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A pictoral review on somatostatin receptor scintigraphy in neuroendocrine tumors: The role of multimodality imaging with SRS and GLUT receptor imaging with FDG PET-CT

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Abstract

Somatostatin receptor scintigraphy is considered as a comprehensive imaging modality for many neuroendocrine tumors. Multiple radiotracers using combinations of gamma or positron emitting radionuclides and tracers are now available. Newer radiopharmaceuticals using ^{99m}Tc labeled with TOC, TATE, NOC are good alternatives to the 68 - Gallium radiotracers where the PET facility is not available. The pictoral depicts the role of SRS using 99m TC – HYNIC –TOC radiotracers in staging and treatment planning of NETs. Characterization of the tumor biology using combined SRS and FDG PET/CT is also demonstrated with a proposed categorization method. The emerging role of SRS in tailored targeted radionuclide therapy is outlined in brief.

Key words: FDG PET/CT; neuroendocrine tumors; somatostatin receptor imaging; ^{99m}Tc HYNIC TOC

Introduction

Neuroendocrine tumors (NETs) originate from neural crest cells which belong to the amine precursor uptake and decarboxylation (APUD) lineage and have both neural and endocrine cell features. These tumors are generally seen in the gastroenteropancreatic tract and lungs and rarely in ovary.[1]

NETs arise from the tissues which are part of the APUD system. These tumors can be imaged using metaiodobenzyl guanidine (MIBG) tagged to 131-iodine; which enters by a specific energy-dependent uptake mechanism competing with norepinephrine and majority of it is trapped in the intracellular granule fraction.[2] This tracer has shown better sensitivity in sympathoadrenomedullary tumors[3] as compared to the other NET though the uptake is heterogeneous.

Over-expression of somatostatin receptors (SSTR) is noted in these tumors and this patho-physiology is exploited in radioimmunoscintigraphy (RIS).SSTR imaging in NET is indicated for detection of the primary, staging, monitoring response to therapeutic somatostatin and treatment planning for SSTR directed Radionuclide therapy.[4] All the subtypes of SSTR expressed by NET have affinity for the native peptide but vary in their affinity for the somatostatin analogues;[5] hence, the sensitivity of the study depends on the density of the SSTR in the tumor and the type of analogue used in the study.

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Indium 111 (In-111) tagged somatostatin analogues were the commonly used tracers and majority of the literature related to somatostatin receptor scintigraphy (SRS) had been done using this tracer. Studies have revealed the sensitivity of In-111 labeledSRSto be in the range of 80-90%. It has shown superiority to other diagnostic imaging methods (such ascomputed tomography [CT] and magnetic resonance) in identifying and assessing the staging of NET, except for insulinoma (density of SSTR is very low).[6-8]

The disadvantages of long half-life, physiological uptake in abdominal organs, and a higher energy of In-111 warranted research in use of a Technitium-99m (99mTc) labeled agent for somatostatin receptor imaging, which is better suited for single photon emission computed tomography (SPECT) imaging.[9,10] ^{99m}Tc labeled Tyrosine-3 octreotide (TOC) has been identified as a suitable tracer which uses hydrazinonicotinic acid (HYNIC) as a complexing ligand. The pharmacokinetic properties of ^{99m}Tc-HYNIC TOC were found to be better than those of ^{111}In-Octreotide. Higher target-to-non-target ratios and higher absolute tumor uptake values were observed for ^{99m}Tc-HYNIC TOC and the optimal acquisition time for imaging was identified as 4 h after injection.[10]

SRS has low sensitivity for lesions that are present in organs having physiological tracer concentration like the liver and lesions smaller in size due to the limitation of the mechanics and tracers used in SPECT.[11,12]

Imaging with PET (positron emission tomography) has higher resolution of the lesions, an inherent property of the modality. Initial data showed the tracer Gallium 68 (Ga 68) DOTA TOC to have a good pharmacokinetic and imaging characteristic as compared to conventional nuclear medicine procedures.[13] A large prospective study also demonstrates a higher accuracy of Ga 68 DOTA TOC in comparison to the anatomical imaging modality, CT, and conventional SRS.[12]

However, the PET/CT modality is not often available and SPECT imaging is still the feasible option for imaging of NET.

Our pictorial will try to demonstrate the utility of SSTR imaging using ^{99m}Tc HYNIC TOC in various clinical settings and project its role in prognostication when done in conjunction with 18F Flouro- Deoxy Glucose (FDG)_PET/CT.

Patients receiving cold somatostatin therapy were asked to refrain from the therapy for 4 weeks, whereas those patients who had undergone a surgery had their imaging done after the 3rd post-operative week.

Patients were injected with 20 mCi (740 MBq) of the tracer; a whole body planar image was obtained at 30 min post-injection (p.i) on a dual head Gamma camera (Infinia Hawkeye, GE, Milwaukee). A repeat whole body planar image and SPECT of the abdomen and regions with abnormal tracer uptake were performed 2 hafter injection in majority of the cases; a pilot study of 15 cases revealed the 2-h images to be as sensitive as a 4-h image (as suggested in literature). In cases with a doubtful lesion in the2-hp.i image, a delayed image at 4 h p.i. was obtained. No additional benefit was obtained in the 4-h image. FDG PET/CT was done 60-90 min after intravenous injection of 18 FDG, with the patient in a fasting state within a week of the SRS. Acquisition was done as per the SNM guidelines, from base of skull to mid-thigh on a dedicated PET/CT scanner (Discovery ST, GE, Milwaukee).

The normal distribution of the ^{99m}Tc HYNIC TOC tracer is seen in thegall bladder, kidneys, liver, spleen [Figure 1], and sometimes in the pituitary and thyroid.

1. Staging of histologically proven neuroendocrine malignancies.
   The management of NET depends on the stage of the disease, i.e., whether it is localized or metastatic. Surgery is offered as an option to patients who have a non non-metastatic primary mass lesion. Patients with locally advanced disease generally undergo a debulking surgery with the residual disease being treated with targeted therapies. Cytoreduction followed by targeted therapies or specific local therapies like radioablation is the treatment option for a local disease with a solitary metastatic site.A disseminated disease is tried to control with targeted therapies.

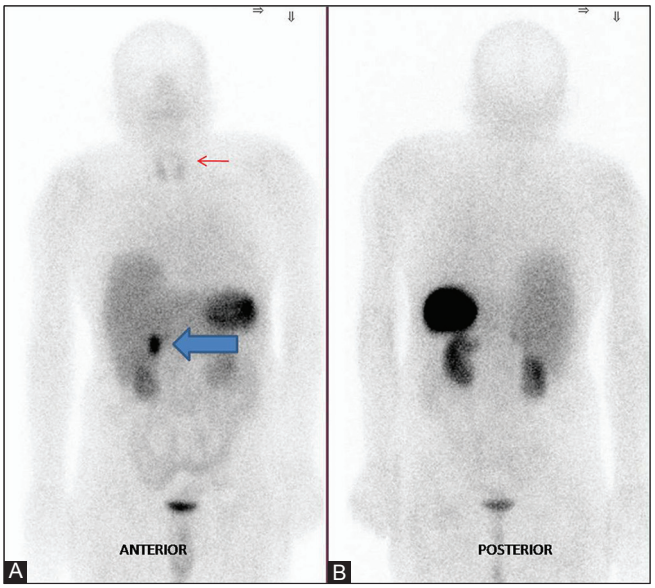

Figure 1 (A, B): This image ((A) anterior and (B) posterior) depicts the normal distribution of the radiotracer, 99m Tc HYNIC – TOC. Note the uptake in the thyroid (small arrow), the liver and spleen. The gall bladder shows intense focal tracer concentration (bold arrow). The kidney and urinary bladder are seen due to the part excretion through this system

The conventional staging for NET is done with a CECT of the suspected local site with CT of abdominopelvic and thorax regions.[10] RIS is now incorporated in the staging of NET as it helps trace the extent of the primary disease and also the spread of the malignancy in a single setting as seen in Figure 2.

NETsshow unusual site of metastases less frequently though not uncommon. RIS helps locate the odd sites of disease as seen in Figure 3.

2. Initial detection and localization of suspected NET and potential metastases in presence of a clinical or biochemical suspicion or to locate primary in a case identified to have a solitary metastatic lesion on conventional imaging.

   Patients with NETsmore often present with symptoms due to high endocrine secretion rather than the pressure effect caused by the primary mass. Identifying the primary tumor site is necessary for treatment management. Conventional imaging modalities are able to map the metastatic sites but tracing the primary site is difficult at times. The sensitivity of SRS in this setting is high. Figures 4 and 5 depict the utility of SRS in this indication.
3. Treatment response assessment of NET:

   Patients with metastatic disease are treated with medical line of treatment and the treatment response assessment is generally done with biochemical markers and clinically. Reduction of the symptoms with a decline in tumor markers is noted with responsive tumors. Imaging studies are used to document treatment response; however, it is difficult to differentiate between functional and non-functioning residual tissue. The ability to identify residual functioning tissue by a non-invasive procedure is useful to plan continuation of therapy. Pre- and post-therapy SRSis a helpful tool in this respect as shown in Figures 6 and 7.

Tumor biology in NET

Change in biology of the tumors is a known phenomenon and is attributed to either a change in the tumor receptor density or expression of a new receptor. Delineating these receptor changes assists in prognosticating the disease and alter management.[14] Patients on follow-up

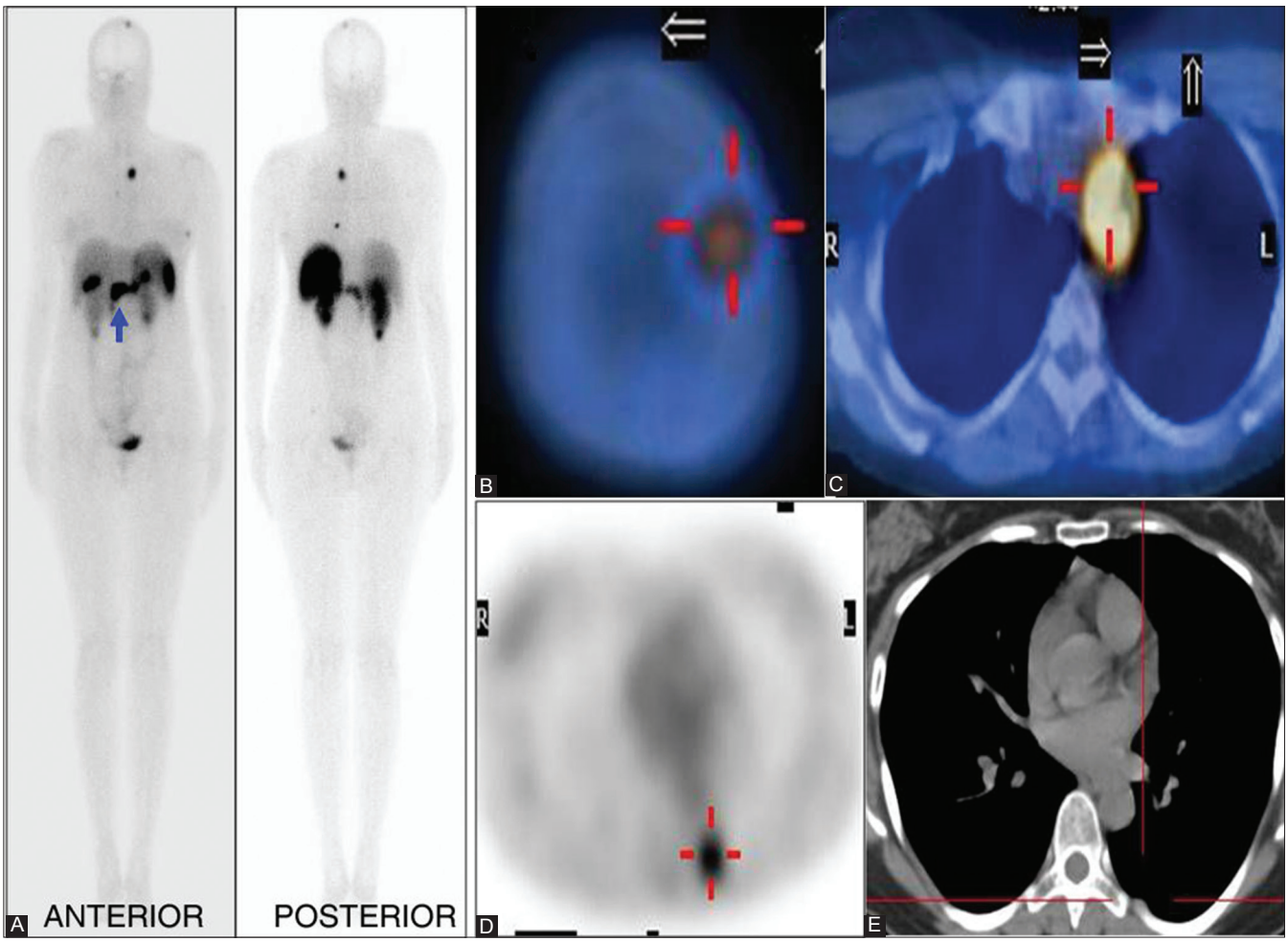

Figure 2 (A-E): Whole body planar images (A) of a 99m Tc HYNIC TOC study of a recently detected case of pancreatic NET reveals the uptake in the primary (arrow) and the metastatic lesions which are localized on the transaxial SPECT/CT images to correlate with the lesion in the skull (B), a enlarged prevascular node (C) and a tiny pleural based pulmonary nodule (D) which is identified on the correlative CT image (triangulated in E). Another pulmonary nodule is seen as a focus of uptake in the left hemithorax on the whole body planar image (A)

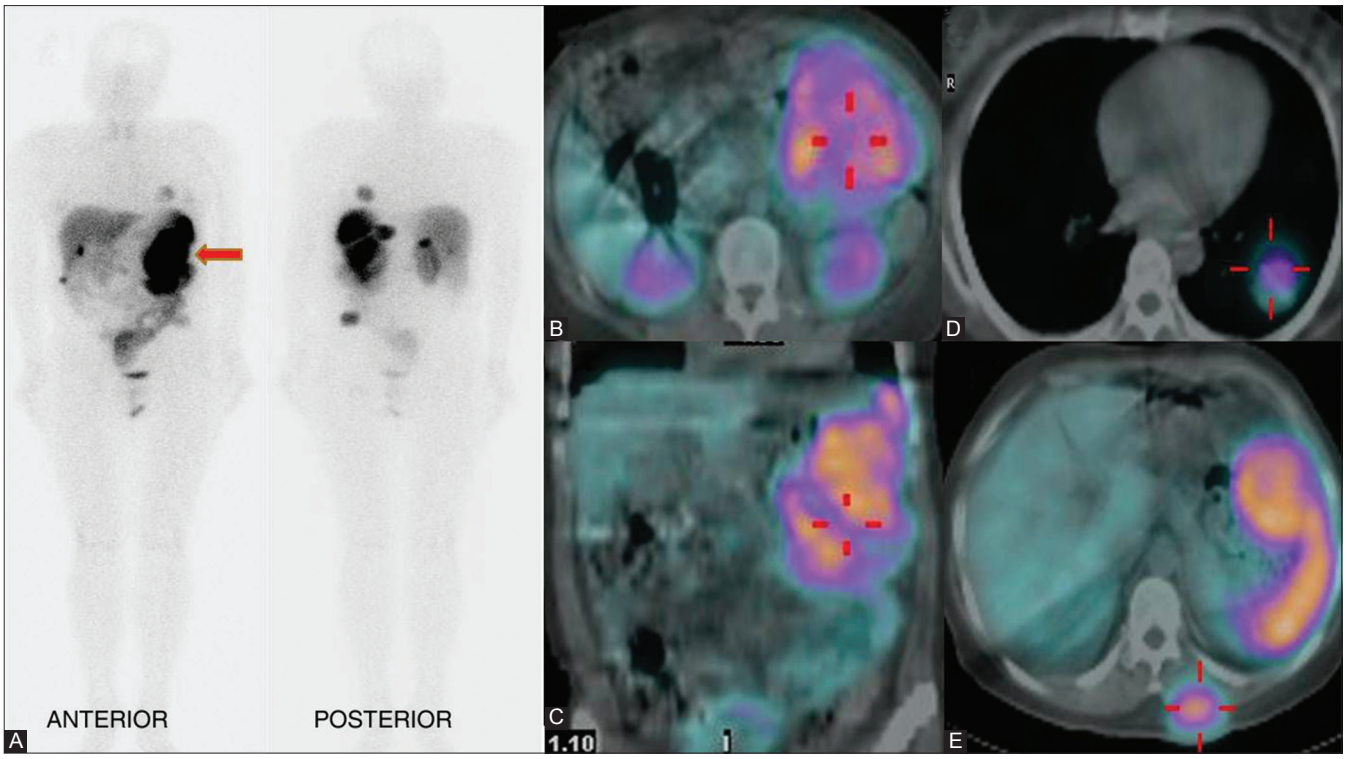

Figure 3 (A-E): A diagnosed case of small cell carcinoma of the lung referred for staging using SSTR imaging revealed a large uptake in the upper abdomen on the whole body planar images (A), better visualized in the anterior aspect (arrow). A SPECT/CT of the abdomen shows a large peritoneal mass (B and C) with focal tracer uptake in the primary in the left lung mass (D) and an unusual subcutaneous metastases in the posterior chest wall in paravertebral region (E). no FDG PET/CT study was done for this patient

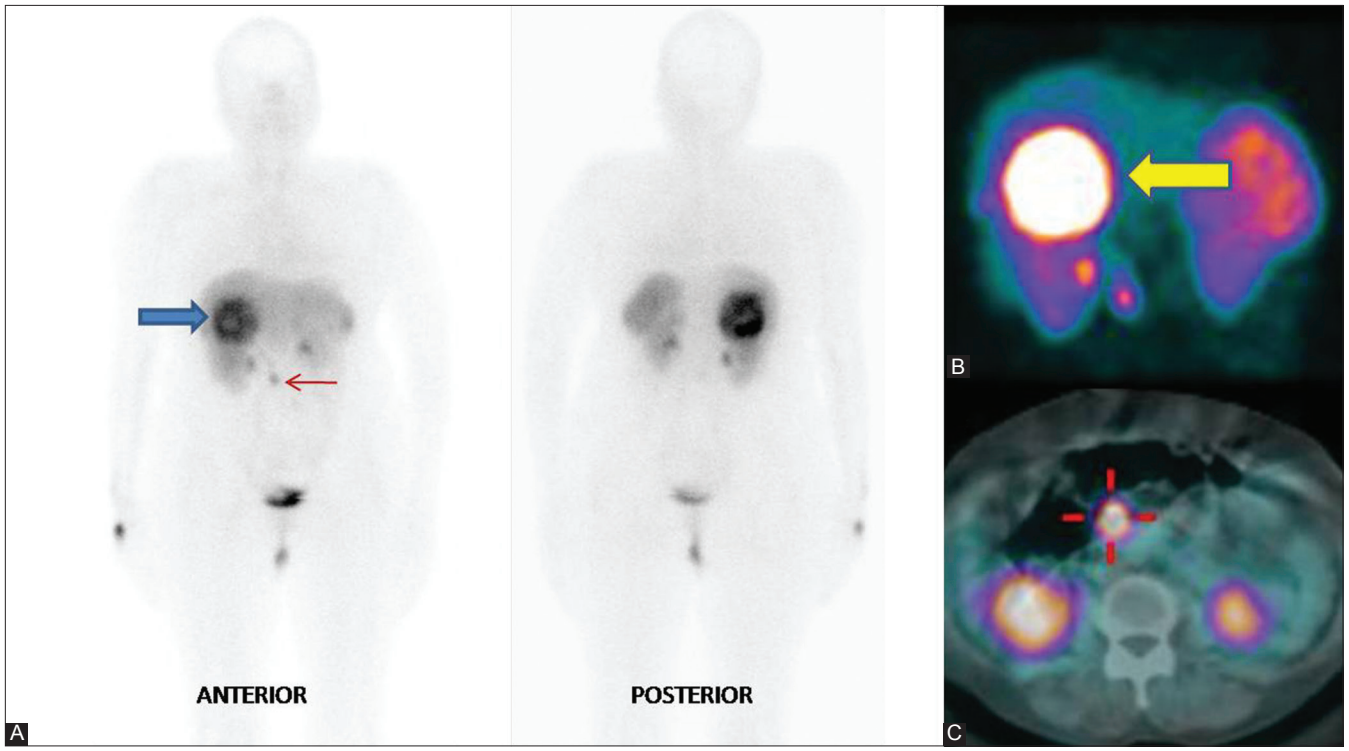

Figure 4 (A-C): Patient with diarrhea evaluated for NET, conventional CT imaging revealed hepatic metastases and was referred for somatostatin receptor scintigraphy. Planar WB images show avid tracer concentration in the known sites of hepatic metastasis (bold arrow in A and B). A small focus of uptake to the right of the midline in the abdomen (small arrow in A) corresponded to site of the primary in the duodenum well depicted on the SPECT/CT images (triangulated in C)

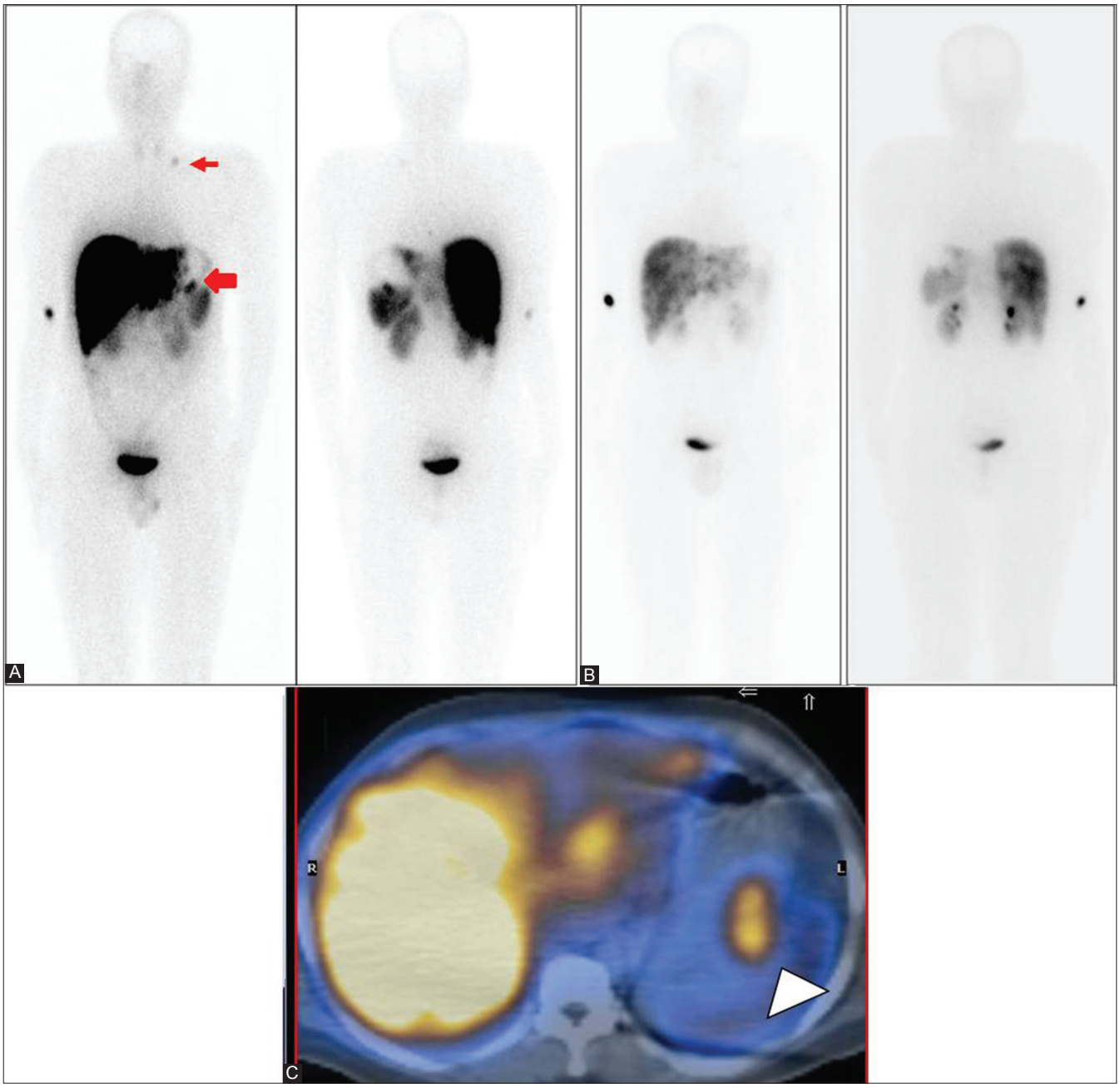

Figure 5 (A-C): Patient who presented with metastatic left supraclavicular node from an unknown NET with multiple hepatic metastases on CECT of the abdomen was investigated with SRS. The WB image in lesser intensity showed multiple hepatic lesions (B), while the darker intensity images (A) showed focal uptake in the left supraclavicular node (thin arrow A) and an uptake in the left aspect of the upper abdomen (thick arrow A) which correlates on the transaxial SPECT CT image to the stomach wall (arrow head in C) suggesting gastrinoma as a possible primary, later confirmed histologically

with clinical or biochemical suspicion of a recurrence evaluated with RIS with poor to absent SSTR expression raise the probability of altering receptor status. NET is a well-differentiated pathology and does not express Glucose Transporter (GLUT) receptors and hence a FDG PET/CT study is not utilized in the work up. Dedifferentiating tumors show an increase in the GLUT receptor expression with a decline in the somatostatin receptor density; hence, a FDG PET/CT study would be efficacious in locating sites of tumor spread.[15,16]

Combination receptor imaging will help in staging the disease as per the WHO classification which is based on the histology–type 1a: Well-differentiated benign, type 1b: Welldifferentiated with low-grade malignancy, and type 2 poorly differentiated. The prognosis of the tumor is dependent on the differentiation of the tumor, poorly differentiated having a bad prognosis.[17]

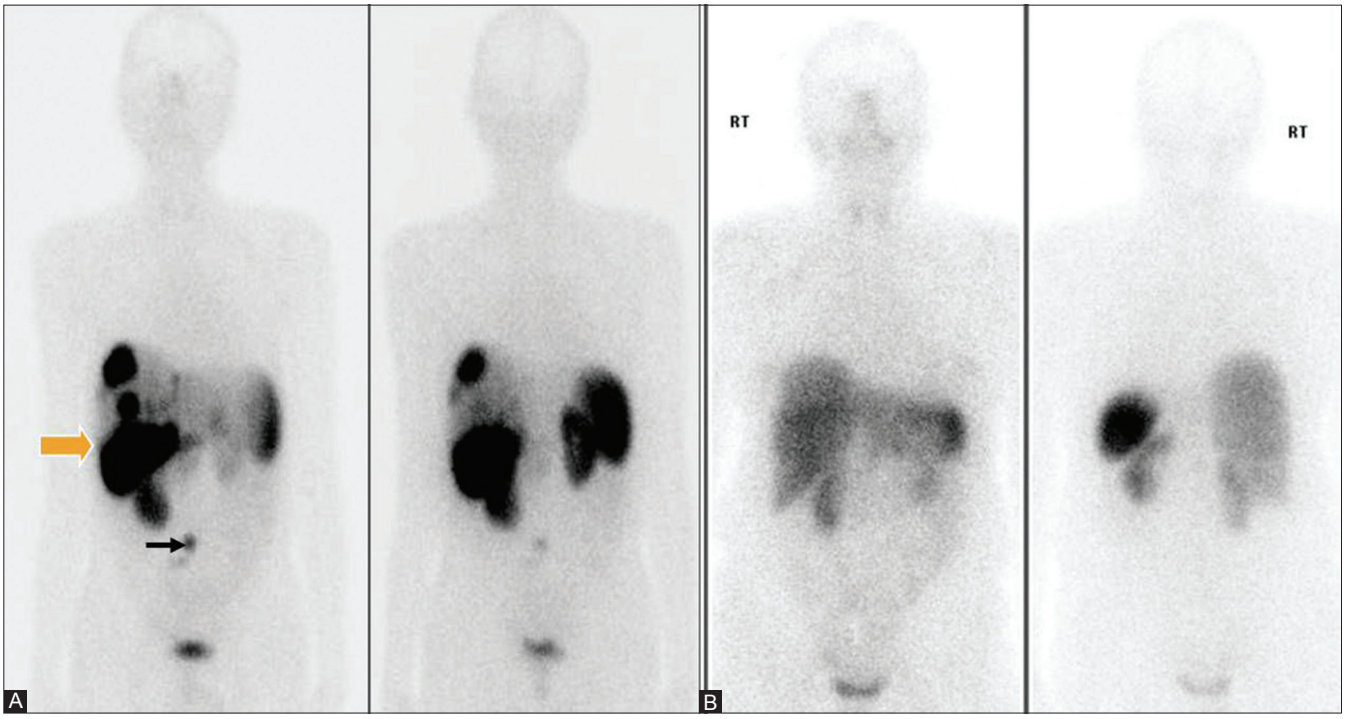

Figure 6 (A, B): Responder: A metastatic case of small bowel NET; the baseline planar whole body image (A) shows uptake in the primary (thin arrow) and the multiple hepatic metastases (thick arrow). Whole body planar SSTR imaging (B) after 3 cycles of somatostatin therapy shows complete regression of the tracer uptake at the primary and the metastatic liver lesions depicting the suppression of somatostatin receptors due to the therapy. The patient was a responder and completed further therapy. He was documented to be DF on his last follow up, 1.5 year post last radioimmunoscintigraphy

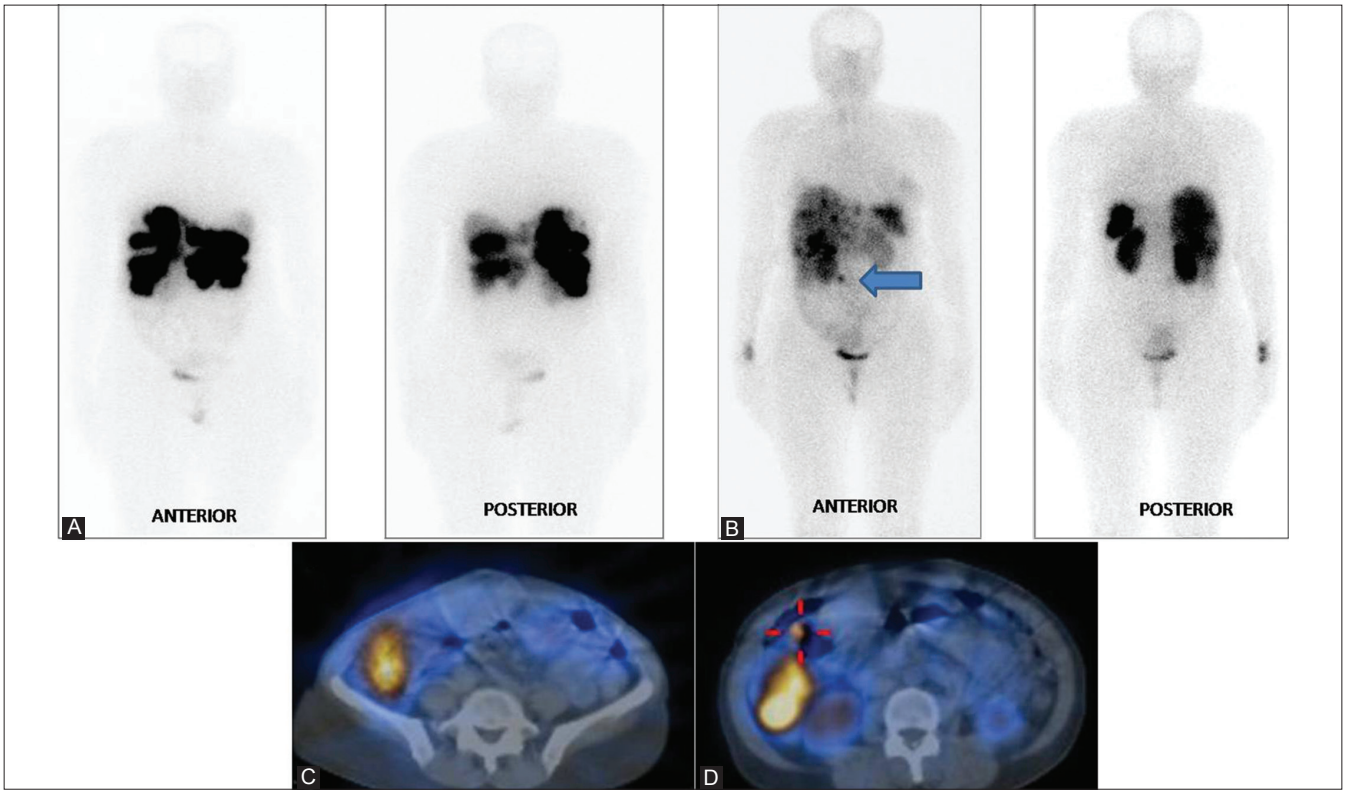

Figure 7 (A-D): Non responders: A case of NET of the duodenum with hepatic metastases, the pre treatment WB planar images show multiple abnormal uptakes in the liver with no obvious focal uptake at the primary site (A), the hepatic lesions showed partial regression in the post therapy scan (B). A small focus of tracer in the right aspect of the abdomen corresponding to the primary (arrow B and D) of the post therapy scan which was not appreciated in the pre therapy scan (C) probably due to masking. The combined studies suggest suboptimal suppression of the somatostatin receptor pathway

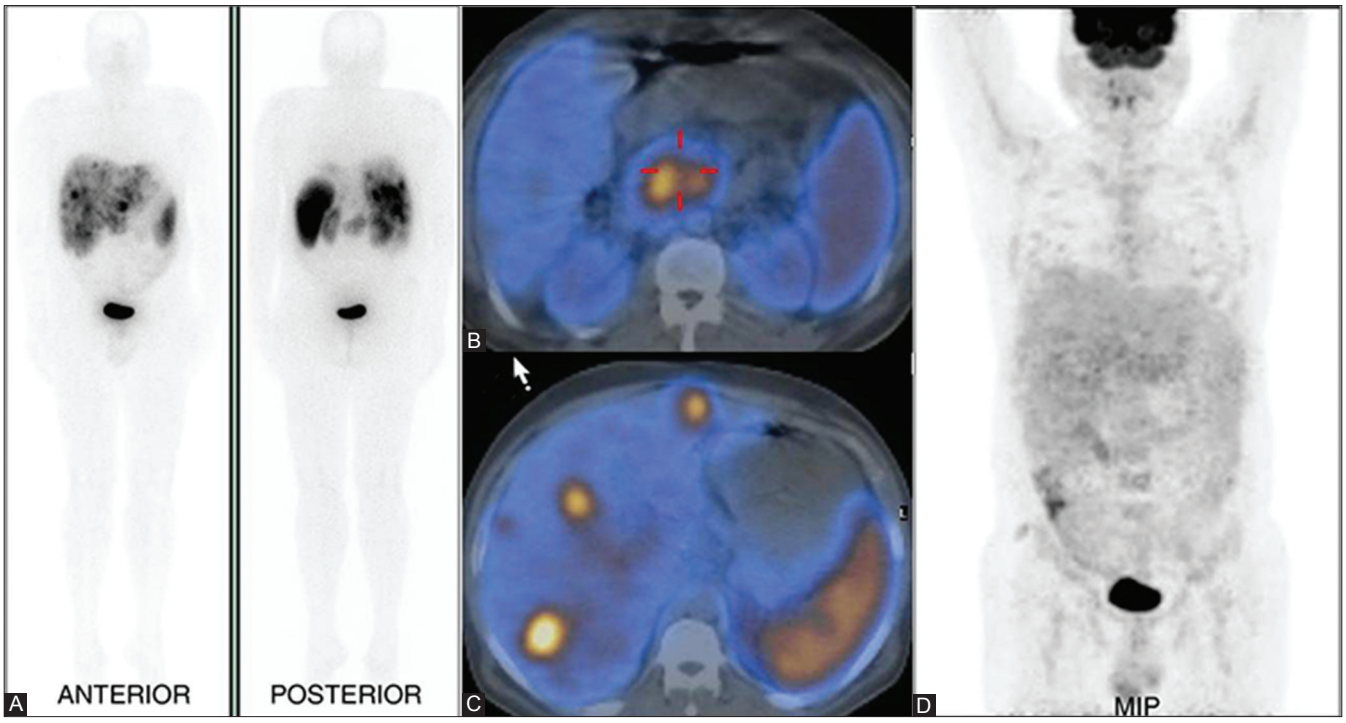

Figure 8 (A-D): Type I uptake pattern: The WB planar images of 99m Tc HYNIC TOC study show multiple hepatic metastases (A). The transaxial SPECT/CT images show focal concentration in the primary in head of pancreas (B) and the fused image of the hepatic metastases (C). The MIP image of the FDG PET/CT study (D) of this patient does not show abnormal focal FDG concentration either in the primary or the hepatic metastases. The histology of this pathology is a well differentiated NET. The combined SRS and FDG images in this patient portray a type I pattern

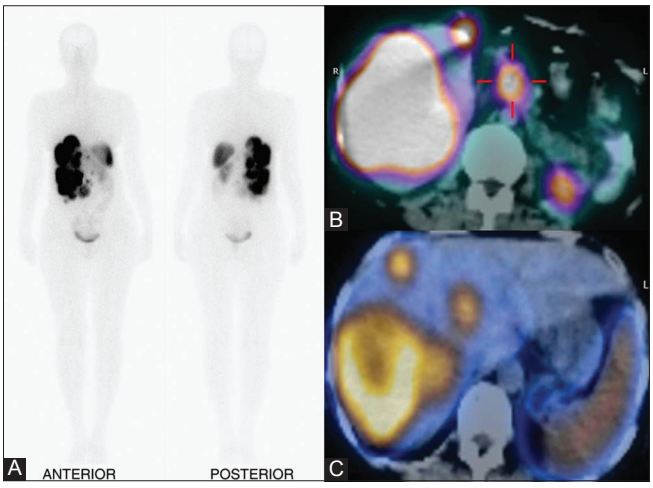

Figure 9 (A-C): Type II uptake pattern: The anterior and posterior whole body planar image of RIS (A) with avid uptakes seen in the liver metastases and right aspect of the midline region, the transaxial SPECT/CT images show the focal uptake in the right of the midline correlating with the primary in the body of the pancreas (B) and the multiple hepatic metastases (C)

NETscan be categorized depending on the pattern of somatostatin and GLUT receptors expression with type I at one end of the spectrum suggestive of a well-differentiated tumor and type IV which depicts a dedifferentiated tumor with poor to absent SSTR at the other end [Table 1].

Figures 8-13 illustrate the various combinations of RIS

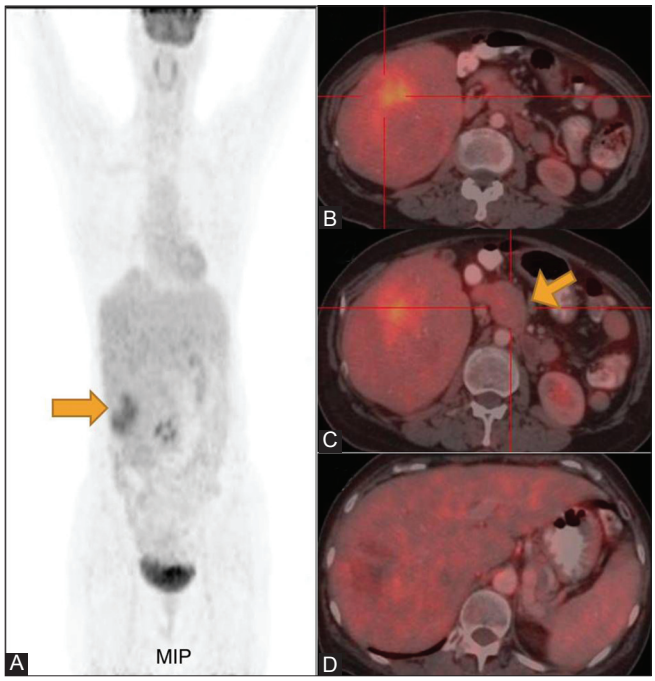

Figure 10 (A-D): Type II uptake pattern (contd): The FDG PET/CT study of the patient in fig 9 revealed an area of minimal increased tracer uptake in the right lobe of the liver on the MIP image (arrow A) which on transaxial images corresponds to the largest hepatic lesion in the right lobe (triangulated in B) with no GLUT expression in the primary lesion at the junction of the body and head of the pancreas (arrow C) or the other larger hepatic lesions (D), these tumors may have a propensity for alteration of tumor biology

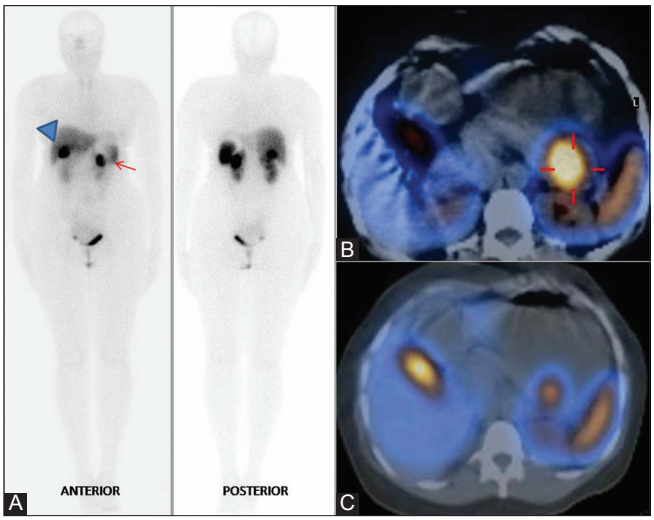

Figure 11 (A-C): Type III uptake pattern: Tumors with poor differentiation show reduction in density of SSTR with increase in density of GLUT receptors; these are visualized as FDG and SRS avid lesions categorized as type III pattern. This is a case of recurrent NET of the tail of the pancreas evaluated with RIS, the planar and the correlative fused transaxial SPECT/CT images show somatostatin avid recurrent lesion in tail of pancreas (thin arrow A and triangulation in (B). Note the intense focal uptake in the gall bladder (arrow head A), confirmed in the SPECT/CT image (C)

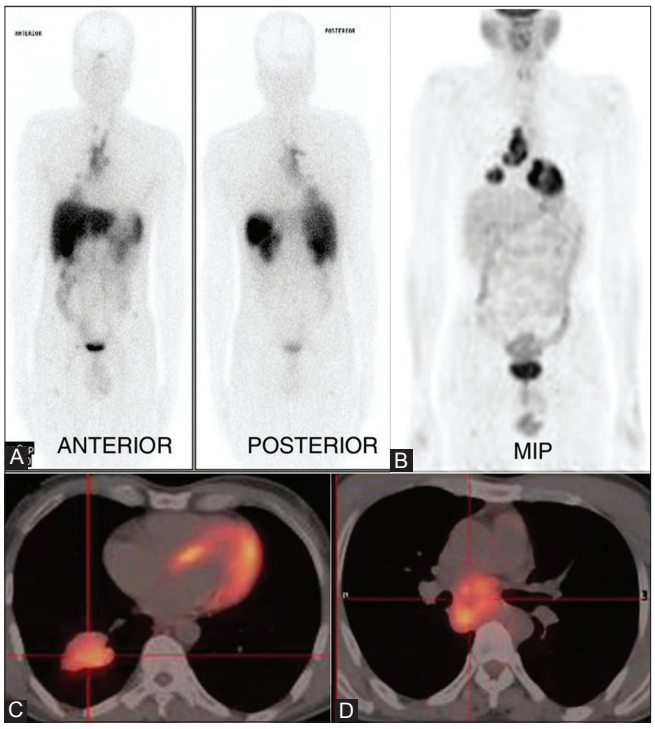

Figure 13 (A-D): Type IV uptake pattern: Dedifferentiated tumors show poor somatostatin receptor expression with high expression of GLUT receptor which shows a type IV pattern of uptake - FDG avid and poor SSTR lesions. A NET of the lung with mediastinal nodal metastases shows poor somatostatin expression as seen by low uptakes on the whole body planar images of 99m Tc HYNIC TOC study (A) with intense FDG concentration in the primary and the nodal disease seen on the MIP image (B) and the transaxial images of the thorax (C and D) of the 18 F FDG PET/CT

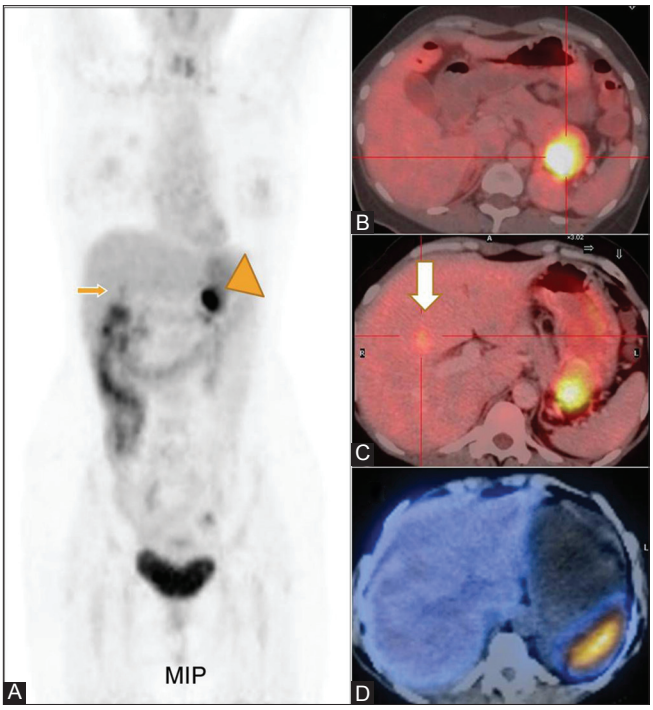

Figure 12 (A-D): Type III uptake pattern (contd): The recurrent pancreatic tail lesion seen in fig 11 showed avid FDG uptake seen on MIP image of the 18 F FDG PET/CT (arrow head A) and the transaxial image (B) suggestive of dense GLUT receptor expression. A low grade FDG uptake is seen in a hepatic lesion on the FDG PET/CT study (arrow A and C) with no HYNIC TOC concentration in the liver on correlative transaxial SPECT image of the RIS (D). The metastatic lesions demonstrate altered biology, no somatostatin receptor expression but expression of GLUT receptor

Table 1: Categorisation of neuroendocrine tumors based on somatostatin receptor scintigraphy and flouro–deoxy-glucose uptakes.

Type I	SRS positive and FDG negative–Well differentiated tumors
Type II	SRS positive and Low FDG–Mixed variety of cells
Type III	Avid somatostatin and FDG uptake
Type IV	Avid FDG and low somatostatin uptake–Increasing loss of differentiation

SRS: Somatostatin receptor scintigraphy, FDG: Flouro–deoxy-glucose

and FDG scans depicting the varied biologies of NETs confirming the utility of conjugate receptor imaging.

It would be appropriate to suggest that in combined SRS and FDG PET/CT studies, an increasing FDG uptake with declining SR uptake would convey loss of tumor differentiation and predict a poor prognosis.

Future role of RIS in therapy planning

Peptide receptor radionuclide Therapy (PRRNT) is emerging as a promising therapeutic option in view of the specific targeting of tumor receptors. The consensus report of the NET Clinical Trials Planning Meeting mentions the need for a randomized phase III trial with use of PRRNT in one arm which is based on the somatostatin receptor expression.[18]

SSTR would be useful in this setting to identify the differentiation of the tumor, its spread, and will also be used for tailored dosimetry. It would be worthy to note the advantage of RIS in that it provides all the necessary treatment planning information in a single study.

Conclusion

SRS is a useful tool in locating the primary disease and staging of NETs. The ability of the modality to delineate the somatostatin receptor expression gives explicit information of the biology of the NET, both at primary and metastatic site and helps in treatment planning.

SRS in conjunction with GLUT receptor imaging helps locate change in tumor receptor expression and thus helps in prognostication of the disease.This can stratify patients who would benefit from somatostatin analogue or peptide therapy, which is the emerging treatment option for NET. RIS will be an effective method to monitor response to radioimmunotherapy, which will identify a non-responder early and help alter treatment in such patients.

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