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Mib1 index stratified assessment of Dual Tracer PET-CT with ^{68}Ga-DOTATATE and ^{18}F-FDG and multimodality anatomical imaging in Metastatic NET of Unknown Primary (CUP-NET) scheduled for PRRT

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Short running title: **^{68}Ga-DOTATATE/18F-FDG PET-CT in CUP-NET**

Conflict of Interest: Nothing to Declare

ABSTRACT

Aim:Comparative assessment of dual tracer PET/CT (^{68}Ga-DOTATATE and ^{18}F-FDG) and multimodality anatomical imaging in studying CUP-NETs scheduled for PRRT for: (i) divergence of tracer uptake on dual tracer PET/CT, (ii) detection of primary and (iii) overall lesion detection vis-a-vis tumor proliferation index (Mib1/Ki-67). **Materials and Methods:**Fifty-one patients of CUP-NETs (M:F=25:26, age:22-74 years), histopathologically proven and thoroughly investigated with conventional imaging modalities (USG, CT/ceCT, MRI and EUS, wherever applicable), were retrospective analyzed. They were primarily referred for deciding on feasibility of PRRT (except 2 patients) and all had undergone ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT as part of pre-treatment work up. The sites of metastases included liver, lung/mediastinum, skeleton, abdominal nodes and other soft tissue sites. Patients were divided into 5 groups based on Mib1/Ki-67 index of 5 point scale: group I (1-5%) (n=35), group II (6-10%) (n=8), group III (11-15%) (n=4), group IV (16-20%) (n=2), group V (>20%) (n=2). Semiquantitative analysis of tracer uptake was undertaken by SUVmax of metastatic lesions and the primary (when detected). The SUVmax values were studied over increasing Mib1/Ki67 index. The detection sensitivity of ^{68}Ga-DOTATATE for primary and metastatic lesions was assessed and compared with other imaging modalities including ^{18}F-FDG-PET/CT. **Results:**Unknown primary was detected on ^{68}Ga-DOTATATE in 31/51 patients resulting in sensitivity of 60.78% while overall lesion detection sensitivity was 96.87%. The overall lesion detection sensitivities (individual group-wise from Group I to Group V) were 97.75%, 87.5%, 100%, 100% and 66.67% respectively. As Mib1/Ki67 index increased, ^{68}Ga-DOTATATE uptake decreased in metastatic and primary lesions (mean SUVmax 43.5 and 22.68 g/dl in group I to 22.54 and 16.83 g/dl in group V respectively), while 18F-FDG uptake showed a gradual rise (mean SUVmax 3.66 and 2.86 g/dl in group I to 7.53 and 9.58 g/dl in group V respectively). There was corresponding decrease in ^{68}Ga-DOTATATE/^{18}F-FDG uptake ratio with increasing Mib1/Ki-67 index (from 11.89 in group I to 2.99 in group V). **Conclusion:**In CUP-NETs, pattern of uptake on dual tracer PET (^{68}Ga-DOTATATE/^{18}F-FDG) correlates well with tumor proliferation index with a few outliers; combined dual tracer PET/CT with Mib1/Ki-67 index would aid in better whole-body assessment of tumour biology in CUP-NETs.

INTRODUCTION

The neuroendocrine tumors (NETs) have been classified into 3 grades by the European Neuroendocrine Tumor Society system based on the proliferative index-Mib1/Ki-67 index *(1,2)*. G1 and G2 are well differentiated NETs whereas the G3 are poorly differentiated ones. Dual tracer PET imaging approach (with somatostatin receptor based ^{68}Ga-DOTATATE and glucose metabolism targeted ^{18}F-FDG PET/CT) is emerging as an important parameter for treatment planning and response evaluation in patients of NETs *(3-7)*. Majority of the well-differentiated NETs express high somatostatin receptors (SSTRs) on their cell surface that is utilized for receptor specific imaging by 68Ga-DOTATATE PET/CT scan. ^{18}F-FDG-PET/CT on the other hand, images the high grade tumors, indicates aggressiveness of the disease and increased ^{18}F-FDG uptake has been associated with a poor prognosis *(3-8)*. In a typical case scenario, the lower grade NETs should show SSTR expression (on ^{68}Ga-DOTATATE PET/CT scan) more than the GLUT expression (on ^{18}F-FDG PET/CT scan) and vice versa with poorly differentiated cases. In the clinical setting, however, frequent outliers occur and therefore the dual tracer imaging aids in a great way individualization of peptide receptor radionuclide therapy (PRRT) and also deciding the combination of PRRT with other treatment modalities (such as chemotherapy and TKIs) based upon the scan findings *(7)*.

Metastatic NET with unknown primary (CUP-NET) constitutes around 20-25% of all the cases of NET. In these patients, detecting the site of primary is an important step which would help in planning a more definitive and appropriate treatment to the patient. Identification and knowledge of the primary site is also of immense importance as other aspects of management are highly dependent on it, ranging from disease prognosis, treatment outcome, and survival rates. The role of ^{68}Ga-DOTATATE (and of the others 68Ga-DOTA-peptides) is universally recognized for the study of NET localization and the procedure is now included in international guidelines for the detection of the unknown primary (among other indications) *(8)*. Furthermore, a number of papers have been or being published on the role of somatostatin analogue for the characterization of the unknown primary in NET (detailed in discussion section): however, the performance of dual tracer PET in patients of CUP-NET is relatively less explored methodically. Hence, the main aim of the present work to analyze the dual tracer imaging characteristics this particular group of patients and also look at the performance of individual tracers vis-a-vis the Mib1 index on histopathology.

MATERIALS AND METHODS

A retrospective evaluation was undertaken analyzing the cases of metastatic NET with unknown primary (CUP-NET). The study protocol was approved by the Institutional Ethics Committee. The institutional review board (Medical Ethics Committee) approved this retrospective study and the requirement to obtain informed consent was waived.

Most of the patients were referred to our centre for PRRT (except for 2 patients, who were referred to search for the primary by the ^{68}Ga-DOTATATE PET/CT). ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT scans were available in all patients and evaluated as a part of the pre-treatment work up protocol for PRRT during which special emphasis given to review all cases in which the primary was unknown. The cases selected for the study analysis fulfilled the following criteria- (i) they were diagnosed patients of metastatic NET with unknown primary, (ii) the cases were histopathologically proven to be NET by biopsy evaluation of the metastatic site with availability of MiB1 labeling index in the biopsy report, (iii) evidence of extensive work-up data undertaken by the conventional imaging modalities [included ultrasonography (USG), triple phase contrast enhanced (ceCT), MRI, EUS) as part of initial work up by the referring GI oncologist, that could not detect the site of primary.

A total population of 51 patients (25 males and 26 females, age range: 22-74 years) was included for the analysis. The sites of metastasis included liver, lung, mediastinum, skeleton, abdominal and retroperitoneal nodes, pericardium and other soft tissue sites (detailed in Table 1). The patients were divided into groups of 5 based on the proliferative index- Mib1/Ki67 index (Table 2). Among these, 12 out of 51 patients had a suspected site of primary with evidence of metastasis from the prior work-up imaging and ^{68}Ga-DOTATATE PET-CT was utilized for definite characterization of the suspected primary site. The final confirmation was established either by histopathology or further correlative imaging.

Each patient were analysed for the following parameters, both at the metastatic sites and primary (if could be located)- (i) Measurement of the tracer uptake by semiquantitative SUVmax on ^{68}Ga-DOTATATE and ^{18}F-18F-FDG PET/CT studies, (ii) correlation of the dual tracer uptake with the biopsy reported Mib1/Ki67 labelling index, (iii) number of cases in which ^{68}Ga-DOTATATE or 18F-FDG -PET/CT could detect the site of primary in which the conventional imaging modalities failed to conclusively diagnose (iv) total

number of metastatic lesions in each patient detected by ^{68}Ga-DOTATATE PET-CT scan in comparison with USG, CT/ceCT, MRI and ^{18}F-FDG PET/CT study.

RESULTS

The details of study population included and the patient subdivision according to MiB1 index has been depicted in Tables 1 and 2 respectively. Separate patient based and lesion based analyses was undertaken as follows:

A. <u>Patient based Analysis: Performance of dual tracer PET in relation with Mib1/Ki-67 labelling index</u>

Group I (Mib-1/Ki-67 index of 1-5%) consisted of 35 patients. 25/35 (71.48%) patients showed both scan positivity on both SSTR targeted and GLUT targeted imaging whereas 10/35 (28.57%) patients showed positivity only on SSTR based imaging and was negative on 18F-FDG-PET/CT (an expected finding in a low Mib1 index case) (Figures 1,2).

Among the 25 patients positive on both ^{18}F-FDG and ^{68}Ga-DOTATATE PET-CT imaging, on visual assessment, uptake on SSTR based PET was higher in 14/25, equal in 10/25 and less in 1/25 patients compared to the 18F-FDG - PET uptake in the lesions.

On further sub-analysis, in 10 out of 14 cases showing predominant ^{68}Ga-DOTATATE uptake, the Mib 1 index was found to be </= 2% (i.e. grade I NET) and in 4/14 cases it ranged from 3-5% (Grade II NET). Both the aforementioned findings are commensurate with what can be expected of the performance ^{18}F-FDG and ^{68}Ga-DOTATATE in patients with low MiB-1 labeling index.

Group II (Mib-1/Ki-67 index of 6-10%):

A total of 8 patients belonged to Group II, among which 4/8 (50%) cases were negative on ^{18}F-FDG PET/CT and 4/8 (50%) showed increased uptake by both tracers. All cases demonstrated high uptake on ^{68}Ga-DOTATATE PET-CT scan.

In 4 patients that were positive on ^{18}F-FDG PET-CT, 2/4 showed ^{18}F-FDG uptake equal to ^{68}Ga-DOTATATE uptake, 1/4 showed predominant ^{18}F-FDG uptake and the remaining 1 patient showed ^{68}Ga-DOTATATE uptake predominantly (Fig. 3).

Group III (Mib1/Ki67 index of 11-15%) consisted of 4 patients of which all the patients showed increased ^{18}F-FDG as well as ^{68}Ga-DOTATATE uptake (Fig 4) on the dual tracer PET (i.e. 100% concordance with regard to scan positivity). In 2 out of 4 patients, the FDG uptake was equal to SSTR based imaging, in rest of the 2 patients uptake on ^{68}Ga-DOTATATE was more as compared to the 18F-FDG –PET.

Group IV (Mib1/Ki67 index of 15-20%) consisted of 2 patients. Both the patients showed ^{18}F-FDG and ^{68}Ga-DOTATATE uptake, one of them (50%) exhibited predominant ^{18}F-FDG uptake whereas the other (50%) displayed predominant ^{68}Ga-DOTATATE uptake (Figure 5a).

Group V (Mib1/Ki67 index of >20%) included two patients, one out of two (50%) patients showed no significant ^{68}Ga-DOTATATE uptake (Figure 8) but significant ^{18}F-FDG uptake while the other (50%) showed both ^{18}F-FDG and ^{68}Ga-DOTATATE uptake, though the latter was much more compared to 18F-FDG (Figure 5b).

Thus from the aforementioned data, we observed that ^{68}Ga-DOTATATE uptake was typically predominant in the low Mib1/Ki-67 index tumours/well differentiated NETs and ^{18}F-FDG uptake predominated in the high Mib1/Ki67 index tumours/poorly differentiated NETs. However, it was also noted that a low grade 18F-FDG uptake can be observed in a fraction of low grade NETs and high grade tumours (Mib1 index >20%) can also demonstrate significant ^{68}Ga-DOTATATE uptake. When the SUVmax was calculated for either PET study, a fall was noted in the uptake of ^{68}Ga-DOTATATE as the Mib1/Ki67 index increased while ^{18}F-FDG uptake demonstrated a gradual rise, resulting in a decrease in the ^{68}Ga-DOTATATE/^{18}F-FDG uptake ratio (Table 3). The decrease in uptake ratio with increasing proliferative index is an expected finding signifying that lesional uptake of ^{68}Ga-DOTATATE decreases and ^{18}F-FDG increases with increasing proliferative activity of the tumour (Fig 6).

B. Lesion based Analysis

I. Performance of ^{68}Ga-DOTATATE in detecting site of Primary

Out of a total of 51 patients who had been thoroughly worked up with conventional imaging modalities (USG, CT/ceCT, MRI, EUS) previously and yet

the site of primary was not detected, ^{68}Ga-DOTATATE could detect primary in 31 patients resulting in an overall sensitivity of 60.78% in this group of patients. The most common site identified were gastroenteropancreatic NETs, others included lung and mesentery (Table 4).

II. Comparative Performance of 68Ga-DOTATATE and 18F-FDG PET/CT in detecting the primary in relation to Mib1 labeling index

The comparative sensitivity of dual tracer PET imaging in detecting the primary was also studied in connexion with Mib1/Ki67 index.

In group I, the primary could be detected in 23/35 cases (65.7%), out of which only 4 primaries showed increased ^{18}F-FDG uptake and all the 23/23 primaries showed clearly enhanced ^{68}Ga-DOTATATE uptake. In Group II, among 8 patients, 3 (37.5%) sites of primary could be identified out of which none of the sites showed increased 18F-FDG uptake. However, all three patients displayed high uptake on SSTR targeted imaging. In group III, two sites of primary could be detected among a total of 4 patients (detection sensitivity=2/4 i.e. 50%) of which both the sites demonstrated increased ^{18}F-FDG and ^{68}Ga-DOTATATE uptake. Site of primary could be found out only in 1 out of 2 patients (50%), in both group IV and group V which showed positivity on both PET-CT scans (Table 5).

III. Group-wise comparison of overall disease STAGING: ^{68}Ga-DOTATATE and ^{18}F-FDG-PET/CT versus conventional anatomical modalities

In all the groups, the sensitivity of the ^{68}Ga-DOTATATE PET/CT scan was clearly superior as compared to the standard imaging modalities such as USG, ceCT/CT and even ^{18}F-FDG PET/CT, which was 96.87% as compared to 42.96%, 57.81% and 51.56% respectively (Table 6). ^{68}Ga-DOTATATE is a potential investigation to be selected as the prime imaging modality for initial investigation and staging of the disease. It has been noted that 68Ga-DOTATATE and 18F-FDG PET/CT scans together complementarily can become a superlative staging modality, particularly in patients with relatively higher Mib1 labelling index. Another noteworthy finding in this analysis was the increasing sensitivity of ^{18}F-FDG PET/CT scan with increasing proliferative index (Mib1/Ki67 index).

To summarize the results, the following imaging characteristics of dual tracer PET-CT imaging in correlation with Mib 1/Ki-67 index: (i) In low Mib 1/Ki-67 index (especially </= 2%), ^{68}Ga-DOTATATE uptake predominated even though low grade ^{18}F-FDG uptake can be seen in a number of cases: this is consistent with features of well differentiated NET. (ii) As the Mib 1/Ki-67 index rises (>3%-15%), the^{18}F-FDG uptake shows a progressive rise both in primary and metastatic lesions. Significant ^{68}Ga-DOTATATE uptake in the tumour persists inspite of the intermediate proliferative index. (iii) In high Mib 1/Ki-67 index (>15%), ^{18}F-FDG uptake progressively increases and predominates in an increasing percentage of patients. However a low grade ^{68}Ga-DOTATATE uptake can be seen given the type of tumour. (iv) The ^{68}Ga-DOTATATE to ^{18}F-FDG uptake ratio showed a decreasing trend with increasing tumor proliferation (Mib1) index (Fig 6). (v) ^{68}Ga-DOTATATE PET/CT has a potential role to become the sole investigation for staging of the disease in a patient of NET (particularly upto Mib1 index of 20%, with superior overall lesion detection sensitivity (96.87%). Moreover, it should become the first investigation in a work up of patient of NET of unknown primary (CUP-NET) as it can detect primary a substantial fraction of patients who were designated CUP-NET after extensive investigation with conventional anatomical imaging modalities. The sensitivity of 18F-FDG PET/CT for staging the disease rises with the increasing proliferative activity in the tumour signified by Mib1/Ki-67 index. (vi) ^{18}F-FDG uptake progressively increases with increasing tumor grade and should be used for disease prognostification. (vii) The overall detection sensitivity of ^{68}Ga-DOTATATE PET/CT scan in detecting the site of primary in cases of metastatic NET of unknown primary (CUP-NET), where the conventional imaging modalities could not identify the primary was 60.78%. One area where it can have potential role is confirming through characterizing a suspected site and clearly depicting the primary when it was missed by conventional ceCT (Fig 7).

DISCUSSION

There is a rapid expansion and increasing application of functional somatostatin receptor-targeted imaging with ^{68}Ga-DOTA labeled somatostatin analogues and therapy (PRRT) with ^{177}Lu-DOTATATE in the clinical management of metastatic and inoperable NETs *(9-14)*. ^{68}Ga-DOTATATE PET/CT scan has proven to be a pertinent tool in management of NETs, its utility extending right from diagnosis till prognostification of the disease *(9-12)*. Another important role that ^{68}Ga-DOTATATE PET/CT can play is the detection of the primary tumor site in patients of metastatic NETs with unknown primary (CUP-NETs), an essential step towards patient management *(15-20)*.

One of the salient decision-making factors for choosing the appropriate therapy in metastatic NETs has been the tumor grade, which is based upon the proliferation index (also known as Mib1/Ki-67 labeling index) *(21-24)*. The European Neuroendocrine Tumor Society system grades the NETs based on the proliferative index (Mib1/Ki-67 labelling index) into G1 (well differentiation), G2 (intermediate differentiation) and G3 (poorly differentiated) NETs [1]. A "flip-flop" phenomenon is usually seen in which ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT findings are inversely related at either end of the European Neuroendocrine Tumor Society system spectrum *(3-8)*. G2 tumors, representing the middle of the spectrum, can demonstrate uptake of both ^{68}Ga-DOTATATE and ^{18}F-FDG [3-8,18]. ^{68}Ga-DOTATATE PET-CT as a relatively superior disease characterizing and localizing modality that plays a very important role during planning of treatment for NET and furthermore, combined with ^{18}F-FDG PET/CT, constitutes a major prognostification tool in management. Functional imaging with both ^{68}Ga-DOTATATE and ^{18}F-FDG has potential for a more comprehensive tumor assessment in both intermediate and high-Mib1 index tumors *(3-8)*.

^{68}Ga-DOTATATE PET/CT scan has proven to be superior compared to the conventional imaging modalities in detecting the primary in patients of CUP-NET *(15-20)*. All the cases of CUP-NET are usually initially worked up with conventional imaging modalities such as USG, CT/ceCT and MRI and EUS where applicable, which are unsuccessful in identifying the site of origin. In this study, we have strictly included those cases of histopathologically proven metastatic CUP-NETs, which have been thoroughly worked up with conventional imaging modalities, e.g. USG, CT/ceCT (triple phase), MRI and EUS (for suspected pancreatic and duodenal primaries) by which the site of primary could not be detected. Our centre being a tertiary care centre with a very busy clinical PRRT service in the country, we primarily got cases that were referred for PRRT. This might have introduced some bias in the cases that were retrospectively included as all of them had high uptake on ^{68}Ga-DOTATATE (this could also explain why our study had high grade 1 tumours), however to our advantage was the availability of complete imaging and histopathological (Mib1 index) work-up data in each patient included in the analysis. This made it possible to make a unique study design to examine the performance dual tracer PET in patients of CUP-NET vis-a-vis the Mib1/Ki-67 labelling index not only for detection of the primary but also the other characteristics such as the dual tracer uptake intensity and pattern and overall lesion detection sensitivity

across the varying Mib1 labelling index. All these were undertaken along with the conventional anatomical imaging modalities.

The sensitivity of ^{68}Ga-DOTATATE PET/CT scan in detecting primary was highest in G1 well differentiated NETs (65.7%) and decreased as the proliferative index increased (37-50% in G2 and G3 NETs). We had extended the objectives of this study to scrutinize how the overall lesion detection sensitivity of each of the functional imaging (^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT) can differ with that of the proliferative activity and whether they have a complementary role. ^{68}Ga-DOTATATE PET/CT study demonstrated higher sensitivity than conventional modalities and ^{18}F-FDG PET/CT scans. As could be theoretically expected, we observed that the sensitivity of ^{18}F-FDG PET/CT scan increased with intermediate and high grade NETs. Also the number of lesions detected was greater when ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT scan findings were combined, that would argue for adoption of this approach in clinical routine while evaluating NETs.

The concept of dual tracer imaging with somatostatin receptor scanning with ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT scans (signifying glycolytic metabolism) is forthcoming in the management of NETs and is being continued to be explored upon. The number of patients has been divided into 5groups based on Mib1/Ki67 labelling index within a range of 5% between each successive group so that the variability in the tumour behavior can be studied with dual tracer PET imaging within a narrow width of proliferation. Majority of the cases were concordant with the typical flip flop pattern of dual tracer uptake with highest ^{68}Ga-DOTATATE uptake in low grade tumours and highest ^{18}F-FDG uptake in the high grade ones. Atypical partial concordance was also observed with regard to uptake of both ^{68}Ga-DOTATATE and ^{18}F-FDG in a few cases; this signified different tumour biology in metastatic and primary lesions as well as different sites of metastasis. The finding of atypical uptake pattern suggests that in such cases histopathological diagnosis alone would not suffice. Interestingly, the recent literature on NETs have reported behavioral and treatment response heterogeneity amongst the same grade tumors *(21-24)*, which, at least in part, could be explained in part by our finding of atypical uptake pattern in dual tracer PET imaging. This would warrant an amalgamation of histopathology and dual tracer PET imaging for improving diagnosis, therapy selection and prognostification, which in turn has the potential to better the overall outcome of disease.

The sensitivity of ^{68}Ga-DOTATATE/ PET/CT in detecting the site of primary in cases of CUP-NET as observed in our study (60.78%) not only conforms well with the current facts, but also the high sensitivity of overall lesion detection ability in low and intermediate grade tumors (in our study upto Group IV) makes it a preferred modality compared to the others.

While the limitation of this study has been small population in each subgroup (especially group III, IV and V), on a broader perspective, however, this was a unique group of CUP-NETs that were specifically and examined in a PRRT work-up setting; even in this specific population group there was an overall trend noted between MiB-1 index and PET index (68Ga-DOTATATE/18F-FDG uptake ratio) as demonstrated by the results.

CONCLUSION

^{68}Ga-DOTATATE PET/CT scan is an important imaging modality for detection of site of unknown primary in CUP-NETs and also for overall lesion detection of the disease. It scores over the conventional imaging modalities and also ^{18}F-FDG PET/CT in staging of the disease. However, a better assessment and sensitivity for staging can be acquired by combining ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT scans. An amalgamation of dual tracer uptake imaging with ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT should be done with histopathological diagnosis of disease to study the divergent tumour biology for better management and outcome in patients of NETs.

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Table 1: Characteristics of Study Population

Patient characteristics	Values
AGE RANGE MEAN	 22-74 YEARS 48 YEARS
SEX MALES FEMALES	**51 patients** 25 26
METASTATIC SITES LIVER LUNG/MEDIASTINUM SKELETAL ABDOMINAL NODES PERICARDIUM OTHERS(SOFT TISSUE)	**No. of patients presenting with these sites** 48 03 12 25 01 03

Table 2. Division of the patients into groups of five based on the Mib1/Ki67 labelling index and the depiction of number in each category

GROUP	Mib 1/Ki-67 INDEX	NO. OF PATIENTS
I	1-5%	35
II	6-10%	08
III	11-15%	04
IV	16-20%	02
V	>20%	02

Table 3. Semiquantitative analysis of uptake intensity (SUVmax) in cases demonstrating both the tracer uptake in Metastases

GROUP	Mib1/Ki-67 INDEX	^{68}Ga-DOTATATE Mean SUVmax	^{18}F-FDG Mean SUVmax	^{68}Ga-DOTATATE/^{18}FDG uptake ratio
I	**1-5%**	43.5	3.66	**11.89**
II	**6-10%**	38.90	3.98	**9.77**
III	**11-15%**	29.80	5.60	**5.32**
IV	**16-20%**	24.36	5.88	**4.16**
V	**>20%**	22.54	7.53	**2.99**

Table 4. Performance of ^{68}Ga-DOTATATE in detecting primary in patients of Metastatic NET with unknown primary by conventional imaging modalities

Number of cases in which primary was detected by ^{68}Ga-DOTATATE PET/CT and not by any other conventional imaging modality	31
Number of cases in which primary could not be detected by ^{68}Ga-DOTATATE PET/CT	20
Percentage Sensitivity of ^{68}Ga-DOTATATE PET/CT in detecting in NUP	60.78%
Sites of primary	**No. of cases**
Pancreas	10 (31.03%)
Duodenum	05 (17.24%)
Mesentry	05 (17.24%)
Ileum	03 (10.34%)
Jejunum	02 (06.89%)
Lung	02 (06.89%)
Stomach	01 (03.44%)
Rectum	02 (06.45%)

Table 5. Scan Positivity and Semiquantitative analysis of uptake intensity (SUVmax) in cases demonstrating both the tracer uptake in the detected sites of primary: comparison with Mib1 Labelling index stratified group

GROUP	Mib1/Ki-67 INDEX	^{68}Ga-DOTATATE Mean SUVmax	^{18}F-FDG Mean SUVmax	Sensitivity in detecting primary
I	**1-5%**	22.68	2.86	**65.7%**
II	**6-10%**	10.33	--	**37.5%**
III	**11-15%**	11.5	4.58	**50%**
IV	**16-20%**	20.22	5.95	**50%**
V	**>20%**	16.83	9.58	**50%**

Table 6. Comparison of all imaging modalities in detecting the number of lesions and calculation of their sensitivity

GROUP	USG	CT/ceCT	18F-FDG	68Ga-DOTATATE	TOTAL LESIONS
I	37 (41.57%)	48 (53.93%)	40 (44.94%)	87 (97.75%)	89
II	9 (56.25%)	13 (81.25%)	9 (56.25%)	14 (87.5%)	16
III	4 (33.33%)	8 (66.66%)	9 (75%)	12 (100%)	12
IV	3 (60%)	3 (60%)	5 (100%)	5 (100%)	5
V	2 (33.33%)	2 (33.33%)	3 (50%)	4 (66.67%)	6
TOTAL	**55 (42.96%)**	**74 (57.81%)**	**66 (51.56%)**	**124 (96.87%)**	**128**

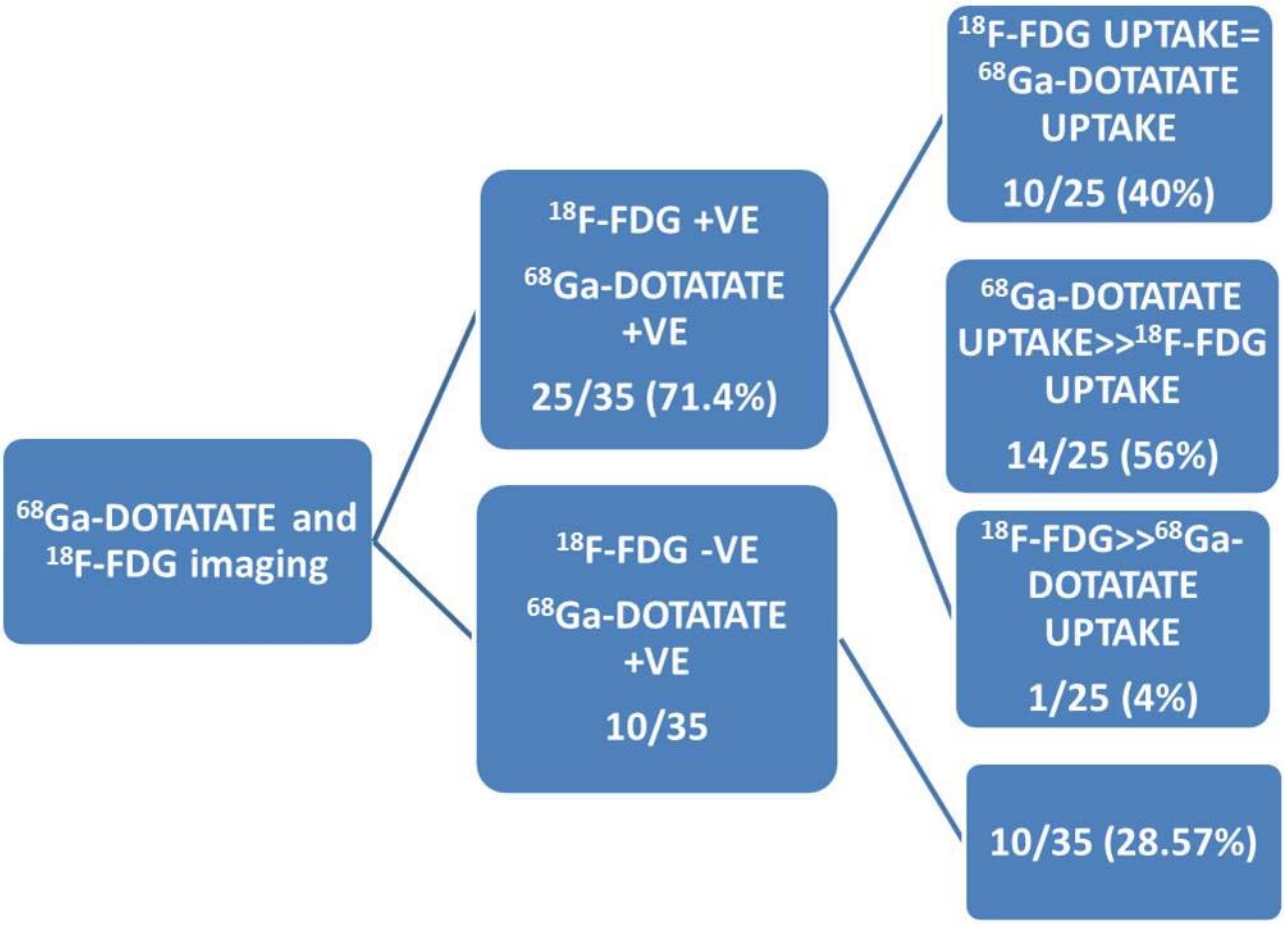

Fig 1. Flow-chart demonstrating the patient specific analysis observed on ^{68}Ga-DOTATATE and ^{18}F-FDG-PET/CT scan in group I cases (Mib 1 index 1-5%)

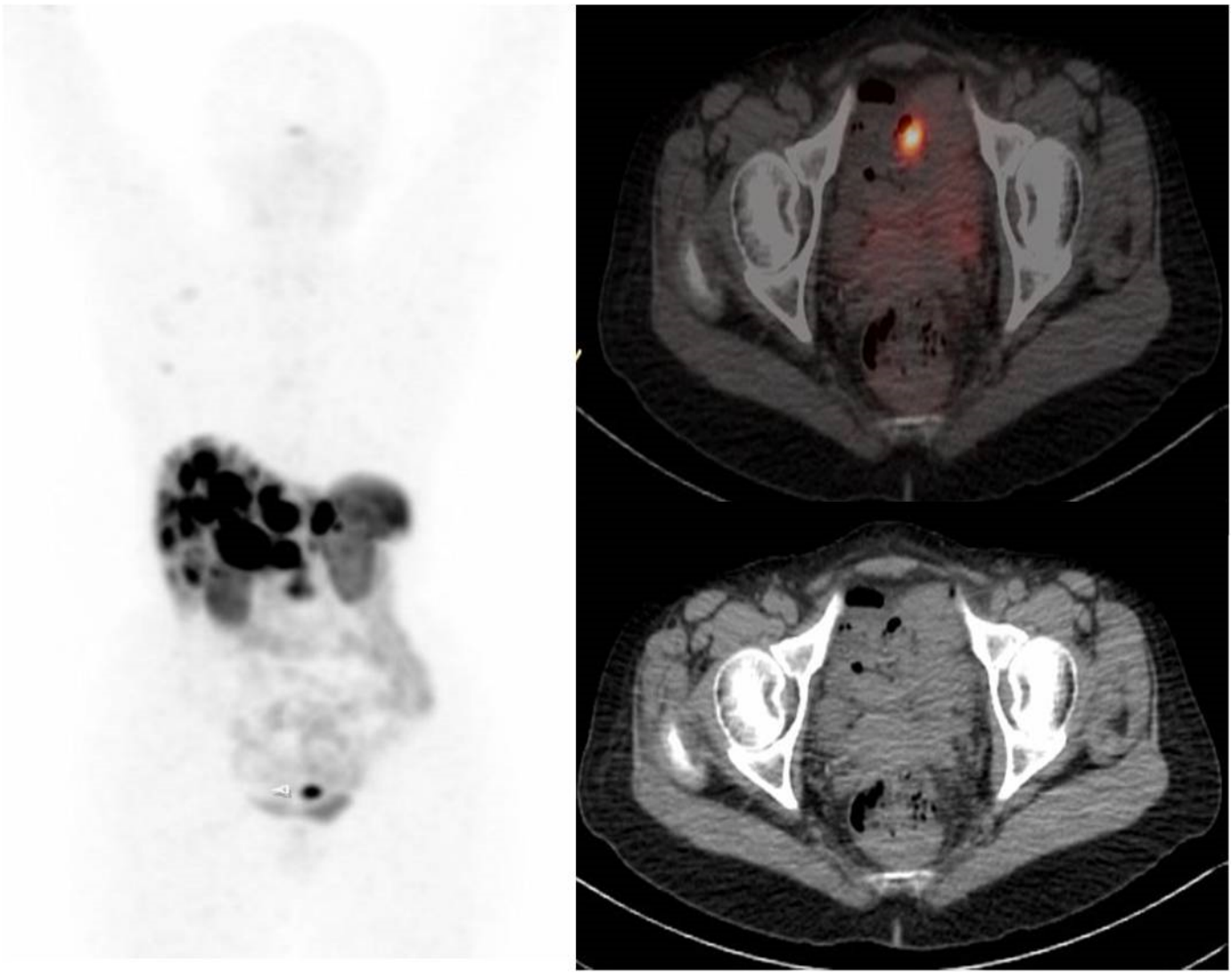

Fig 2. 56 years old female, liver biopsy suggestive of metastatic NET of liver, Mib 1 index: <1%. The primary was undetected by conventional imaging. 68-Ga-DOTATATE PET/CT scan showing multiple metastatic liver lesions and a focal tracer concentration in the pelvic ileum. Final diagnosis: Ileal NET with bilobar hepatic metastases.

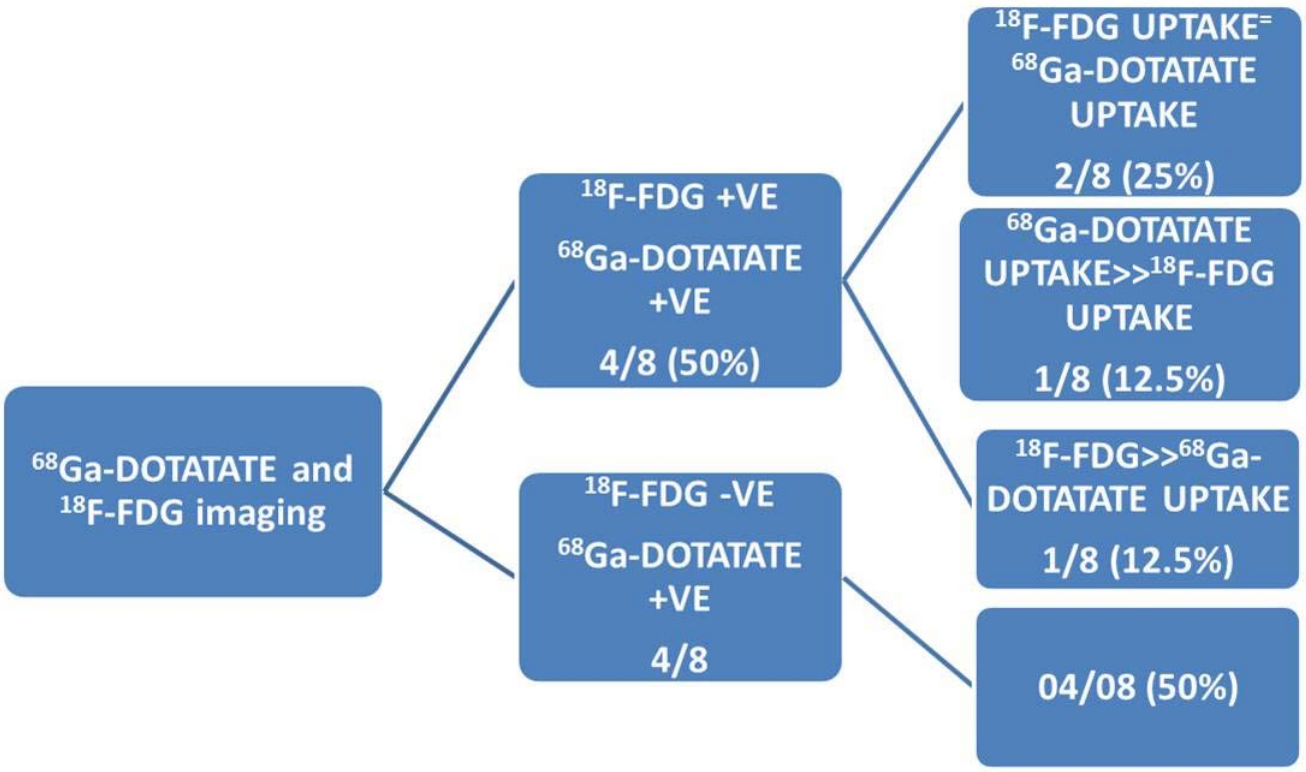

Fig 3. A decision tree type ramification analysis to assess relative performance and uptake intensity in metastatic lesions by ^{68}Ga-DOTATATE and ^{18}F-FDG-PET/CT in group II (Mib-1/Ki-67 index of 6-10%)

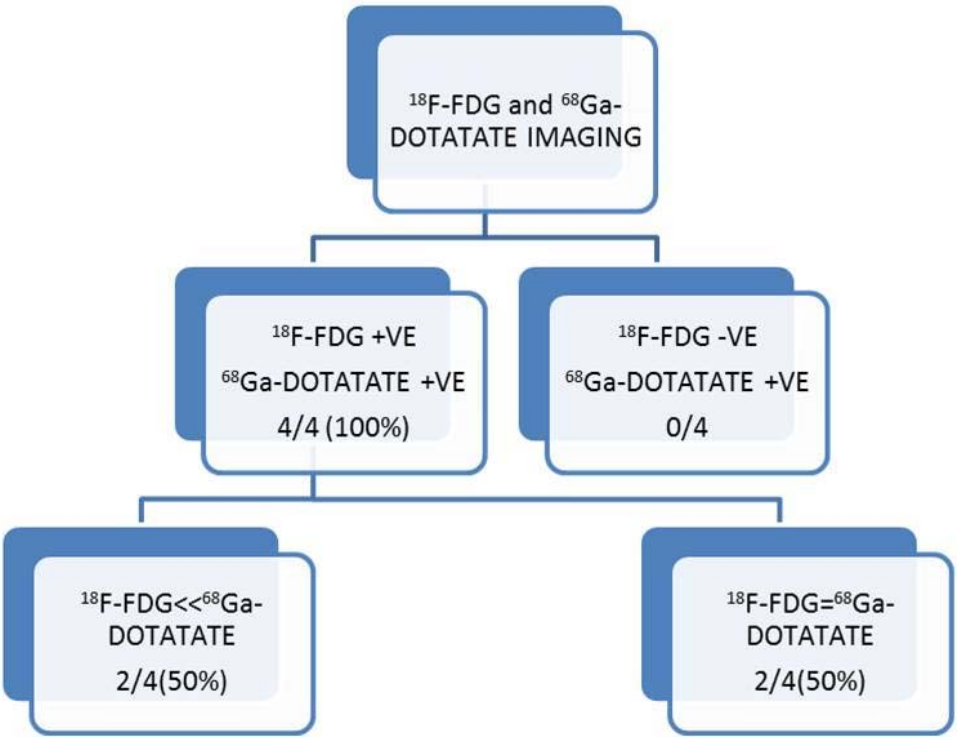

Fig 4. A Decision tree type ramification analysis to assess relative performance and uptake intensity in metastatic lesions by ^{68}Ga-DOTATATE and ^{18}F-FDG-PET/CT in group III

5A

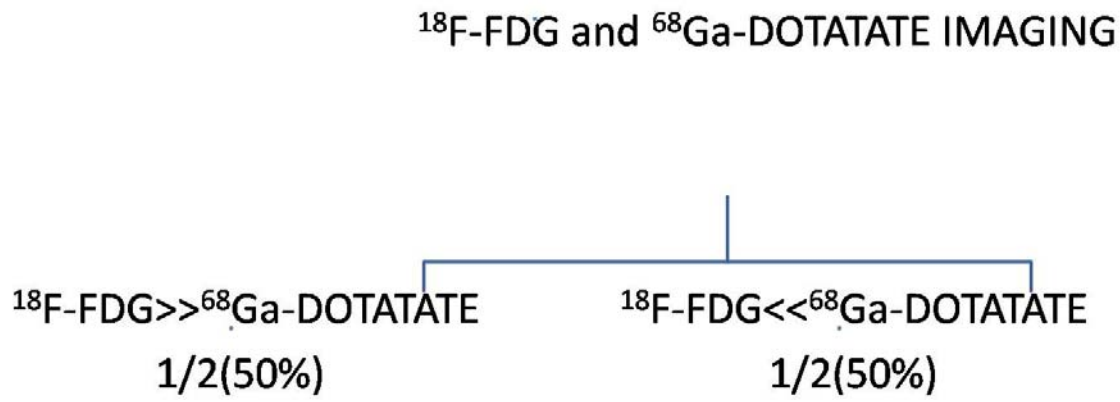

Figure 5a. Flow chart of assessment of relative positivity and uptake intensity in metastatic lesions by ^{68}Ga-DOTATATE and ^{18}F-FDG-PET/CT in group IV.

5B

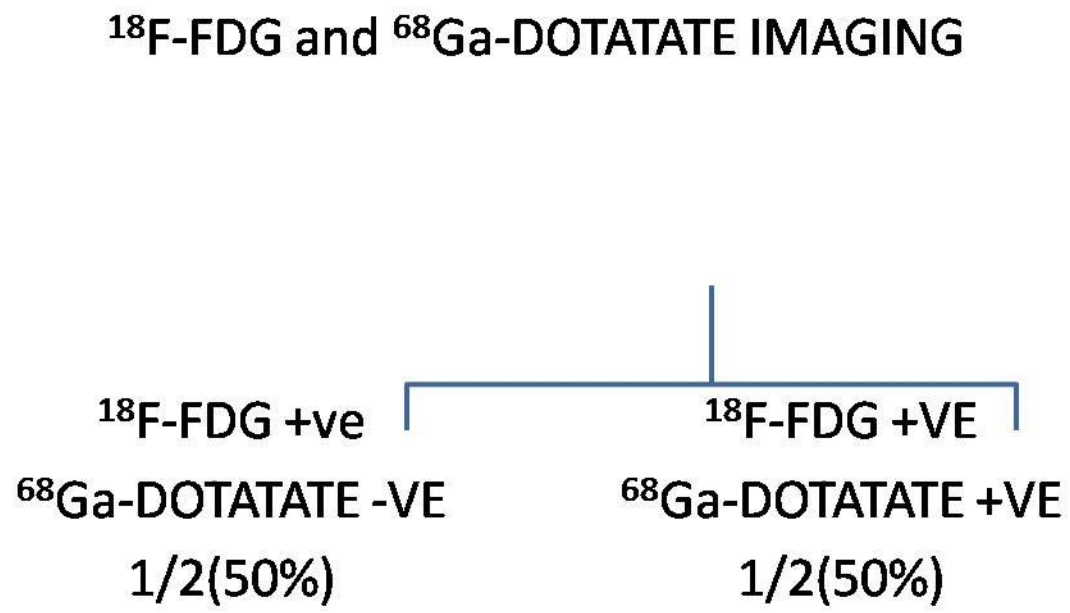

Figure 5B. Flow chart of assessment of relative positivity and uptake intensity in metastatic lesions by ^{68}Ga-DOTATATE and ^{18}F-FDG-PET/CT in group V.

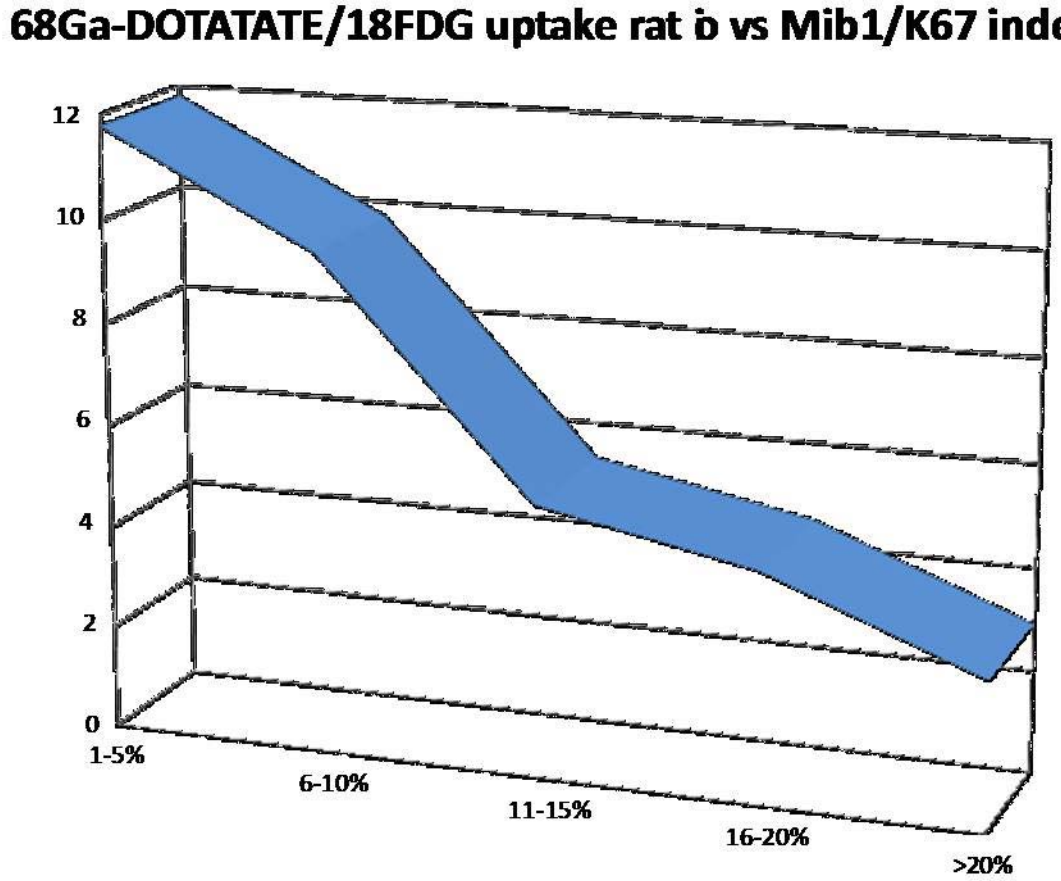

Fig 6. Graphical representation of the variation in the ^{68}Ga-DOTATATE to ^{18}F-FDG uptake ratio in relation to the increasing tumor proliferation (Mib1) index

7A.

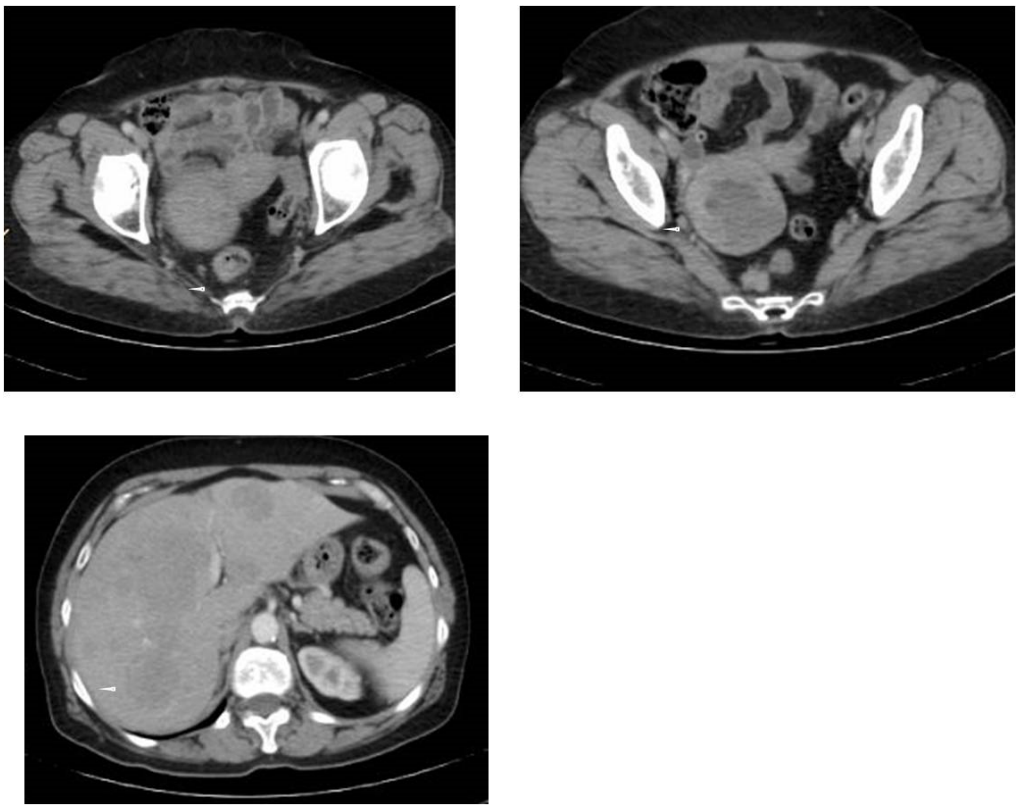

Fig 7A. 56 years old female, diagnosed as a case of metastatic NET. ceCT showed multiple hypodense liver lesions, abdominal nodes, multiple skeletal lesions, para-rectal node and a right adnexal mass. An irregular wall thickening was seen in the rectum, but was missed due to relative non enhancement of the lesion. In view of the histopathology, the patient was referred to us for ^{68}Ga-DOTATATE scan

7B.

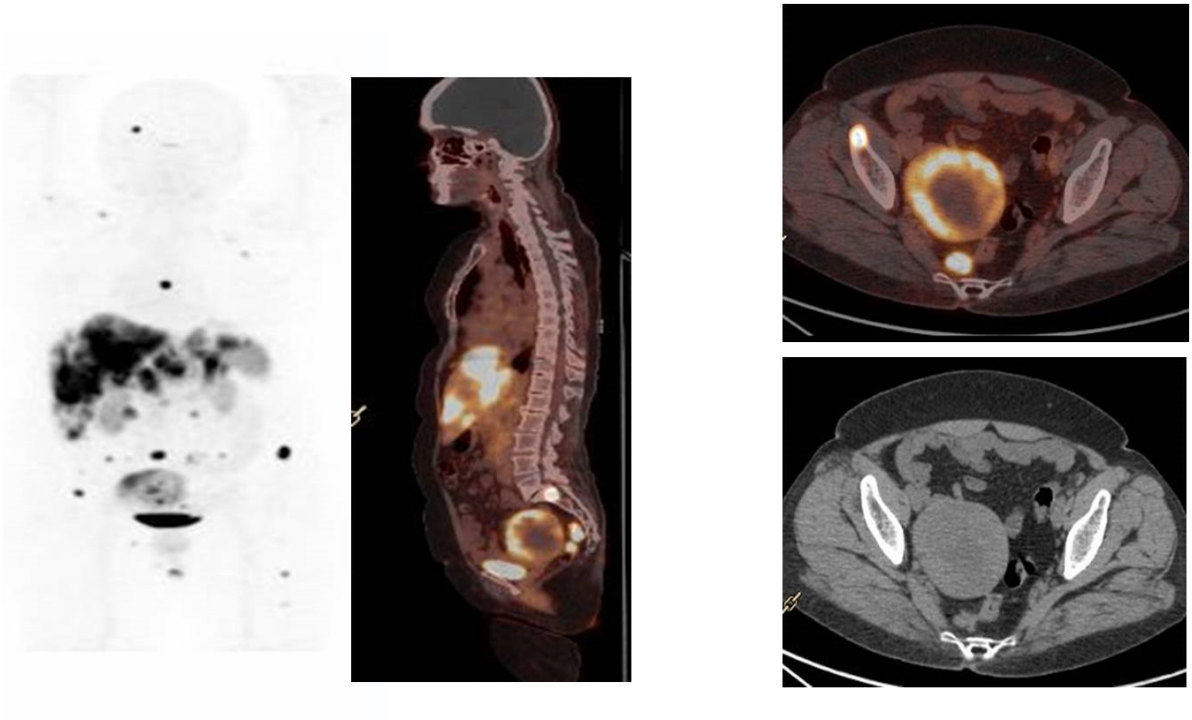

Fig 7B. ^{68}Ga-DOTATATE scan showed increased uptake in the rectal wall, left adnexal mass, pararectal node, muliple liver and skeletal lesions, thus confirming that this was a case of metastatic NET with a rectal primary.

7C

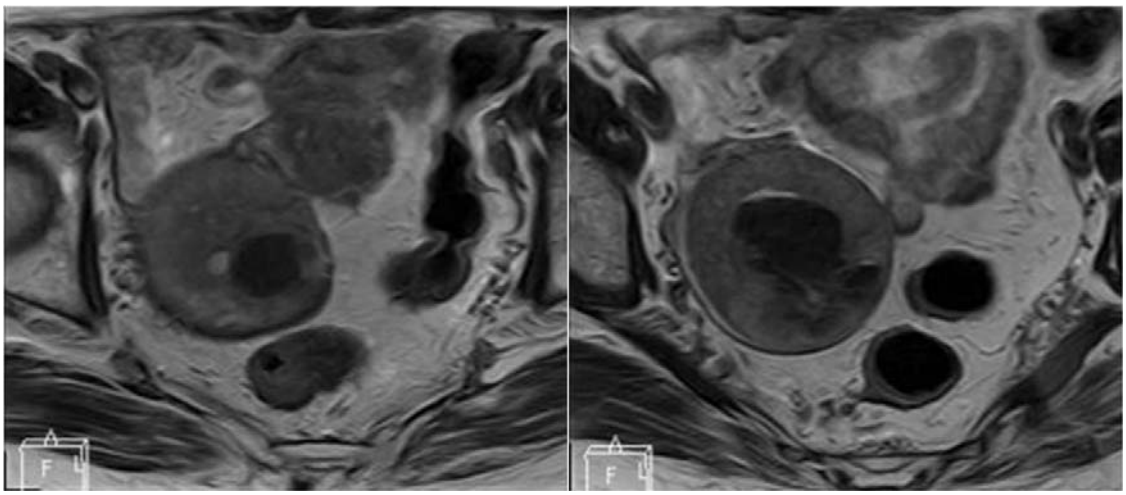

Fig 7C. Corresponding images of MRI pelvis: confirming the right adnexal mass and the rectal primary.