIA

^{177}Lu-DOTA-TATE: From bench to bed !!

Was available in only 3-4 countries with prohibitively high cost (~US$40,000 per injection)

Tracer level radiochemistry

↓

High yield, purity and stability at low [L] / [M] ratio

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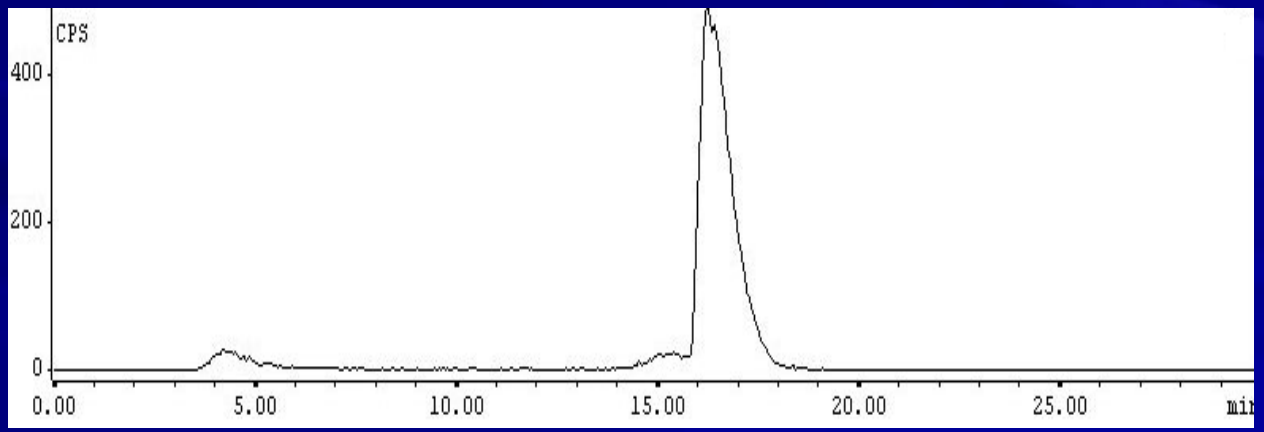
Optimization of protocol for the preparation of therapeutic dose



PRRT in India: Factors for the Boost in Recent Years

- Two developments as a part of radiopharmaceutical research in the country's premier atomic energy establishment BARC:

(1) The availability of 177Lu-LuCl3 at a much lower cost due to indigenous production (less than one-third of commercially available material)

and

(2) Indigenous production of a single-vial kit for the formulation of 99mTc-HYNIC-TOC, which has played an important role in centres that do not have access to a germanium/gallium generator.

Use of BARC Indigenous production: Several sessions of successful treatment

1. Production of ^{177}Lu in Research Reactor

Direct Route

Lu-176 (2.6% nat, enriched) $\xrightarrow{(n, \gamma)}$ **Lu-177** 6.65 d + **Lu-177*m*** 160.5 d

σ = 2090 b & 2.8 b

Indirect Route

Yb-176 (12.7% nat, enriched) $\xrightarrow{(n, \gamma)}$ **Yb-177** 1.9 h

σ = 2.85 b

β^-

PRRNT Centres in India: A geographical Overview

Nodal Point for availability of 177Lu-DOTATATE:

Radiopharmaceutical Division, BARC

Clinical Centres: 13

- **New Delhi: 1**
- **Chandigarh: 1**
- **Mumbai: 2**
- **Pune: 2**
- **Bangalore: 1**

^{177}Lu-DOTA-TATE therapy in India

Use of BARC protocol: Several patients successfully treated

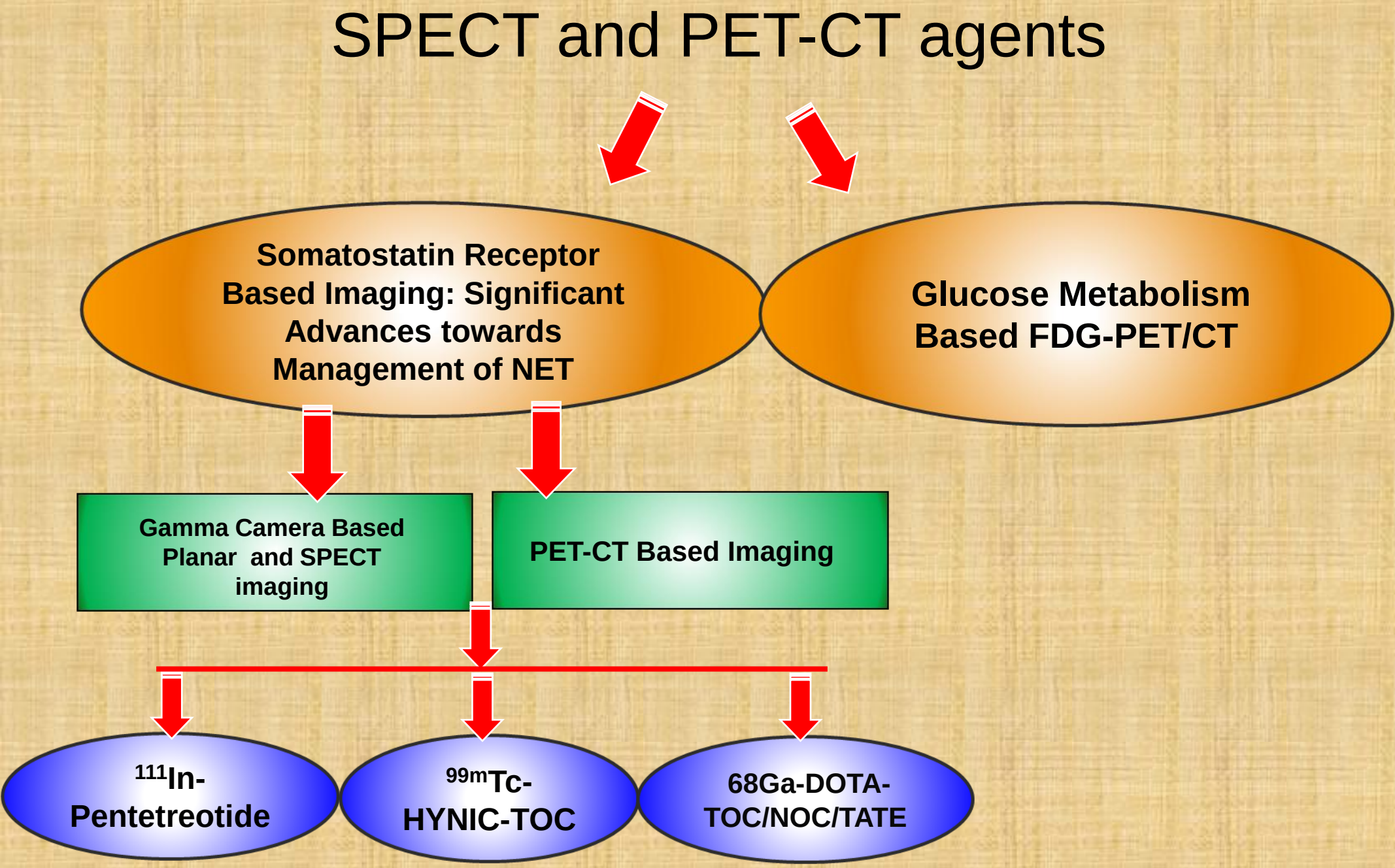
- All India Institute of Medical Sciences, New Delhi *(March, 2008)*
- Bangalore Institute of Oncology, Bangalore *(August, 2009)*
- INLAKS and Budhrani Hospital, Pune *(September, 2009)*
- Jaslok Hospital and Research Centre, Mumbai *(Feb, 2010)*
- Radiation Medicine Centre (BARC), Tata Memorial Centre Annexe, Mumbai *(January, 2011): More than 1500 sessions in last 5 years*
- SPECT Lab, Pune *(May, 2012)*
- PGIMER, Chandigarh *(September 2012)*

Courtesy: Sudipta Chakrabarty; Radiopharmaceutical Division, BARC, Mumbai

Theme 2. The range of tumors where PRRT employed

- **NET of the gastroenteropancreatic and bronchial tracts**
- Medullary thyroid carcinoma
- Pheochromocytomas
- Paraganglioma
- Neuroblastoma
- Merkel Cell Carcinoma
- Non-iodine concentrating metastasis of DTC

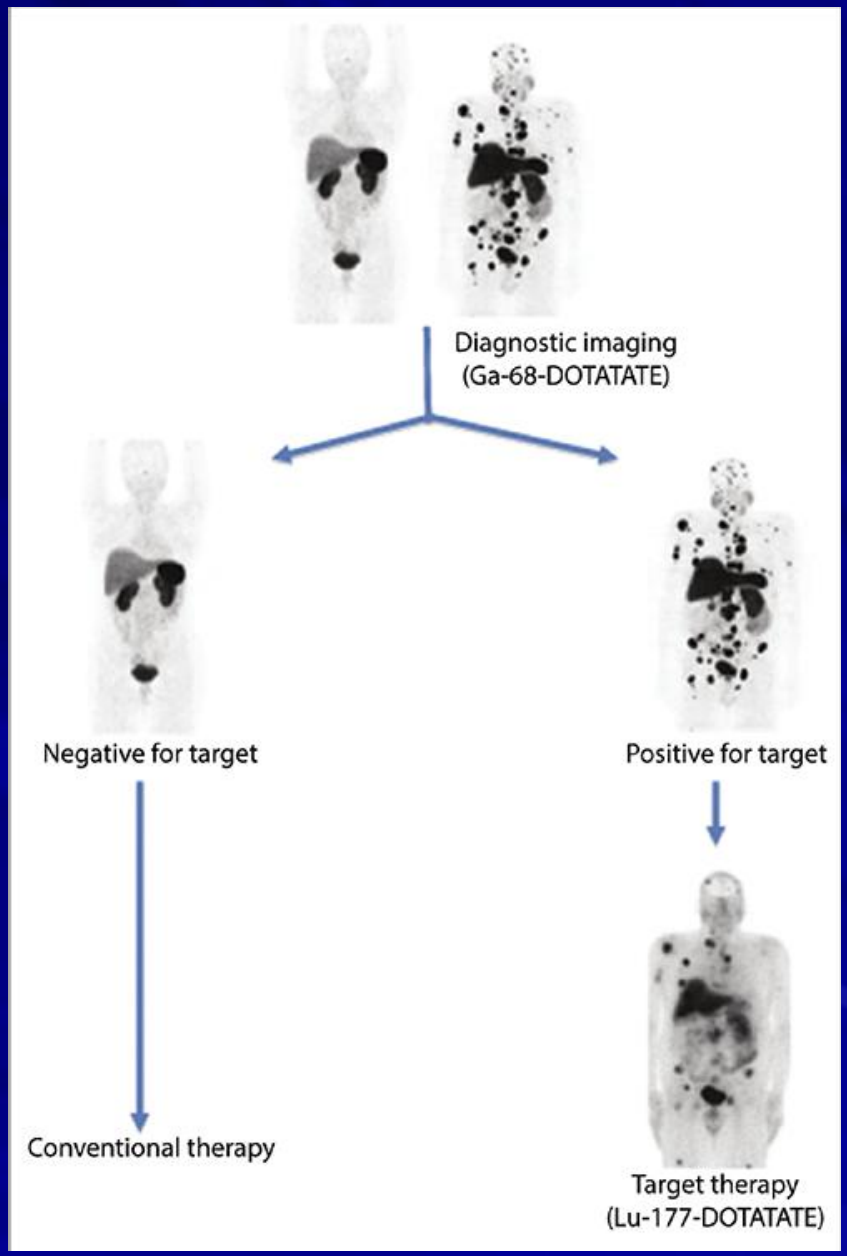
3. Decision Making Scan Options for 177Lu-DOTATATE PRRT/Chemotherapy

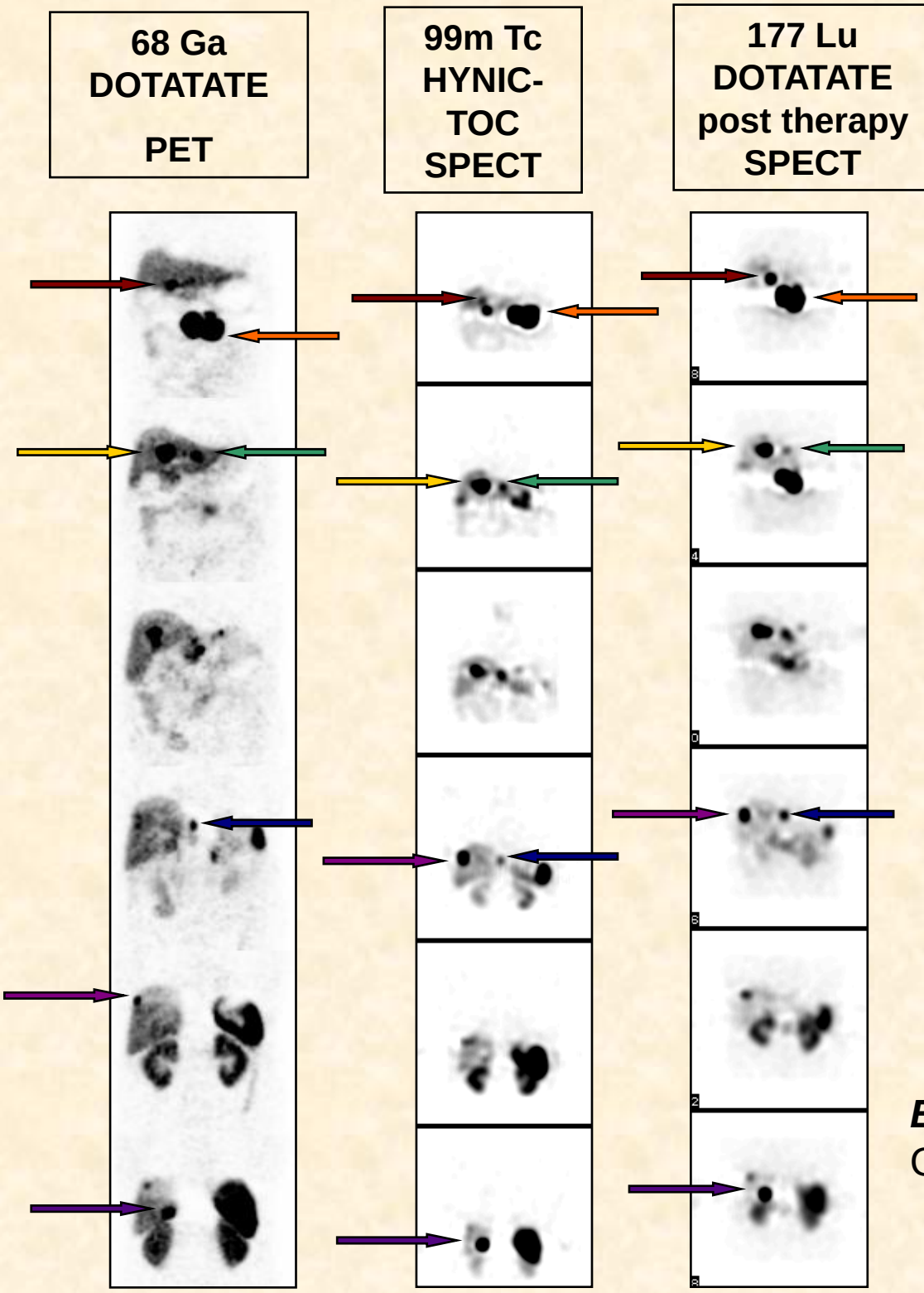


PRRT: A somatostatin receptor based targeted radionuclide therapy

The goal of targeted radionuclide therapy is to selectively deliver radiation to cancer cells and/or diseased tissue with minimal toxicity to surrounding normal tissues.

The basis for successful radionuclide therapy is a theranostic approach that integrates diagnostic testing for the presence of a molecular target for which a specific treatment/drug is intended





Gratifying Experience with BARC produced Indigenous ^{99m}Tc-HYNIC-TOC

Eur J Nucl Med Mol Imaging. 2013 Oct;40(10):1622-4.

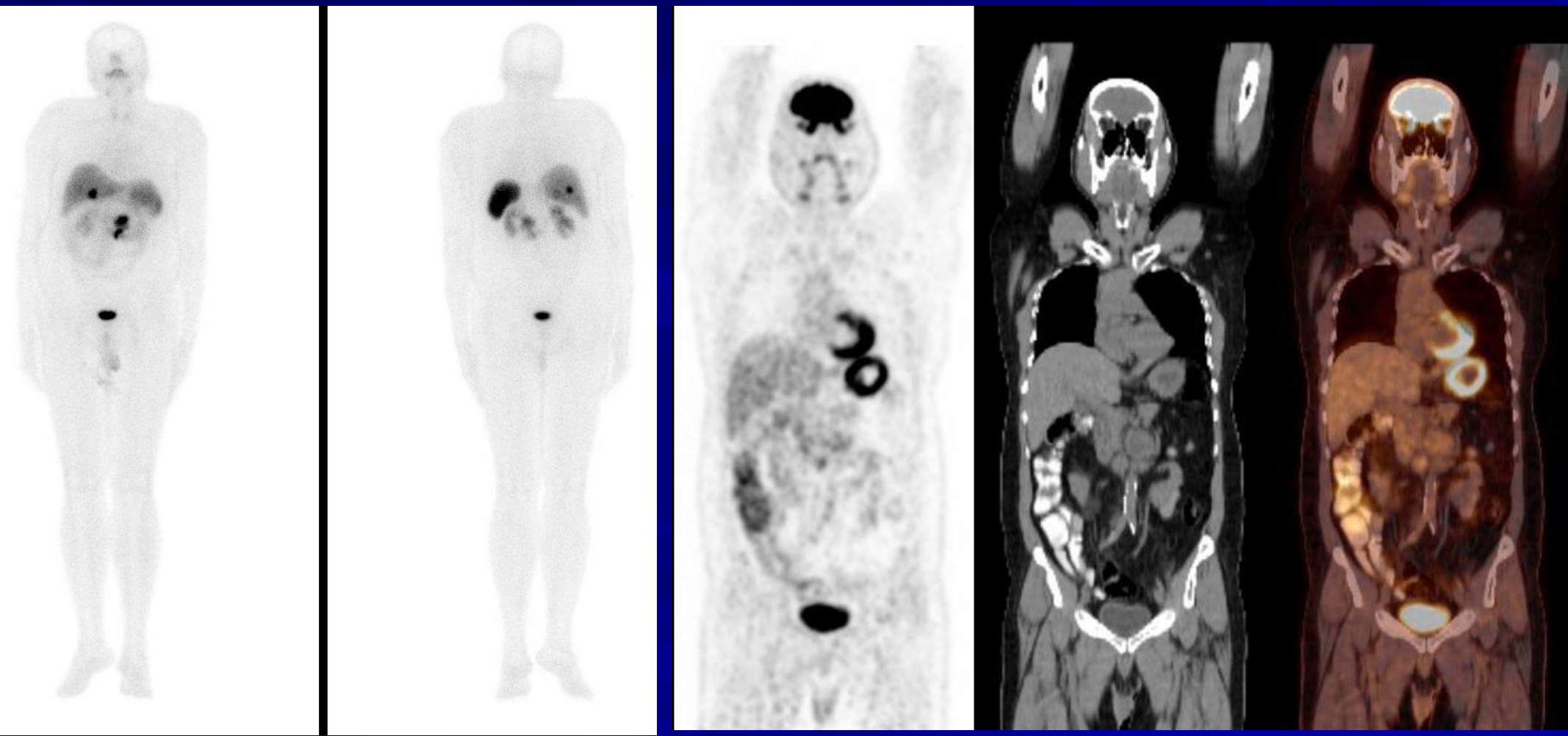
4. Radioligand Used: **[177 Lu-DOTA 0 ,Tyr] Octreotate**

- Octreotate: differs from octreotide only in that the C-terminal threoninol is replaced with threonine.
- Nine-fold increase in affinity for the SSTR 2 for [DOTA 0 ,Tyr 3]octreotate when compared with [DOTA 0 ,Tyr 3]octreotide
- Translates into 6-to 7-fold increase in affinity for their Radiolabeled counterparts and 4-5 times enhancement in the tumor uptake

5. Dual Tracer Imaging: 59/M, postoperative case of NET of the head and body of pancreas presenting with recurrent heterogeneously enhancing paraduodenal mass with liver metastasis; The Mib1 LI was reported 1-2% and serum Cg A was 1375 ng/ml. The recurrent mass and the hepatic lesion shows high grade uptake in SRI but negligible uptake on PET-CT

Somatostatin Receptor Imaging

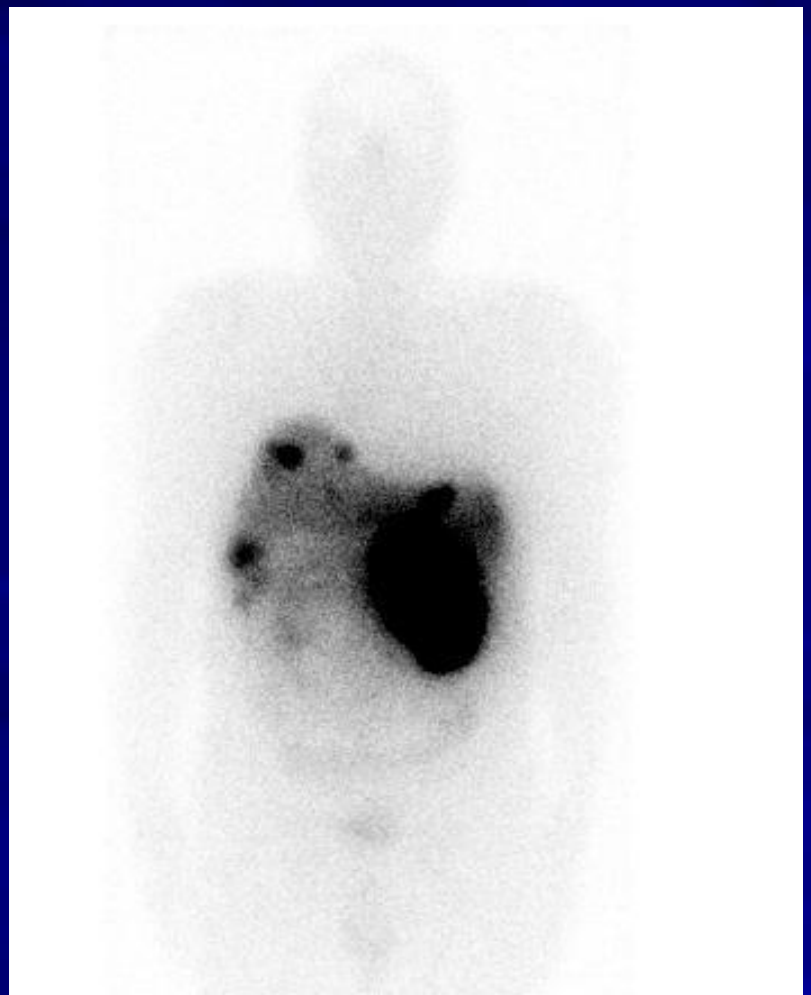
18F-FDG PET CT



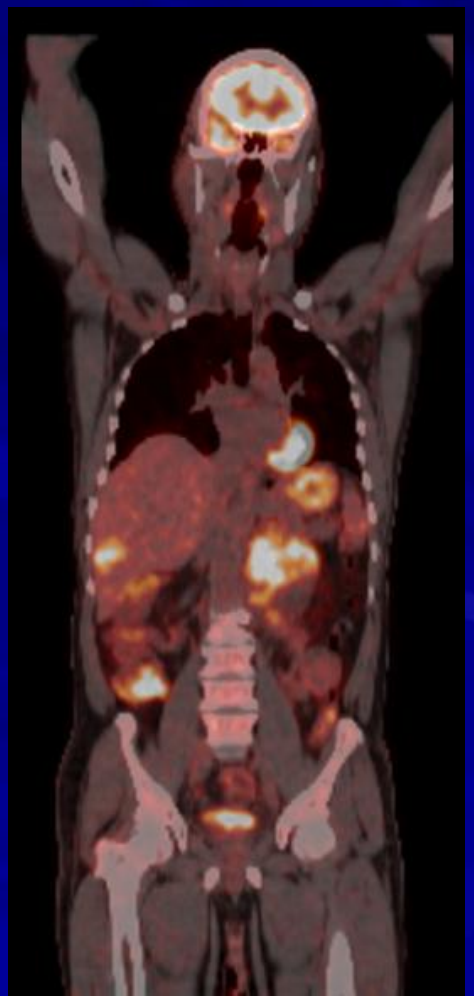
TOTAL DISCORDANCE: SOMATOSTATIN RECEPTOR EXPRESSION AND TUMOR GLYCOLYSIS

60/M, presented with 11x9x11 cm heterogeneous mass arising from pancreatic body and tail with liver metastases; Mib1 Index of the primary: 4%. A partial concordance was observed between SRI and FDG-PET/CT both in the primary and at the metastatic lesions. Both intralesional (in the primary) and interlesional heterogeneity (amongst the hepatic metastases) is well observed in the images with regard to FDG avidity and positivity. Received 2#: 215 and 181 mCi 177Lu-DOTATATE in 2 sittings ; CgA: 4775-→2770

Somatostatin Receptor Imaging



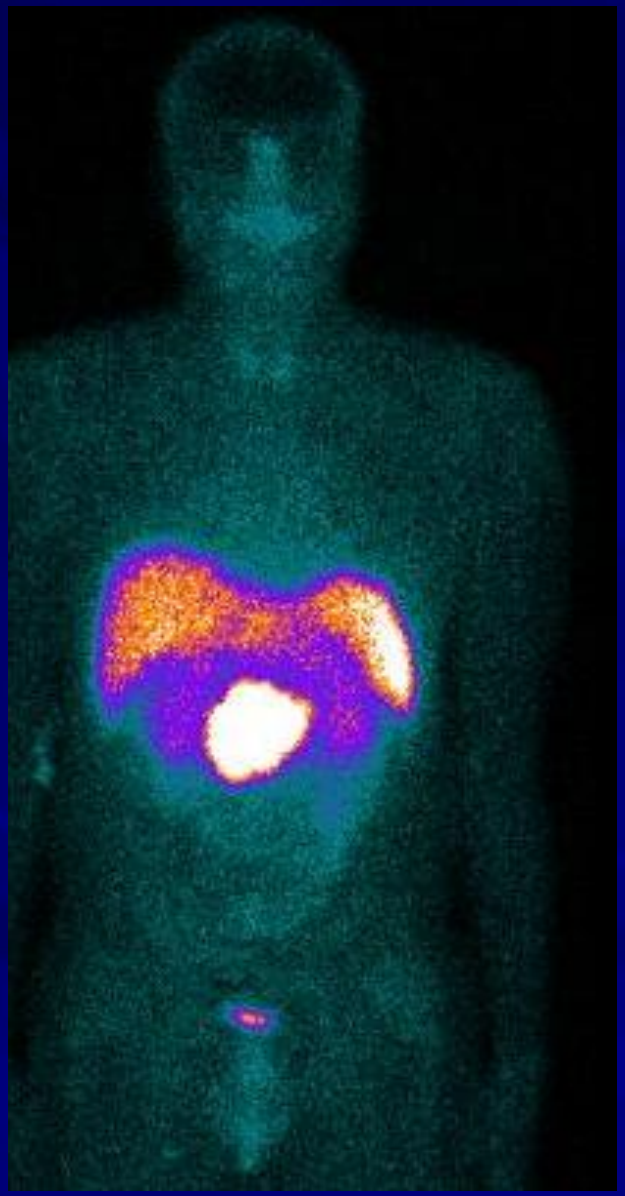
18F-FDG PET CT

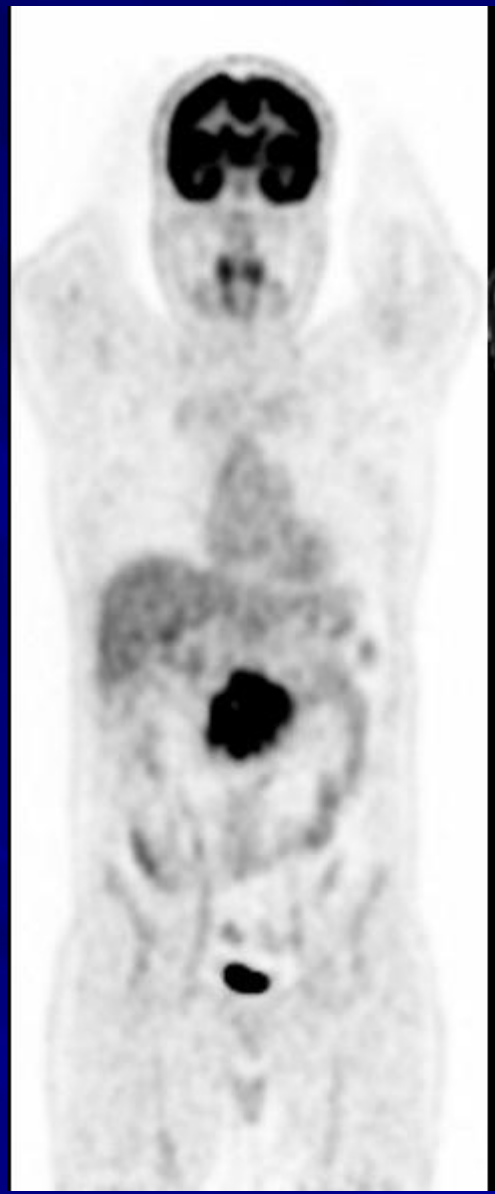


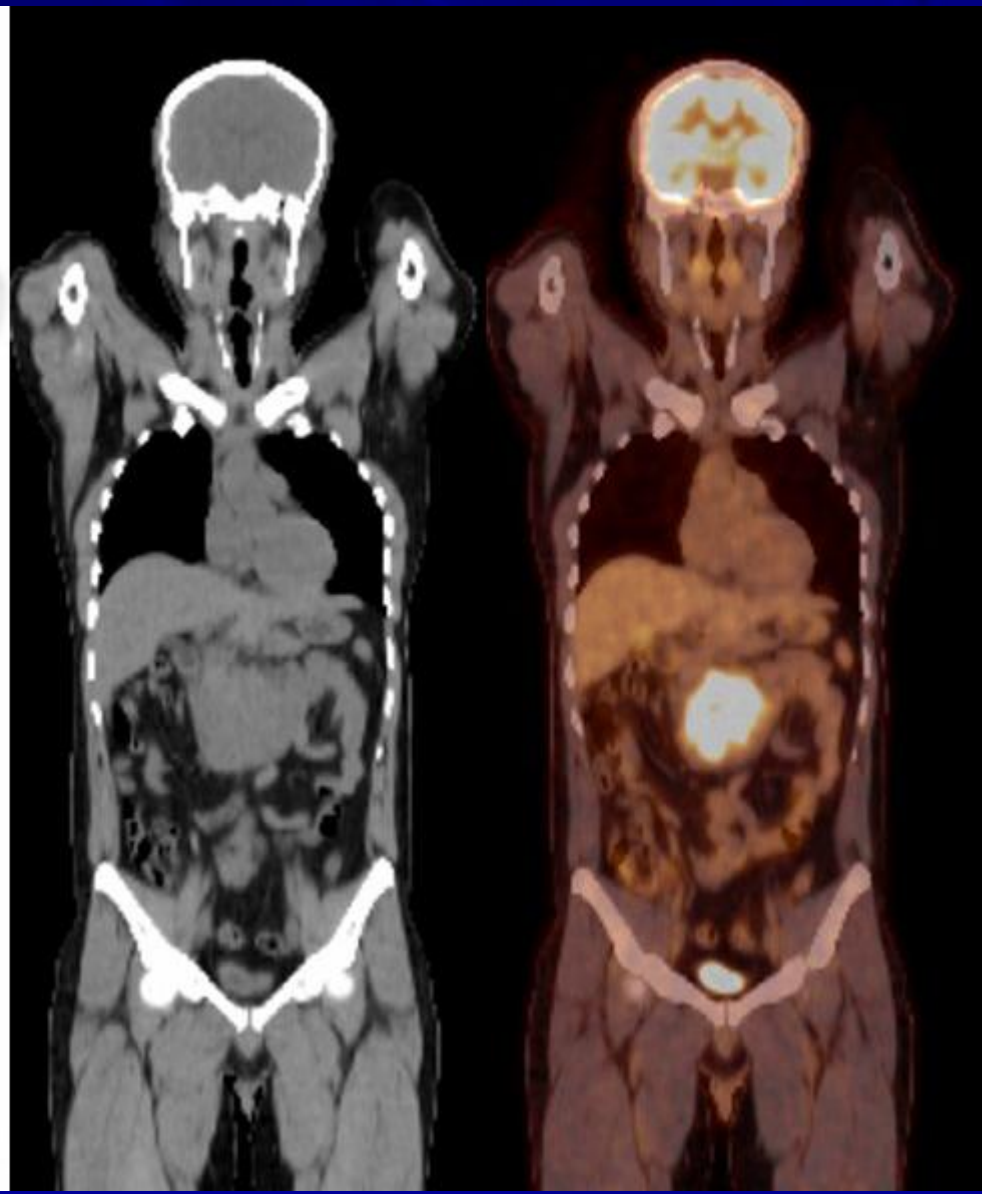
44/M, 6.1x6.3x4 cm highly vascular mass in the uncinate process of pancreas with duodenal and SMA infiltration on ceCT. HPR: Poorly differentiated NE Ca; Mib1 Index->30 % : Total concordance of SOMATOSTATIN RECEPTOR EXPRESSION AND TUMOR GLYCOLYSIS

Somatostatin Receptor Imaging

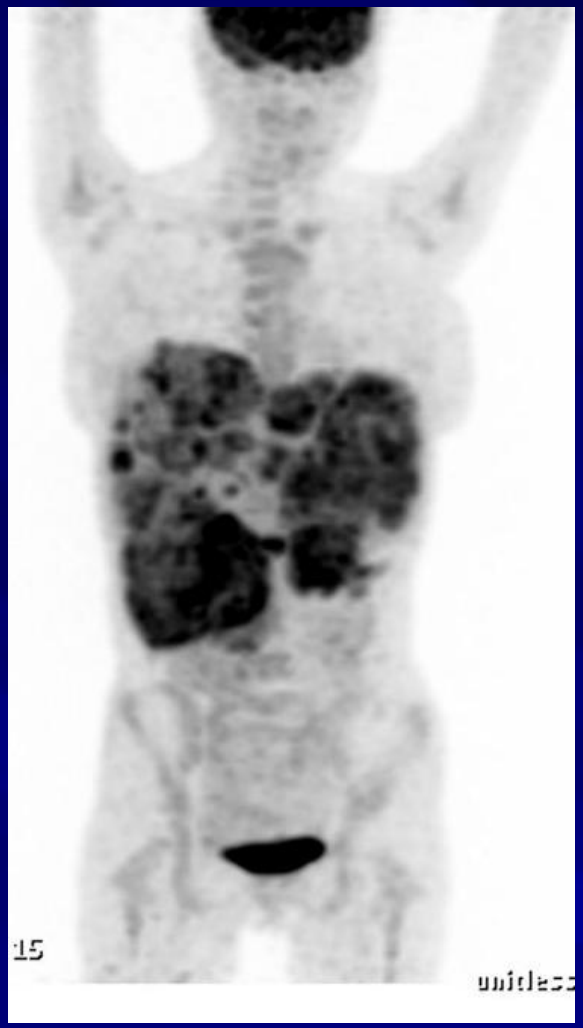
18F-FDG PET CT



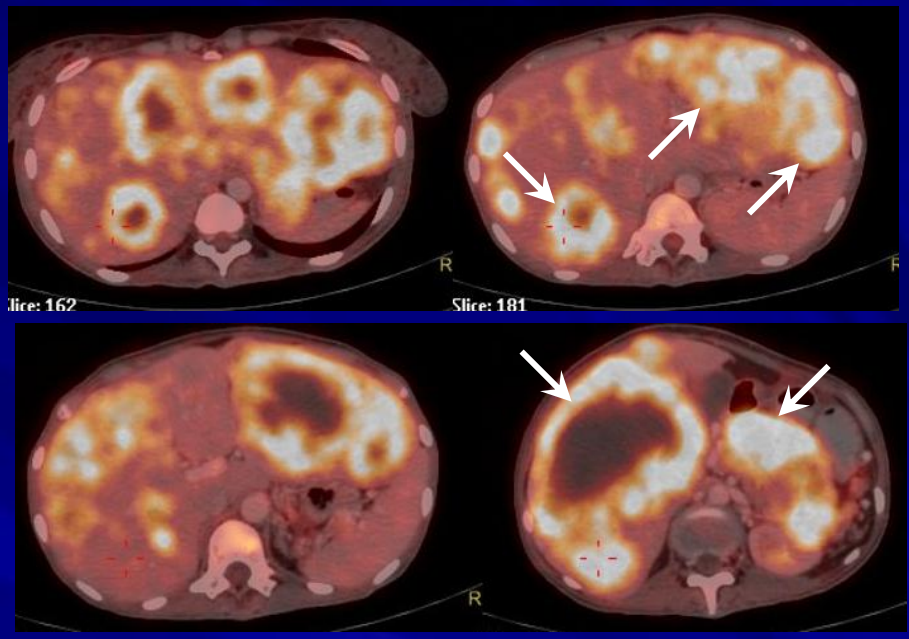




99mTc-HYNIC TOC



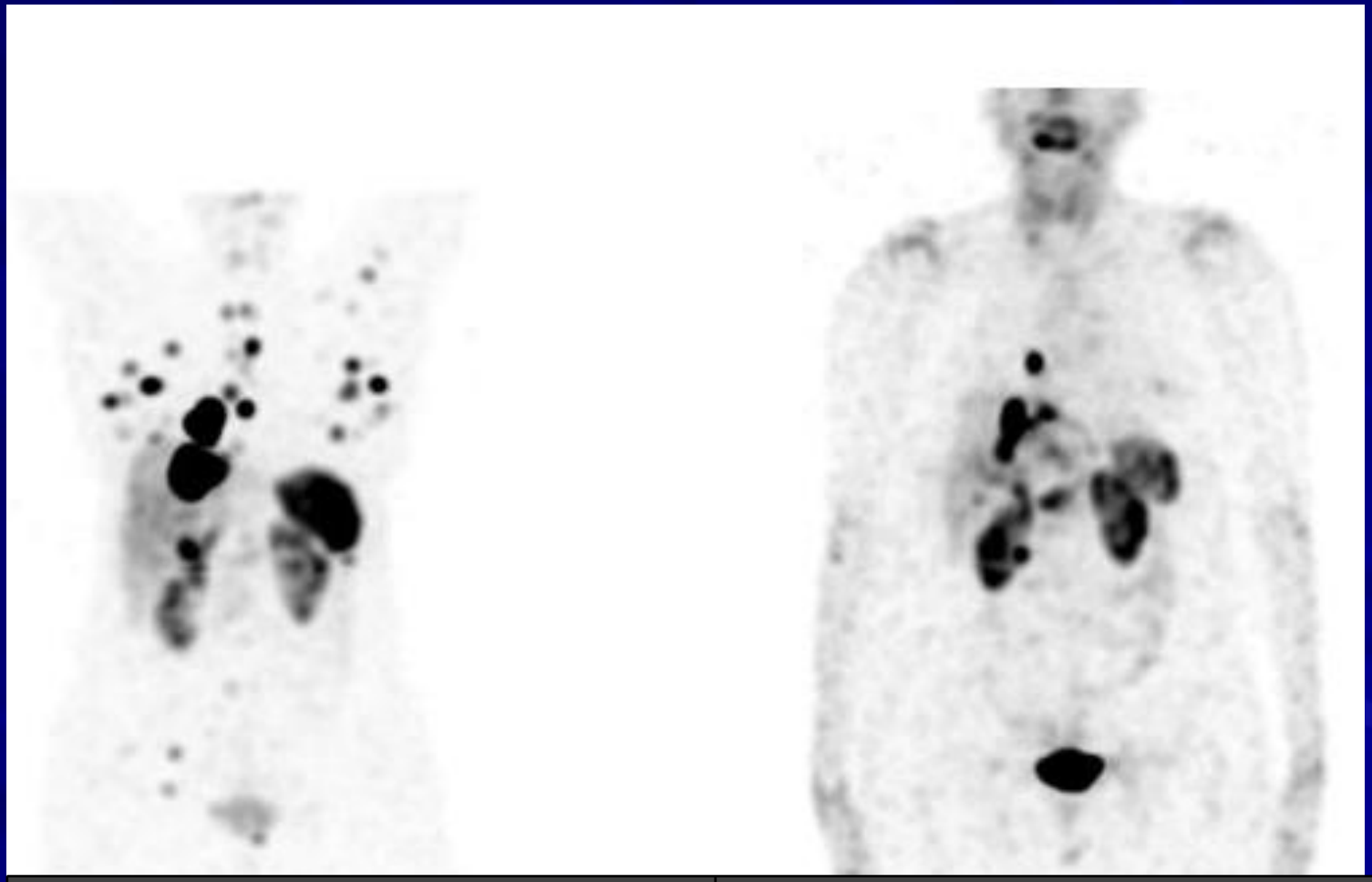
FDG-PET/CT



25 year old female initially presented with vomiting and generalized weakness. CT scan abdomen demonstrated **mass in body and tail of pancreas and multiple liver lesions**. CT guided liver biopsy showed it as neuroendocrine carcinoma with **Mib 1 index being 45 %.** 99m-Tc HYNIC TOC showed no SSTR positive lesions. The right kidney was pushed to the front by the huge mass. FDG-PET/CT showed intense FDG avid lesions in both lobes of liver and body and tail of pancreas. Patient was considered for chemotherapy with carboplatin and etoposide.

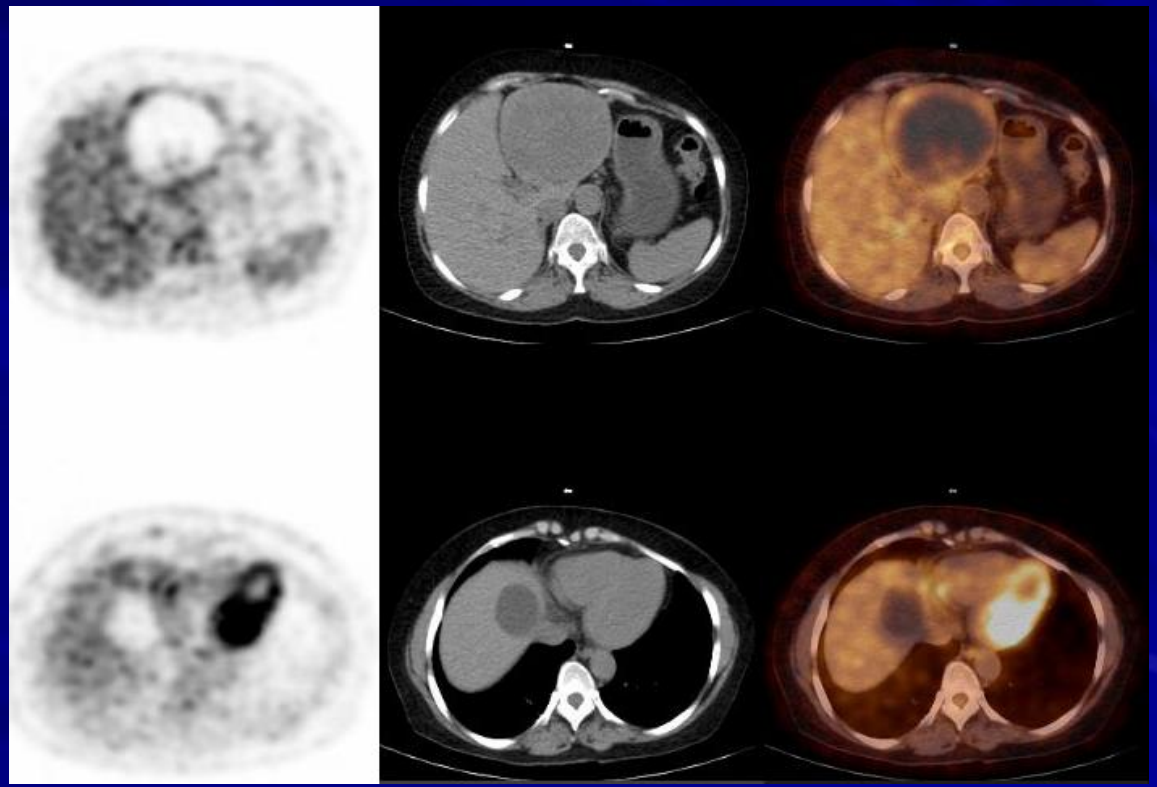
53/F, diagnosed as a case of atypical carcinoid of lung (MiB1 index of 6-10%.), MiB 1 index of 6-10%. Multiple SSTR positive lesions in liver, both lungs, multiple rib & right sided pelvis. received 3 cycles of chemotherapy with cisplatin and etoposide Reported a dramatic decrease in symptoms which includes decrease in abdominal pain and frequency of diarrhea. Also patient reports weight gain and overall improvement in general condition. Received 2 # of PRRT and being worked up for the 3rd.

Before 1st PRRT



Before 3rd PRRT

Timing of Test	Ser CgA (ng/ml)
Before 1st PRRT	496.7
After 1st PRRT and before 2nd PRRT	243.1



FDG-PET/CT images demonstrating non-FDG avid lesions in the lung and liver.

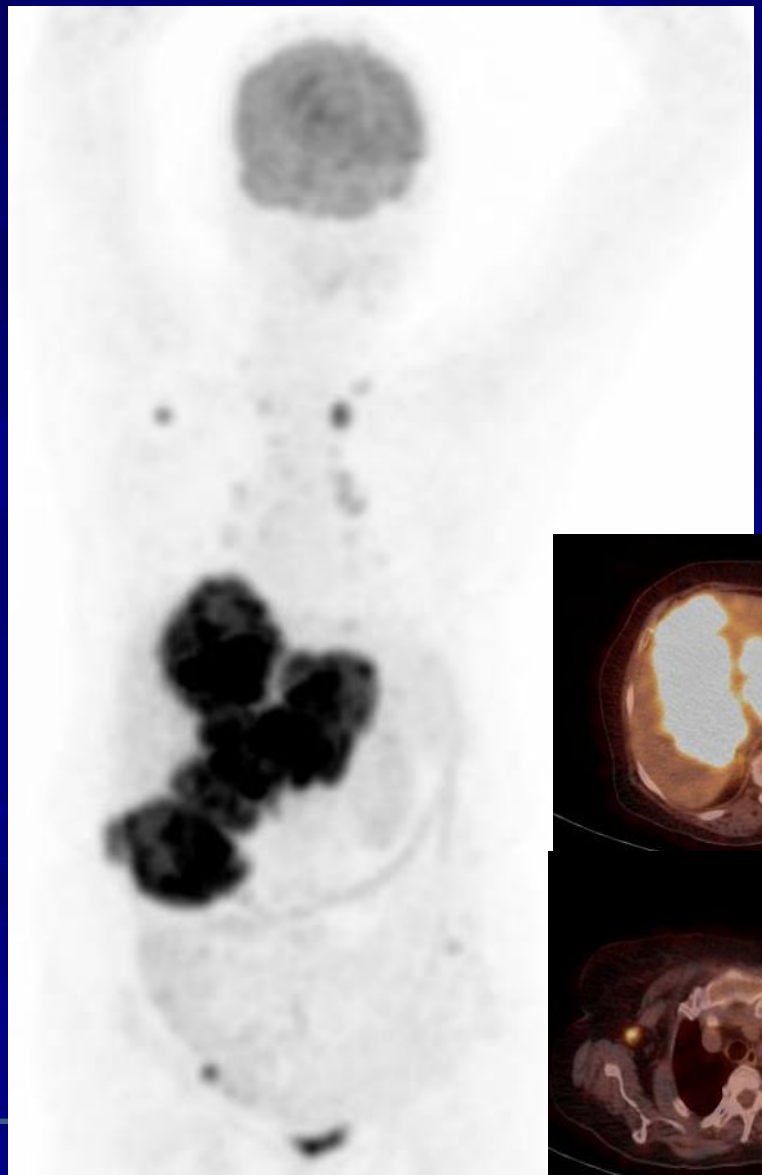
62 year old female initially presented abdominal swelling and diarrhoea. The CT scan of the abdomen showed an irregular polypoidal mildly enhancing soft tissue lesion in fundus and body of gall bladder with loss of fat planes with adjoining seg V of liver. Multiple necrotic lesions in both lobes of liver. Biopsy from liver lesion showed metastatic neuroendocrine carcinoma with Mib 1 index 25 - 30%. Patient was treated with 166 mCi of 177-Lu based PRRT. Patient showed progressive worsening and passed away 21/2 months post PRRT.

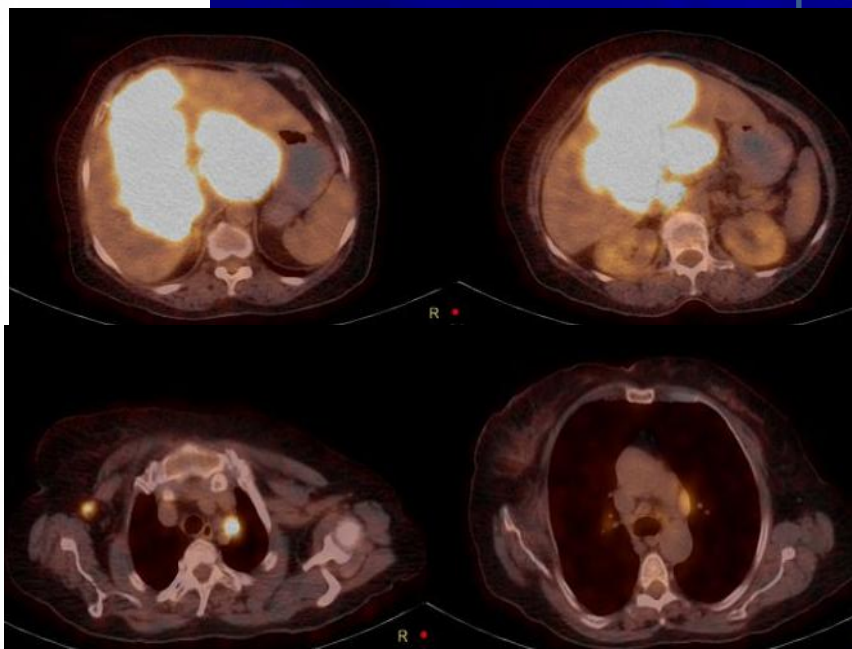
FDG PET CT scan

HYNIC TOC scan

Somatostatin Receptor Imaging

18F-FDG PET CT





Response to PRRT (50 patients' Data):

Multiparametric response evaluation correlating with primary tumor site, tumor proliferation index and dual tracer imaging characteristics

- Symptomatic Response:: Majority (in our series 96%) of patient showed symptomatic response or enhanced HRQOL, irrespective of tumor proliferation index.
- Objective Imaging Response: 30-40%
- Biochemical or tumor Marker Response: 60-70% (83% of scan responders)

Response to PRRT (50 patients' Data):

Multiparametric response evaluation correlating with primary tumor site, tumor proliferation index and dual tracer imaging characteristics

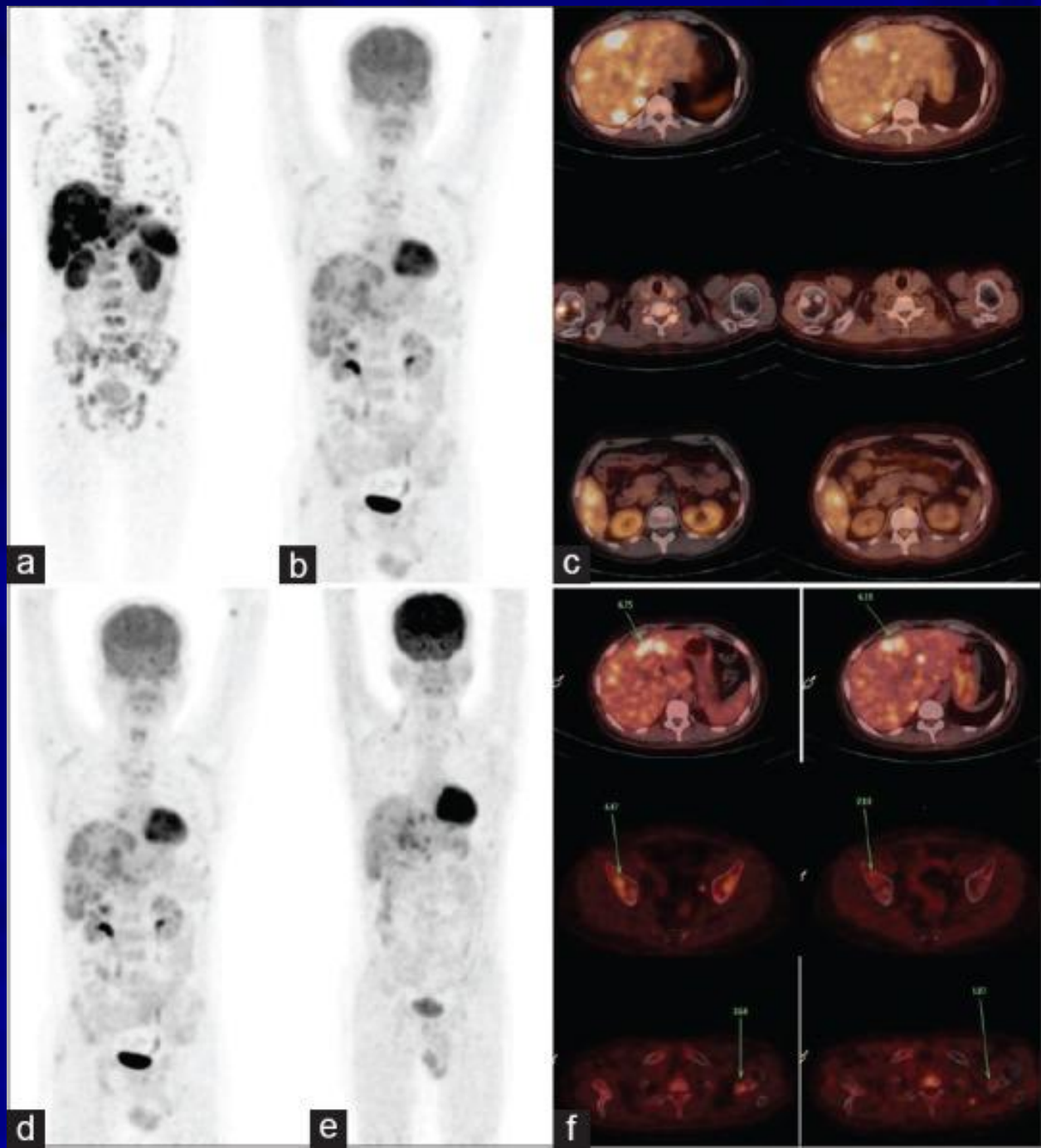
- Among the responders (n=41), 32 patients (78.04%) showed discordance in the FDG-PET/CT and SSTR based imaging whereas 8 out of 9 patients with non-response (88.89%) showed concordance of lesions in SSTR based imaging and FDG-PET.

- Conversely, 32 out of 33 patients (96.97%) with discordance on SSTR and FDG imaging and 9 out of 17 patients (52.94 %) with concordance on SSTR and FDG imaging were finally classified as responders whereas the remaining i.e. 1/33 (3.03%) and 8/17 (47.06%) classified as non-responders in the category of "discordant" and "concordant" subgroups respectively.

6. Relatively Safe Bone Marrow Toxicity Profile: even in Patients of Extensive Bone marrow Metastases…and with great symptomatic response !!

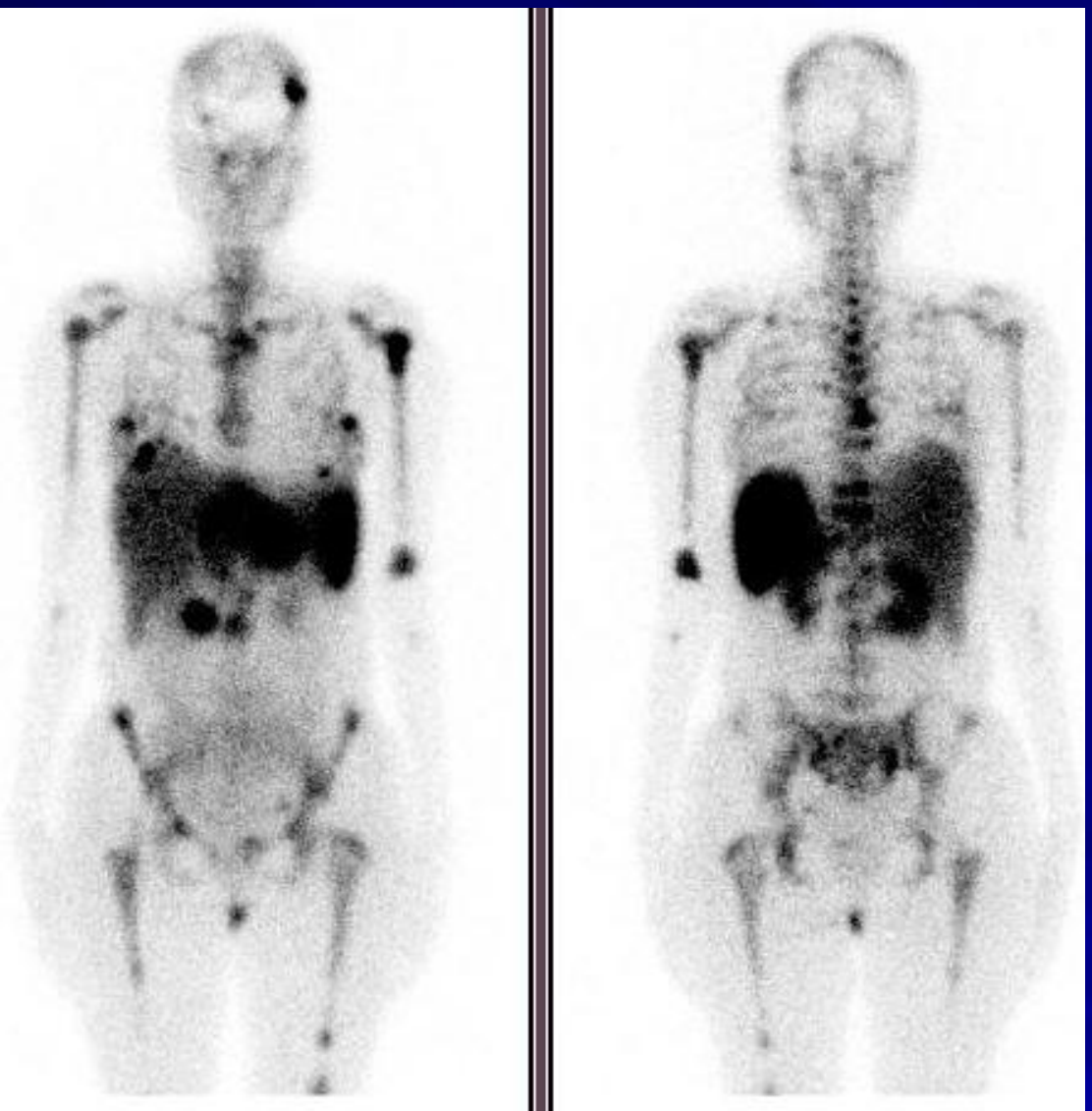
38/M, well-differentiated bronchial carcinoid (operated primary): Multiple uncontrolled episodes of sweating, flushing, and diarrhea. On daily short acting octreotide injections. On ^{68}Ga-DOTANOC PET/CT (a), there was multiple and extensive metsastatic liver and skeletal marrow involvement. FDG-PET/CT (b) demonstrated uptake in some of the hepatic metastatic foci and very low-grade uptake in the bone marrow.

Following 3#, complete resolution of all symptoms with complete cessation of octreotide injections. The FDG-PET/CT comparison (d-f) showed a partial response of the FDG concentrating lesions

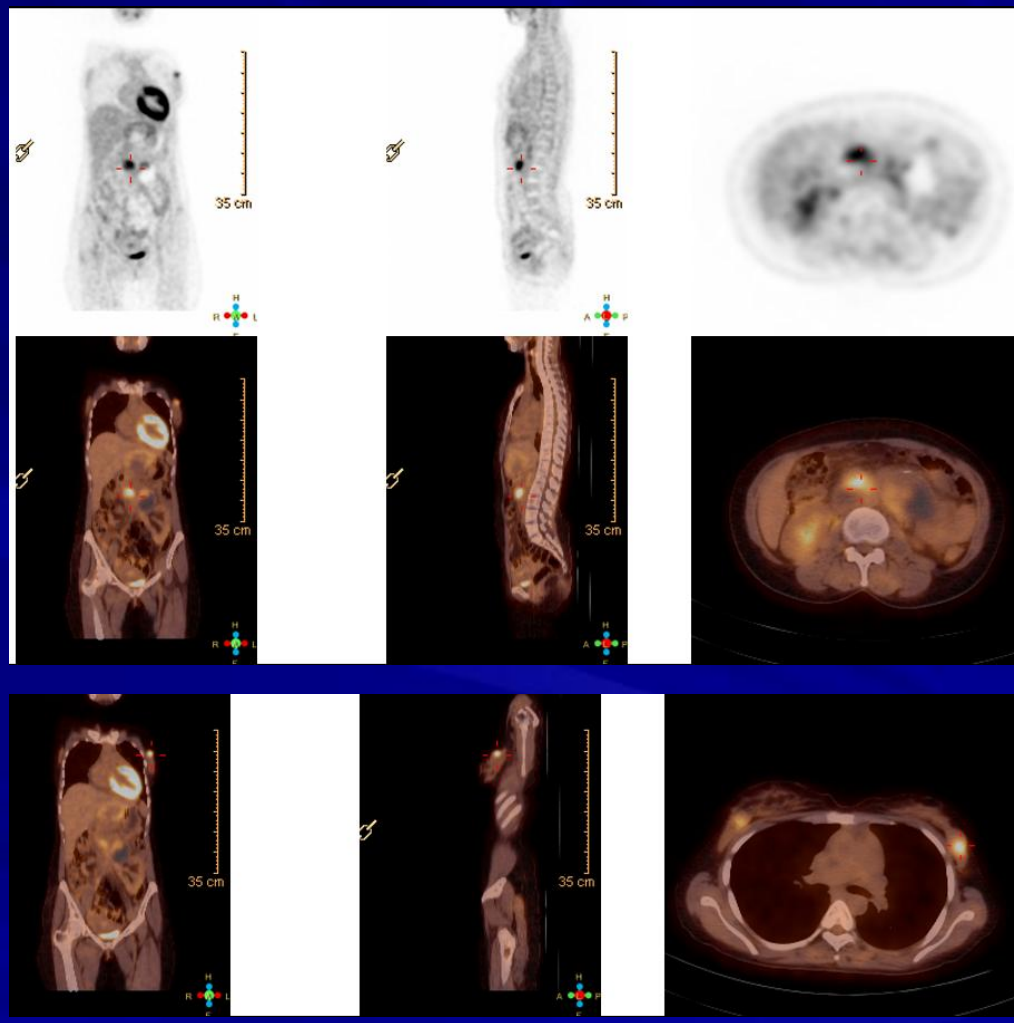


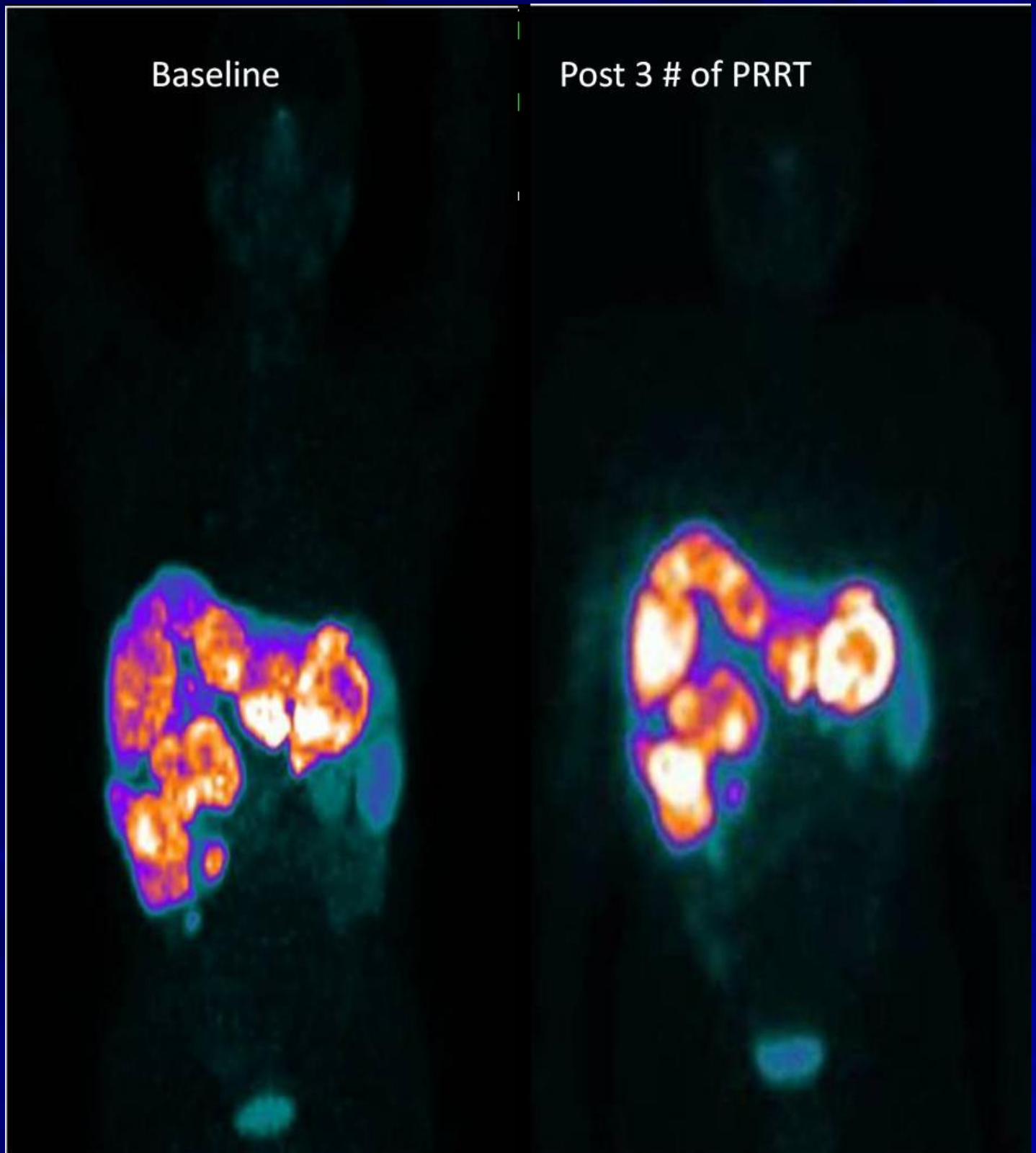
35/F, duodenal NET (MiB1 labeling index 20%) with liver metastasis (involving left lobe) and history of radiofrequency ablation of the liver metastasis and external radiotherapy six months previously, was referred for exploring the feasibility of PRRT……Working at 4 years!!

Somatostatin Receptor Imaging



18F-FDG PET CT

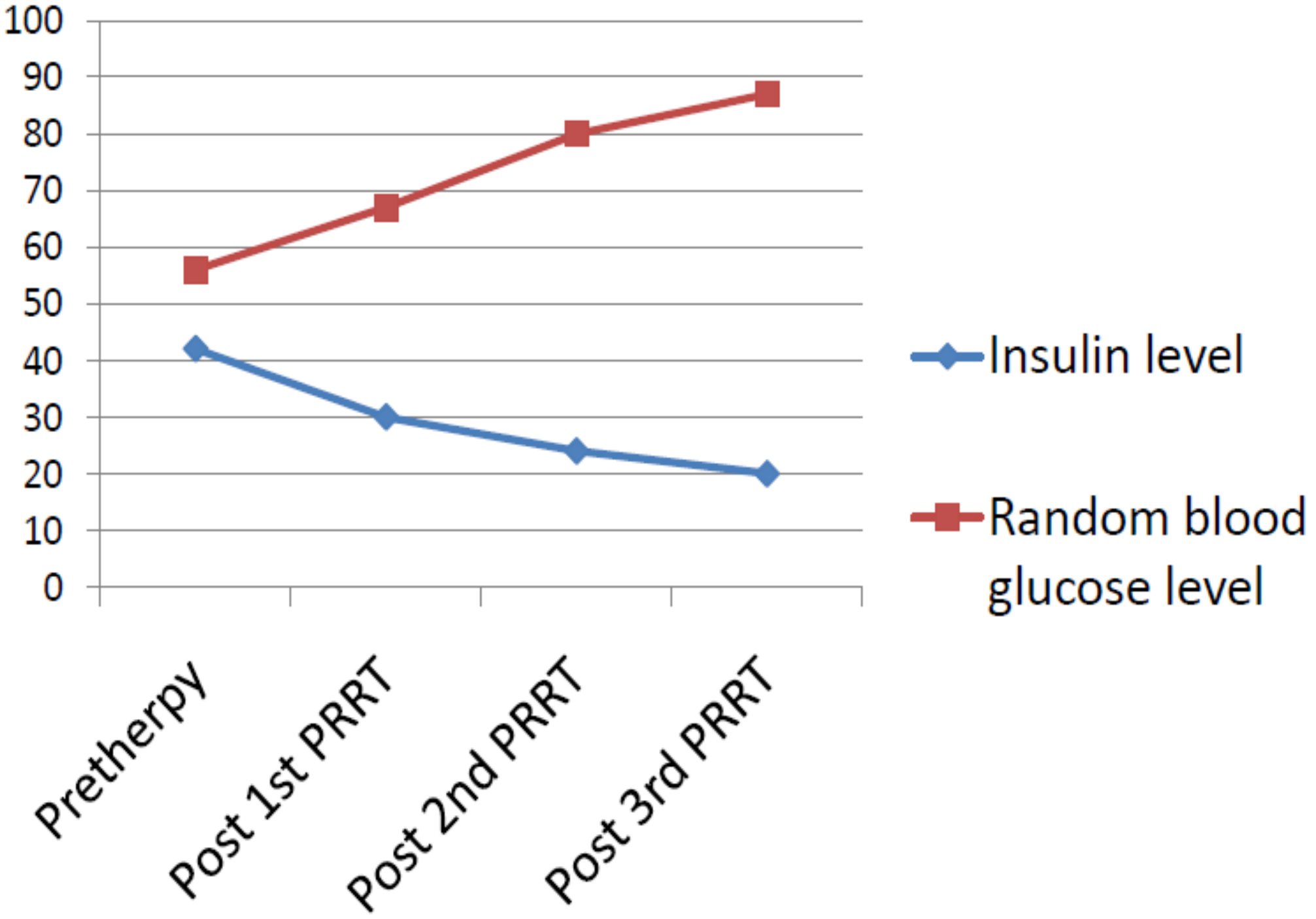




58/f with metastatic Insulinoma. Repeated Episodes of sweating and
Syncope. Needed meal Or sugary drink every 2-3 Hrs. random sugar 50gm/ml Insulin 50 (5-25 mu/ml)

Post 3 cycles of PRRT Dramatic clinical improvement.
No more frequent meals or
Sugary drinks. No syncopes. Unimpressive imaging improvement

Courtesy: Dr Vikram Lele, Jaslok Hospital, Mumbai



Courtesy: Dr Vikram Lele, Jaslok Hospital, Mumbai

7. Treatment decision-making in Mib1 (Ki-67) LI between 20 and 30 %: can the dual-tracer approach help in individualization?

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

Well-differentiated and moderately differentiated neuroendocrine carcinomas defined as NET grade 1 or 2 according to the WHO 2010 classification (i.e. upto 20%)

Eur J Nucl Med Mol Imaging. 2013 May;40(5):800-16.

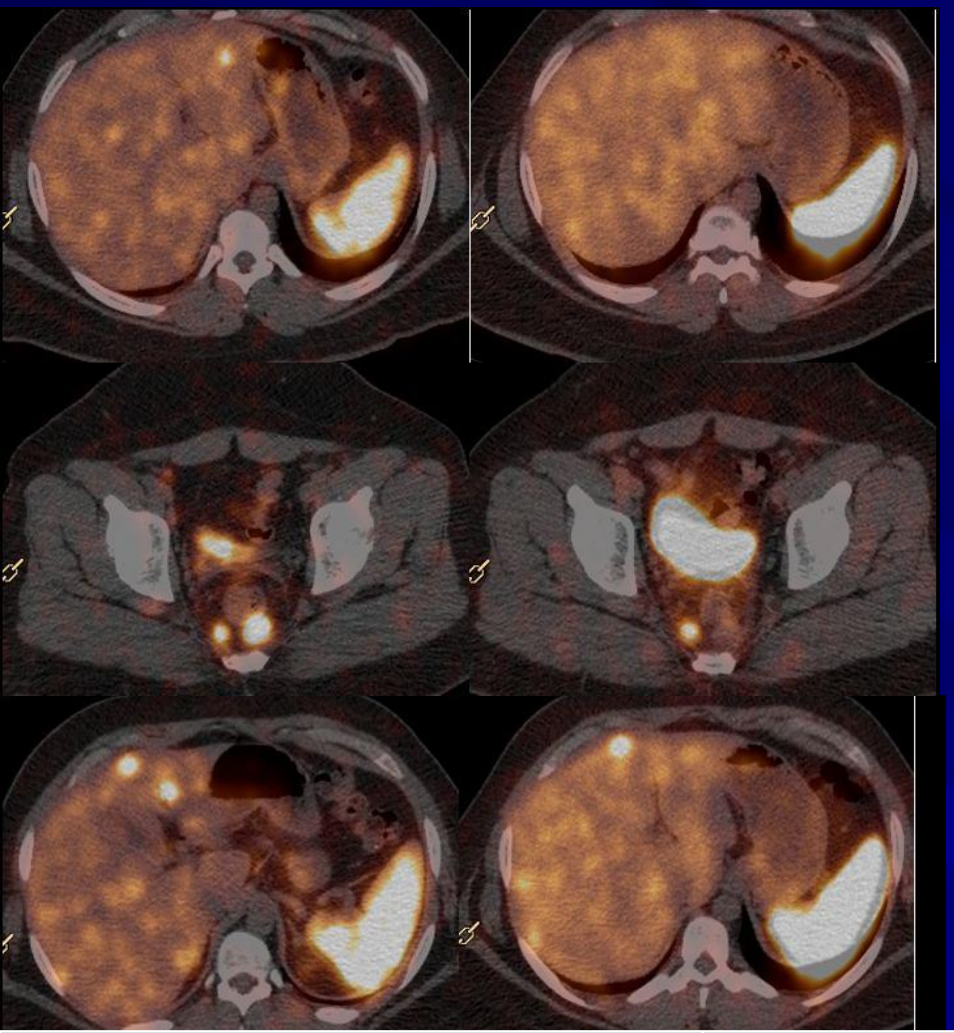
ENETs Classification of GEP NET: the major areas of use of PRRT

Grade	G1	G2	G3
Ki67 index (%)**	≤2	3–20	>20
MI (mitotic count)*	<2	2-20	>20

*10 HPF (high power field) = 2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density.
** MIB1 antibody; % of 2,000 tumour cells in areas of highest nuclear labeling.

MIB-1 labeling index (more commonly observed in histopathology reports, and has essentially replaced the original Ki-67 index in practice), which is directed against different epitopes of the same proliferation-related antigen MKI67 and has the advantage of being estimated on formalin-fixed, paraffin-embedded sections.

Pre-1st cycle PRRT Pre-2nd cycle PRRT



Timing of Test	Ser CgA (ng/ml)
Before 1st PRRT	120.5
After 1st PRRT and before 2nd PRRT	27.15
After 2nd PRRT and before 3rd PRRT	8.0

26 /M, Bleeding PR, anorectal polyp excision in March 2013: HPR : High grade rectal NET with MiB 1 index of 22%.

•Took 5 inj of Long acting Octreotide injections . After the 5th injection started complaining of abdominal pain and flushing.

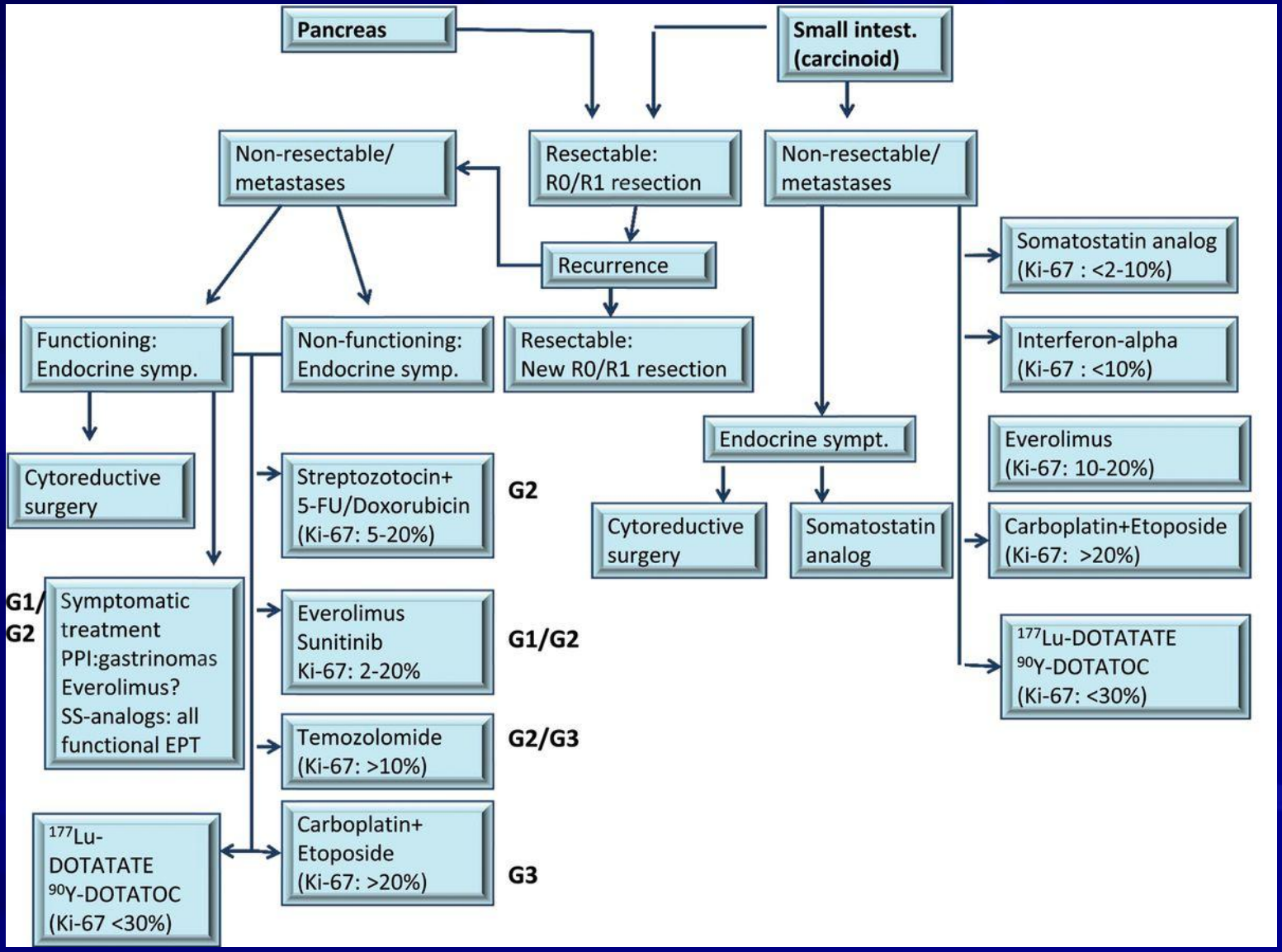
•68-Ga DOTATOC scan showed multiple SSTR positive lesions in liver and pre sacral nodes. Seg III, Seg IV B (SUVmax : 39.7), Seg VI and Seg VIII (SUVmax : 26.3). Presacral node at S1 (SUVmax : 45.6), 2 presacral node at 4 (SUVmax : 48.9 larger and smaller is 22.5).

•Patient was treated with 166 mCi of 177-Lu based PRRT. Follow up 68-Ga DOTATOC scan shows complete resolution of lesions in Seg III and VI (no documented lesion on CT). Other SSTR positive lesions in liver and in pre sacral area have decreased in metabolic intensity. Seg IV B (SUVmax : 24.9), Seg VIII (SUVmax : 25), Presacral node at S1 (SUVmax : 32.9), 2 presacral node at 4 (SUVmax : 5.9 larger and smaller is 16.8)

•Patient has overall reported a dramatic response with total resolution of the abdominal pain and episodes of flushing.

•Subsequently patient again received 2 more cycles of PRRT with the scan findings being now almost same with progressive decrease in the serum chromogranin A

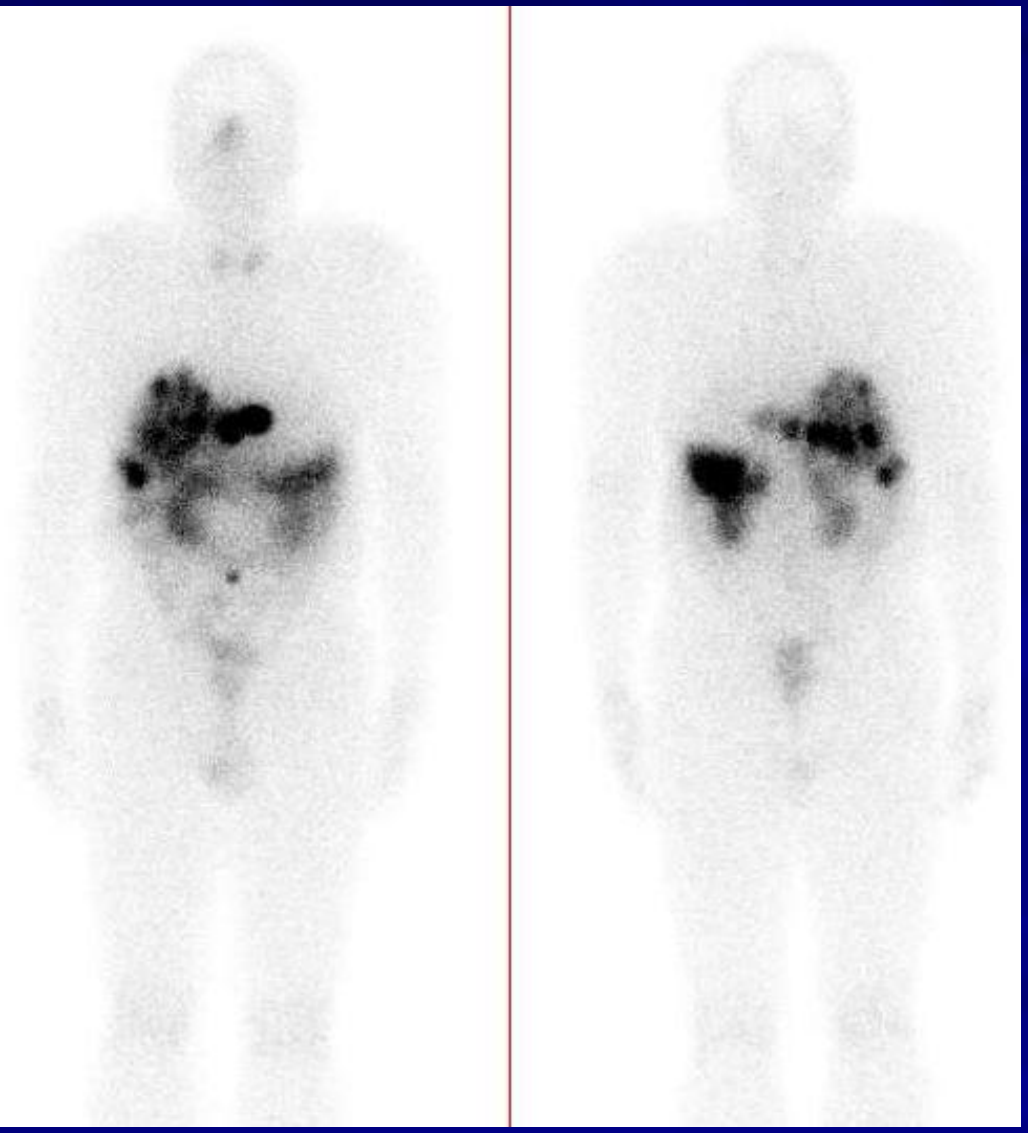
ESMO Clinical Practice Guidelines for GEP-NETs



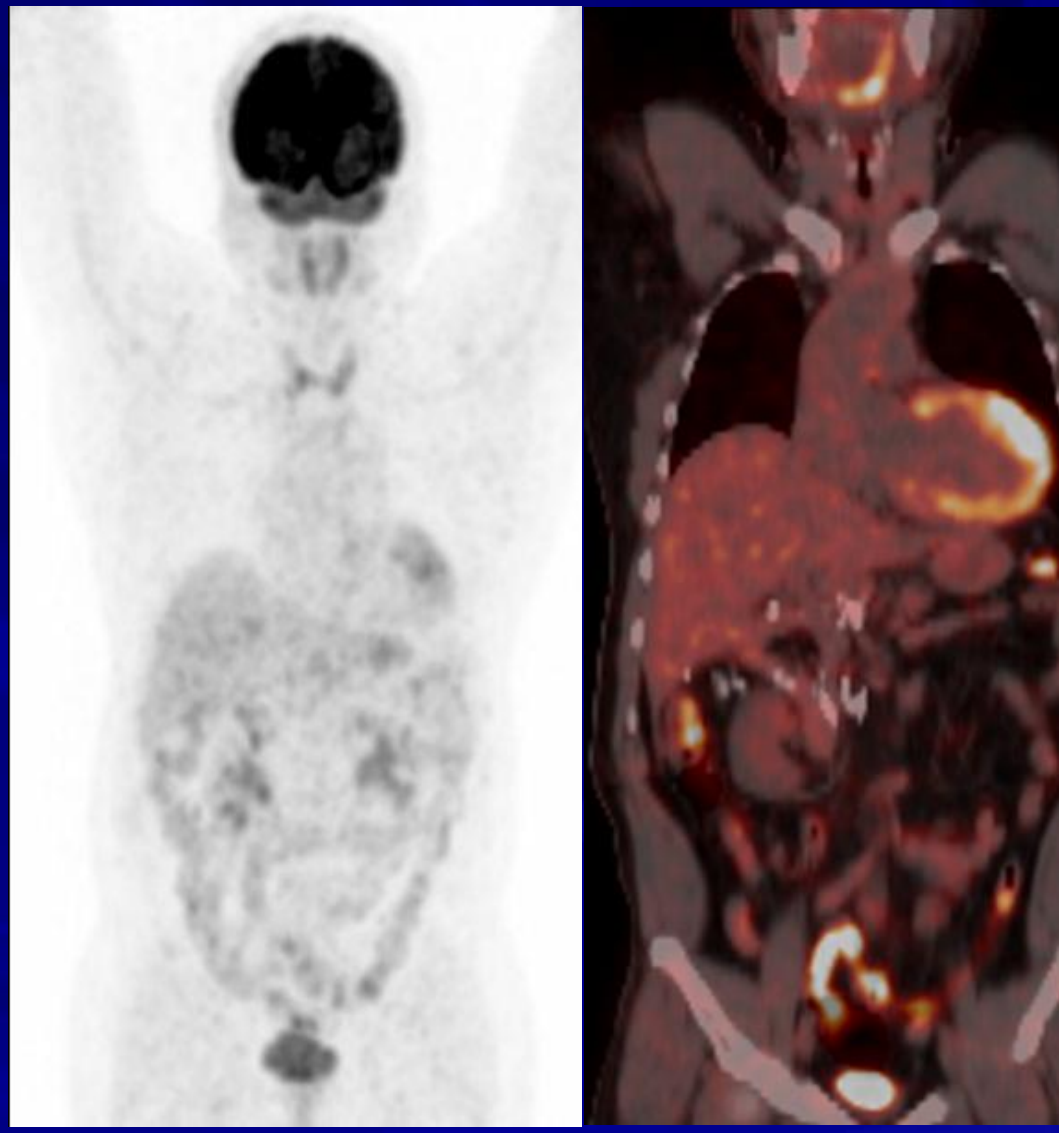
Öberg K et al. Ann Oncol

8. Discordance of MiB1 index and Imaging features: 61/M, Post Whipple's (Primary-Head and Proximal Body of Pancreas); Biopsy- Poorly diff NE Ca; MiB1---20%; FDG-PET/CT: Total Discordance; CgA: 125.01→93.47; with excellent symptomatic response

Somatostatin Receptor Imaging



18F-FDG PET CT

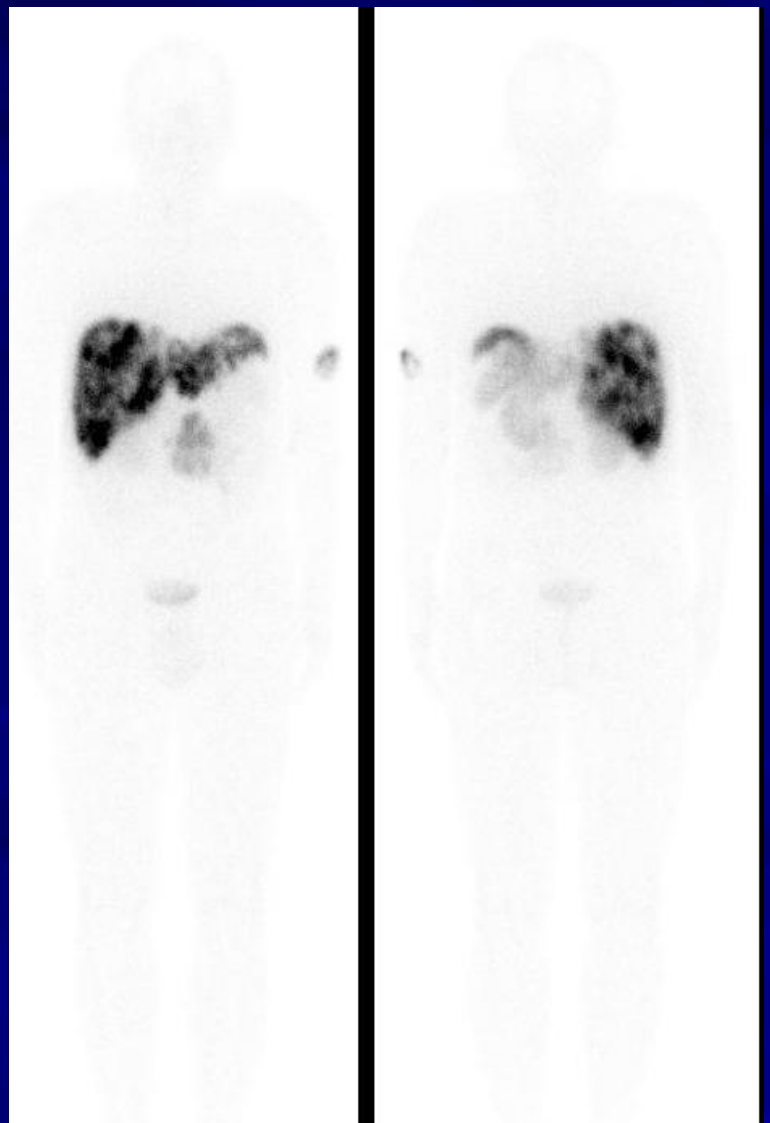


Following 54 months after the 1st therapy the patient is alive, progression free and asymptomatic.

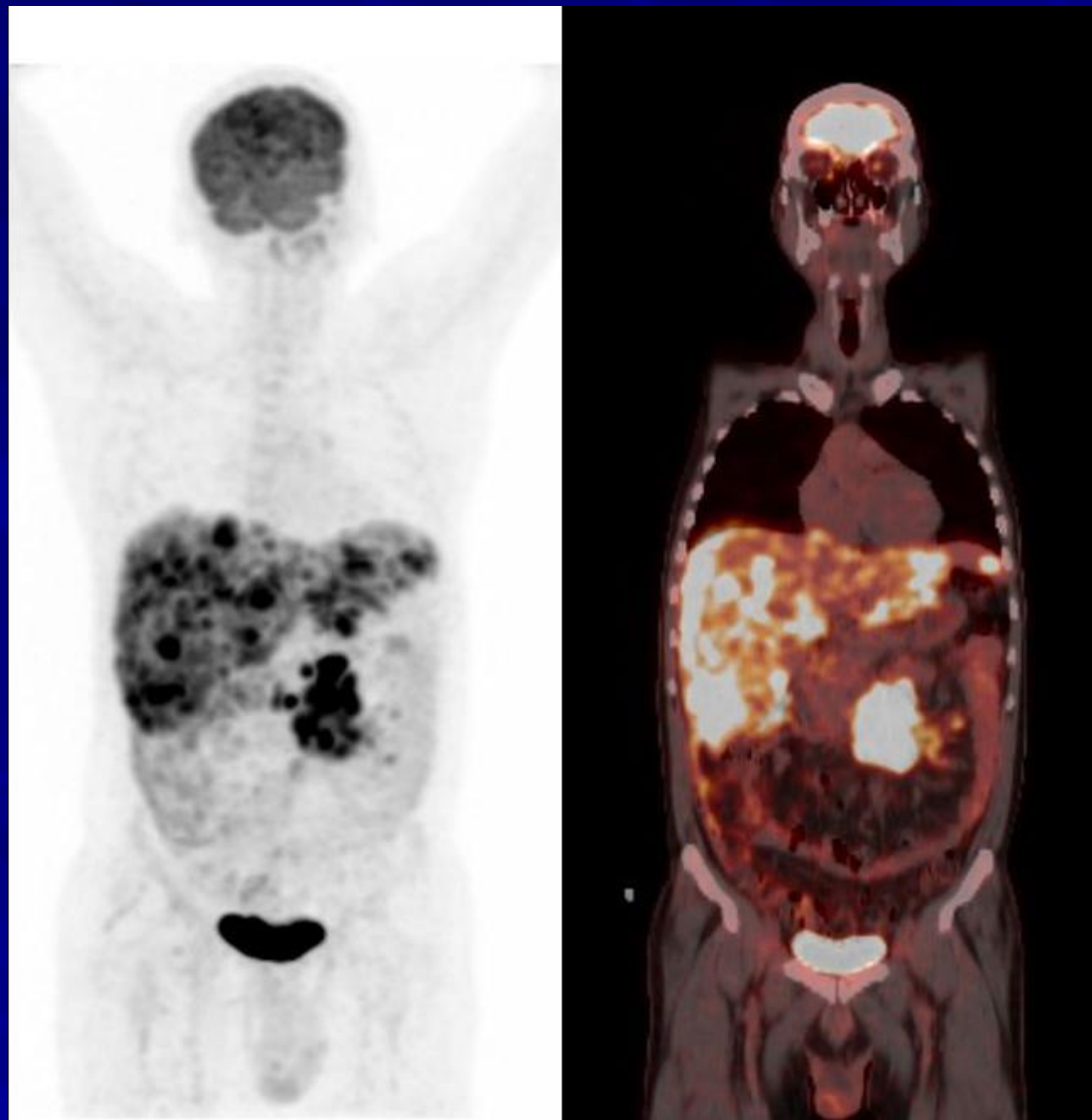
Sunil Walke

54/M, diagnosed case of NET of pancreas (on biopsy Mib 1 LI was reported 2%, serum Chromogranin A- 4365 ng/ml). The patient had extensive hepatic metastases as noted in the SRI and FDG-PET/CT. Both primary and hepatic metastases were heterogeneously FDG avid, with high SUVs. The patient responded poorly to PRRT and demonstrated progressive disease. A dual tracer imaging was a correct predictor of tumor aggressiveness, though the MiB1 LI was reportedly low.

Somatostatin Receptor Imaging

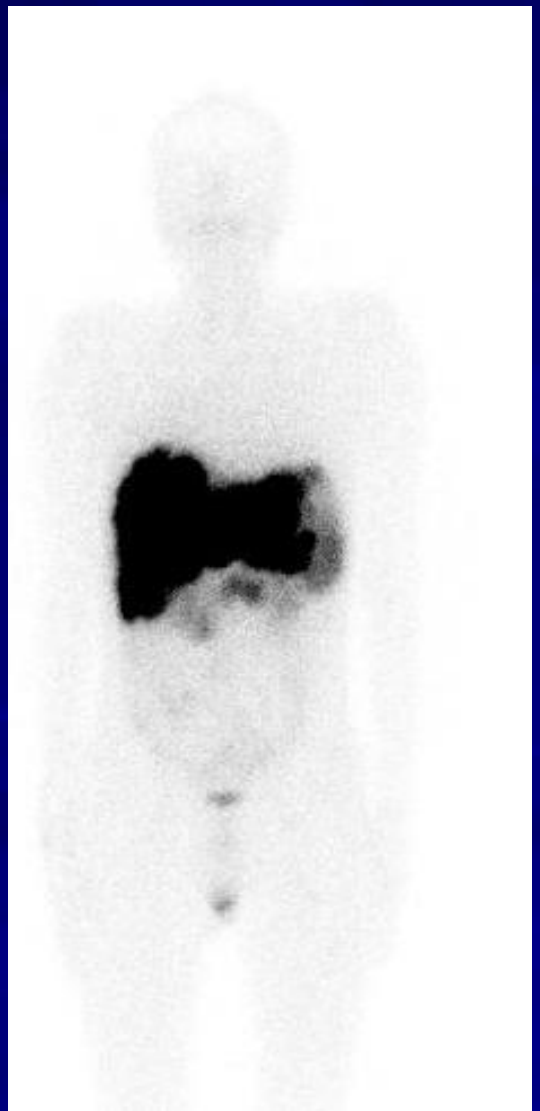


18F-FDG PET/CT

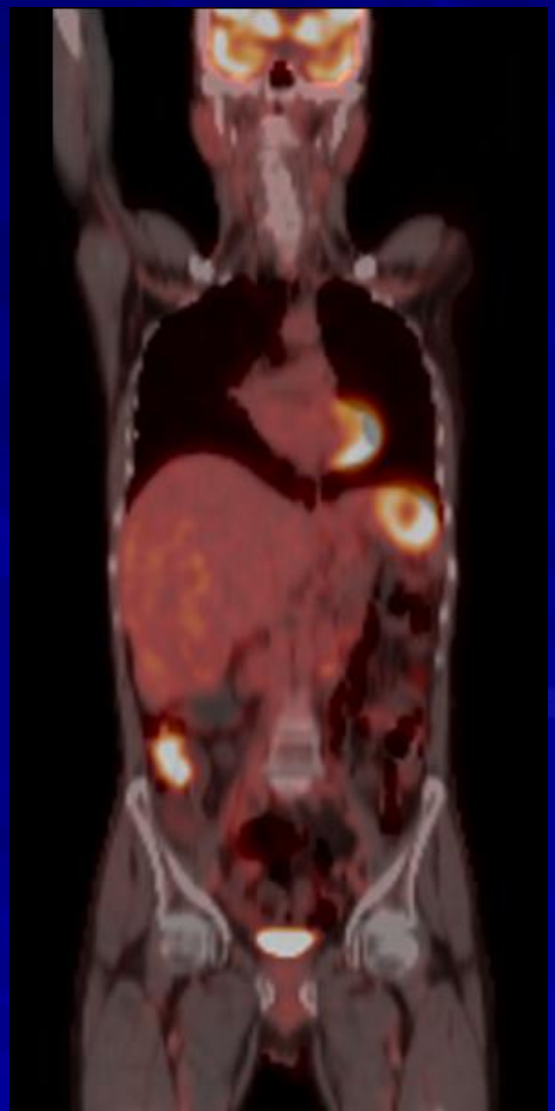


53/M, Primary Head and uncinate process with bilobar hepatic mets; Mib1 : 10%. Near-total Discordance; Referred following disease progression with sandostatin and ChemoRx. 3# PRRT---191/211/183 mCi; CgA---8105---> 4180---->5330; Symptomatic response- Resolution of diarrhoea and weight gain. At 36 months, the patient had received 892 mci over 5 cycles of PRRT and has been progression free and asymptomatic.

Somatostatin Receptor Imaging



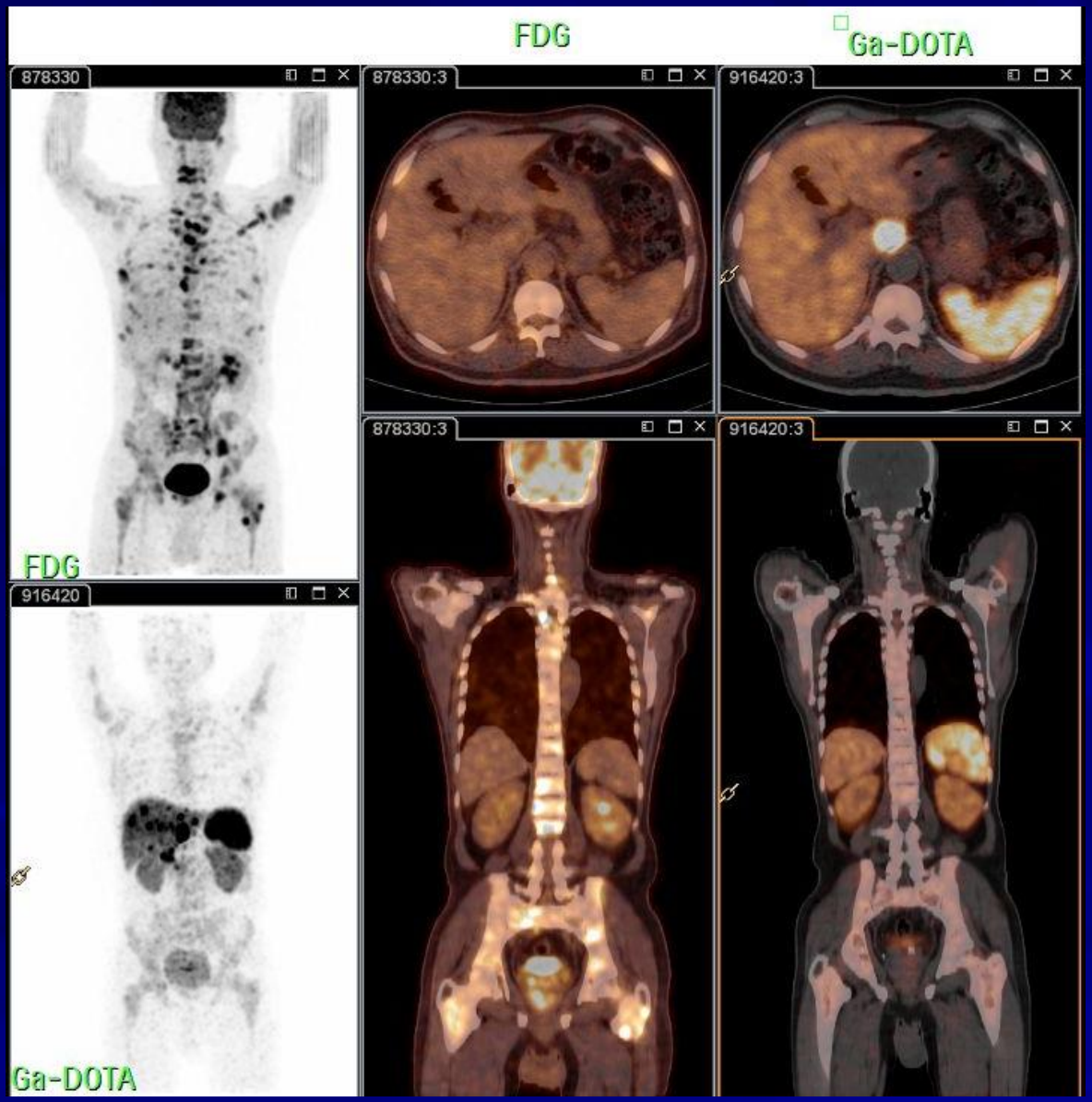
18F-FDG PET CT



Theme 9. Combination with Somatostatin analogues in Functioning NET Patient Preparation & withdrawal

- Withdrawal periods of 4 weeks for long-acting release formulations and substituting in the interim period with short acting formulation
- At least 24 h for short-acting formulations
- Experience only with Octreotide: Lanreotide not available

10. Inter- organ Heterogeneity: Combined therapeutic Strategy?



65/M, Duodenal NET with liver and skeletal metastases; duodenal polyp Bx: Well differentiated NET with Mib1 <2%

Thank You