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Triple tracer positivity in metastatic lymph nodes from well-differentiated neuroendocrine tumor in MEN 1 syndrome

Authors:

Anwin Joseph Kavanal[1], MBBS anwinjosephk@gmail.com

Sanjay K Bhadada[2], MD, DM bhadadask@rediffmail.com

Ashwani Sood[1], DNB sood99@yahoo.com

Gurjeet Kaur[2], PhD Scholar gurjeetkaur268@gmail.com

Amber Parwaiz[3], MD amberparwaiz@gmail.com

Ajay Gulati[4], MD drajaygulati@gmail.com

Divya Dahiya[5], MS dahiyadivya@yahoo.com

Bhagwant Rai Mittal[1], MD, DNB brmittal@yahoo.com

Affiliation:

Department of Nuclear Medicine[1], Endocrinology[2], Cytopathology[3,] Radiology[4] and General Surgery[5]

Postgraduate Institute of Medical Education and Research, Chandigarh-160012, India

Corresponding Author:

Ashwani Sood, DNB

Additional Professor

Department of Nuclear Medicine,

PGIMER, Chandigarh-160012 (India)

Tel: +91 172 2756728

Fax: +91 172 2742858

E-mail: sood99@yahoo.com

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First Author:

Anwin Joseph Kavanal, Junior Resident

Department of Nuclear Medicine

Postgraduate Institute of Medical Education and Research

Chandigarh, India- 160012

Tel: +91-9947384052

Fax: +91-172 2742858

Email: anwinjosephk@gmail.com

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Abstract

Patients with multiple endocrine neoplasia type-1 (MEN-1) usually have combination of endocrine disorders due to lesions in pancreas, parathyroid and pituitary glands. Functional imaging using different tracers in addition to conventional imaging are employed in localizing the primary sites, disease extent and lesions characterization. Here is a diagnosed case of MEN-1 syndrome with interesting incidental imaging findings showing ^{99m}Tc-sestamibi and ^{18}F-choline uptakes in addition to ^{68}Ga-DOTANOC uptake in metastatic mediastinal and cervical lymph nodes arising from gastro-entro-pancreatic neuroendocrine tumor (GEP NET). This shows the possibility of imaging the NETs with three different tracers namely - ^{68}Ga-DOTANOC, ^{99m}Tc-sestamibi and ^{18}F-fluorocholine.

Keywords: Neuroendocrine tumor; MEN-1; F-18 fluorocholine; Tc-99m sestamibi; Ga-68 DOTANOC

Functional imaging using different tracers have been employed in localizing the primary/metastatic sites, characterization of lesions and prognostication in patients with multiple endocrine neoplasia type-1 (MEN-1). These patients usually have the combination of lesions in pancreas, parathyroid and pituitary glands (1). ^{99m}Tc-sestamibi and recently emerging ^{18}F-fluorocholine are known functional imaging modality for localizing the eutpoic and ectopic parathyroid lesions though the mechanism of ^{99m}Tc-sestamibi uptake is essentially different from ^{18}F-fluorocholine uptake in parathyroid lesions (2,3). Whole-body ^{68}Ga-somatostatin receptor (SSTR) imaging has been efficiently used in detecting the neuroendocrine tumors with increased sstr expression (4). However, functional imaging done with these tracers showing tracer avid metastatic disease has never been reported before. We present a diagnosed case of MEN-1 syndrome with interesting incidental imaging findings showing ^{99m}Tc-sestamibi and ^{18}F-fluorocholine uptakes in addition to ^{68}Ga-DOTANOC uptake in metastatic cervical and mediastinal lymph nodes arising from gastro-entro-pancreatic neuroendocrine tumor (GEP NET). The possibility of imaging the NETs with three different tracers namely ^{68}Ga-DOTANOC, ^{99m}Tc-sestamibi and ^{18}F-fluorocholine, having different mechanism of uptake may be evaluated for better understanding of tumor biology. **Case Report:**

A forty-four years-old man presented with complaints of increased frequency of stools with unexplained loss of weight and appetite for last 3 months. Biochemical investigations revealed elevated serum PTH (110.8 pg/ml; normal value 15-65), calcium (10.9 mg/dl; normal value 8.6-10.2), gastrin (>10000 pg/ml; normal value 13-115), chromogranin (>1400 ng/ml; normal value 0-98.1) and low serum phosphate (1.4 mg/dl; normal value 2.7-4.5 mg/dl) levels. USG neck showed hypoechoic lesion in the superior aspect of right lobe of thyroid. Endoscopic guided biopsy from polypoidal lesions in stomach and duodenum revealed well-differentiated NET. MRI brain revealed a lesion in the sella, suggestive of macro adenoma. The diagnosis of MEN-1 syndrome was made with MEN 1 gene analysis.

^{99m}Tc-sestamibi planar and SPECT/CT study done in view of hyperparathyroidism were suggestive of bilateral superior parathyroid adenomas, and tracer avid enlarged mediastinal and cervical lymph nodes (Figure 1). Regional neck ^{18}F-flurocholine PET/CT done for further clarification were also suggestive of bilateral superior parathyroid adenomas along with intense tracer avid enlarged mediastinal and cervical lymph nodes (Figure 1). Patient underwent bilateral parathyroidectomy and histopathology revealed parathyroid adenomas with normalization of serum PTH and calcium levels in post-operative period.

Whole-body ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT were done for extent of disease, differentiation and prognostication to plan for peptide receptor radionuclide therapy in view of widespread metastatic disease. ^{68}Ga-DOTANOC PET/CT images showed sstr expressing tracer-avid primary in stomach and duodenum with extensive metastatic disease, whereas the same lesions showed low-grade FDG avidity in ^{18}F-FDG PET/CT (Figure 2).

Ultrasound-guided FNAC from enlarged cervical lymph node revealed metastatic NET with Ki-67 proliferation index less than < 2% (Figure 3). Patient underwent two cycles of ^{177}Lu-DOTATATE therapy (~7.4 GBq infusion along with amino acid protection at 8 weeks interval). The patients showed significant clinical improvement. The patient is being followed-up for further treatment without any adverse renal and hematological toxicity. The whole-body post-therapy scan showed similar tracer avid lesions as in ^{68}Ga-DOTANOC scan (Figure 4).

Discussion:

MEN1 is an autosomal dominant disease secondary to mutations of tumor suppressor gene *MEN1* with occurrence of pituitary, parathyroid and pancreatic tumors with wide-spectrum of clinical presentations. Evaluation of the organ(s) involved, their localization and extent of disease is required prior to planning the specific therapy (1).

The different functional imaging reflects diverse characteristics of tumor. Cellular ^{99m}Tc-sestamibi uptake is dependent upon mitochondrial over-expression, whereas ^{18}F-fluorocholine

uptake indicates increased choline kinase activity and phosphatidyl choline synthesis. Both the tracers have been used for pre-surgical localization of parathyroid adenoma (2,3). SSTR type-2 over-expression is known to occur in gastropancreatic NETs making them suitable for theranostics with sstr-labeled radionuclides (4). ^{18}F-FDG imaging indicates cellular metabolism with higher metabolic rate indicating the poorer prognosis (5).

Few case reports have shown increased ^{99m}Tc-sestamibi uptake in primary malignant and metastatic NETs like carcinoid tumors, paragangliomas and primary neuroendocrine neoplasms (6-8). In a case series of three bronchial carcinoids having low Ki-67 (non-aggressive neoplasm), choline showed the tumor avidity which was secondary to cholinergic autocrine loop over-expression and high turnover of intracellular vesicles (9). The authors present this MEN1 case showing avidity with three different tracers (^{68}Ga-DOTANOC, ^{99m}Tc-sestamibi and ^{18}F-fluorocholine) because of different uptake mechanisms highlighting the diverse characteristics of tumor.

Conclusion:

This case report shows that radiopharmaceuticals having different mechanism of uptake in GEP NET with widespread lymph nodal metastases may require the better explanation of underlying tumor biology.

Disclosure:

No potential conflict of interest relevant to this article was reported.

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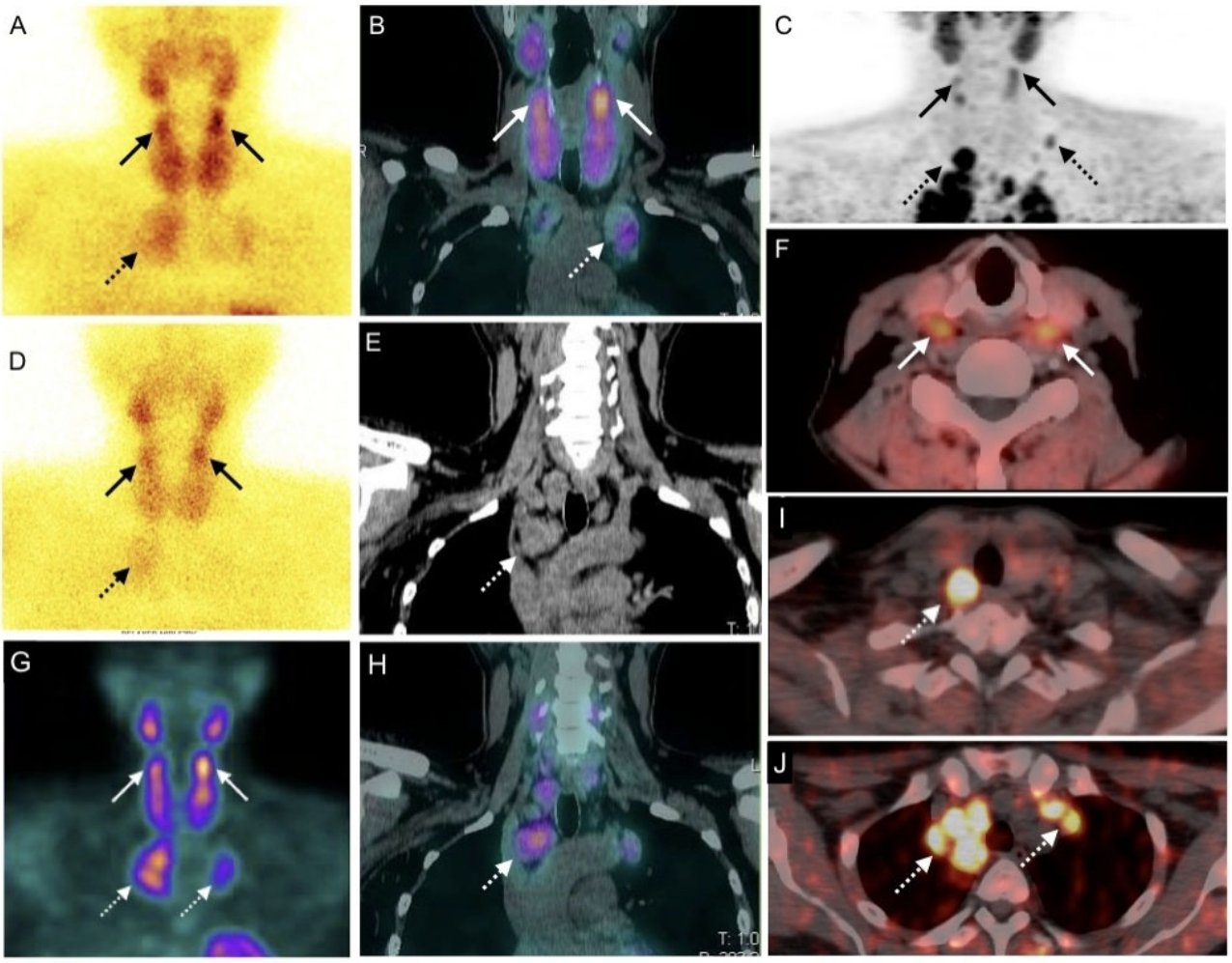

Figure 1: ^{99m}Tc-sestamibi planar study done for hyperparathyroidism showing increased tracer avid foci with tracer retention near the upper poles of both lobes of thyroid glands in early static and delayed images (A, D; solid arrows). Early SPECT MIP and coronal fused images localizing the increased tracer in two hypodense lesions in postero-superior location of the both lobes of thyroid gland (B, G; solid arrows). Tracer avid enlarged mediastinal and cervical lymph nodes were also seen (A, B, D, E, G, H; broken arrows). Regional neck ^{18}F-fluorocholine PET/CT showing tracer avid lesions located near the upper poles of thyroid lobes suggestive of bilateral superior parathyroid adenomas on PET MIP and transaxial fused images (C, F; solid arrows) along with intense tracer avid enlarged mediastinal and cervical lymph nodes (I, J; broken arrows).

MIP: Maximum Intensity Projection

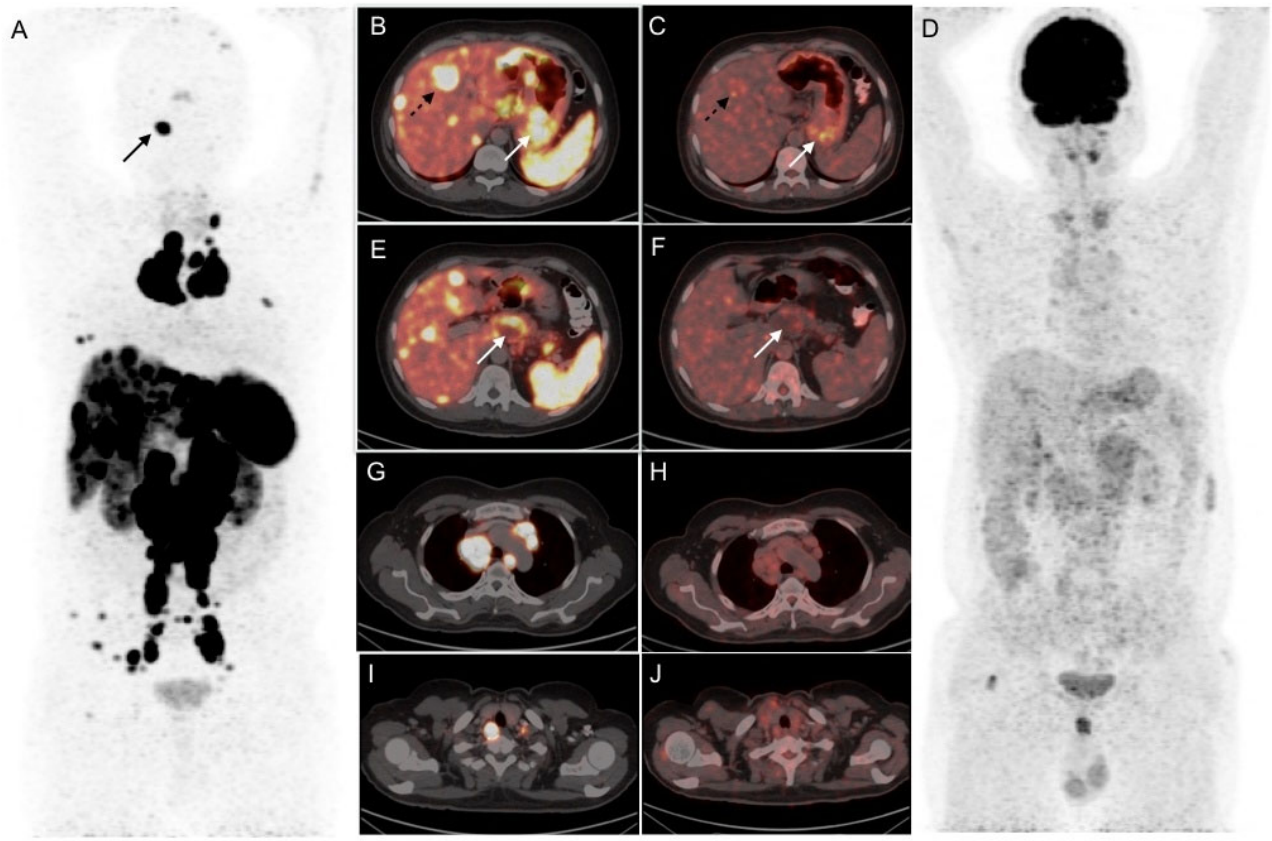

Figure 2: ^{68}Ga-DOTANOC PET MIP image (A) showing sstr expressing extensive metastatic disease, transaxial fused images showing tracer-avid lesions in the stomach, liver (B; solid and broken arrows), duodenum, cystic lesion in pancreas (E; solid arrow), intramuscular and skeletal deposits (A; solid arrow), multiple enlarged lymph nodes in the abdomen, pelvis, mediastinum (G) and cervical regions (I). ^{18}F-FDG PET MIP image (D) and corresponding transaxial fused images (C, F, H, J; solid arrows) with low-grade FDG avidity in the above mentioned lesions.

MIP: Maximum Intensity Projection, sstr: somatostatin receptor

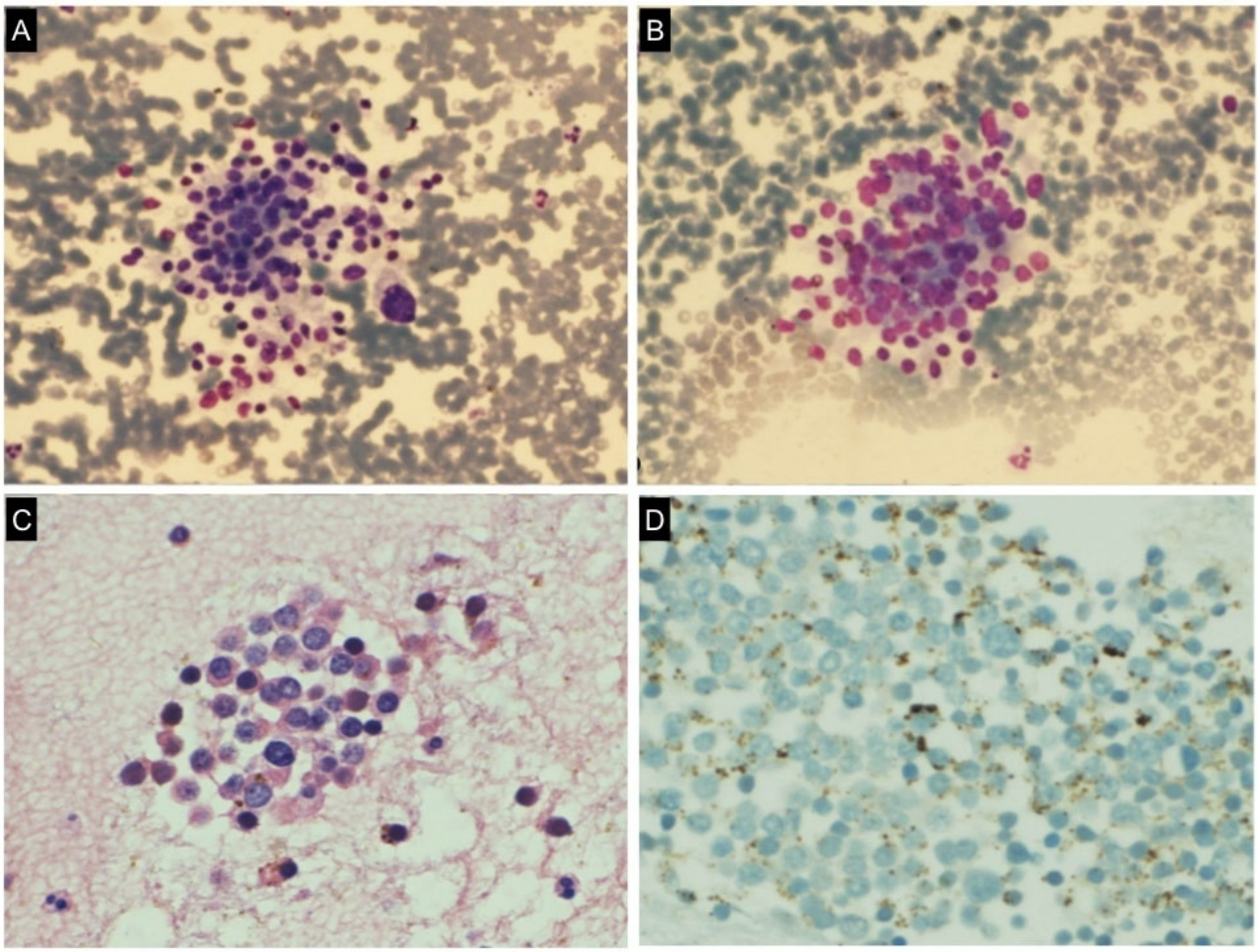

Figure 3: USG-guided FNAC from enlarged cervical lymph node revealing clusters of tumour cells with mildly pleomorphic nuclei, showing sudden anisonucleosis (A, B; MGG stain, 20X). Additional cluster of tumour cells with stippled chromatin and moderate amount of cytoplasm. (C; H&E stain, 20X) suggestive of metastatic NET. Immunocytochemistry for Ki-67 proliferation index found to be < 2% (D).

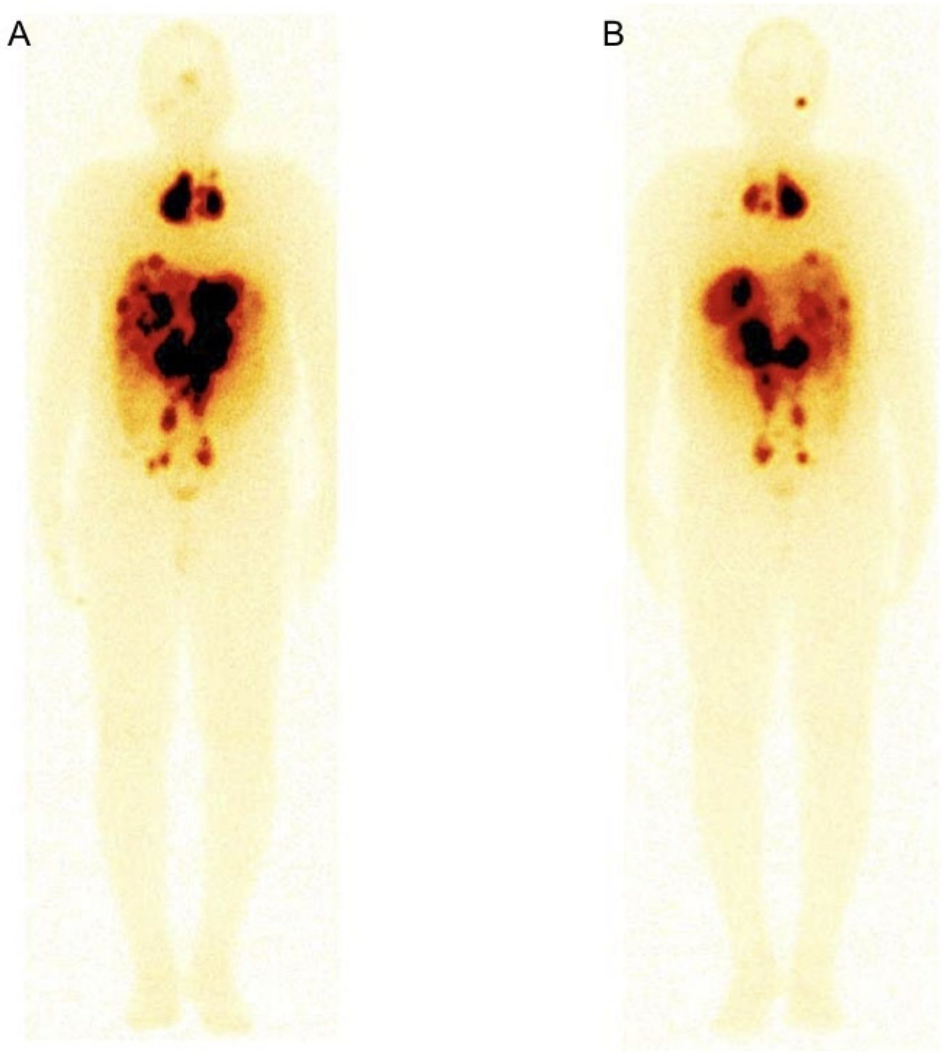

Figure 4: Whole-body anterior and posterior (A,B) post-therapy images (^{177}Lu-DOTATATE therapy; first cycle) showing corresponding tracer avid lesions.