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Metachronous Adenocarcinoma of Lung in the setting of Metastatic Gastric Neuroendocrine Tumor: value of elucidating discordance on Dual Tracer PET/CT (^{18}F-FDG and ^{68}Ga-DOTATATE)

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ABSTRACT

Dual tracer PET/CT examinations (^{18}F-FDG/^{68}Ga-DOTATATE) have become an established practice in management of metastatic Neuroendocrine neoplasms (NENs) and demonstrates the advantages of deciphering the molecular PET characteristics of the tumor in patient management. Judicious elucidation of the findings is important, especially in scenarios of discordance with reported histopathology; this can lead to unsuspected diagnosis such as second primary malignancies (SPMs). Such diagnosis established in early disease course and mostly in an asymptomatic stage, provides patient a lead time for timely appropriate management. This concept is elaborated with a case-example of incidentally detected ^{18}F-FDG avid metachronous adenocarcinoma lung in a patient of metastatic well-differentiated gastric NEN, wherein dual tracer PET/CT assessment had demonstrated FDG avid but non-^{68}Ga-DOTATATE avid lung opacity.

INTRODUCTION

NENs comprise of heterogeneous group of tumors originating from neuroendocrine cells located at different sites and organs. Few reports have highlighted the link between NENs and associated SPMs *(1,2)*, with the prevalence of SPM ranging from 4% to 25% in different cohorts and observed preponderance of gastrointestinal, genitourinary, and breast malignancies, primarily in settings of gastrointestinal and pancreatic NENs. The utility of dual tracer PET/CT imaging (^{18}F-FDG and 68Ga-DOTATATE) in NENs is now evident (*3)*, providing multiple added merits such as understanding tumor biology, intra- and inter-tumoral heterogeneity, treatment decision-making and also rarely detecting multifocal primary NENs and SPMs. Discordant FDG+/SSTR- lesions, esp. in low-grade NEN, might correspond to a second primary or NET tumor heterogeneity. We herein present a case of metastatic gastric NEN in whom a metachronous primary lung malignancy was diagnosed totally out of suspicion by deciphering the discordance on dual tracer PET-CT finding in this asymptomatic patient.

The Case-Study

A 60 years-old-male, diagnosed of metastatic Grade II gastric NEN (giant excavating ulcer with elevated margin at greater curvature, on endoscopic biopsy turned out well-differentiated NEN, Ki-67: 5%), had received 2 cycles of ^{177}Lu-DOTATATE Peptide-Receptor Radionuclide Therapy (PRRT) (cumulative dose of 13.87Gbq) in view of progressive disease, and Krenning's Score 4 uptake in multiple hypodense liver lesions on ^{68}Ga-DOTATATE PET/CT (Fig-1).

The recent follow-up PET/CT with ^{68}Ga-DOTATATE showed somatostatin receptor (SSTR) expressing stable hepatic disease, but there was appearance of minimally SSTR expressing centimetre-sized ill-defined lung opacity at the upper lobe of the right lung, initially suspected as metastatic disease. The lesion was ^{18}F-FDG avid (Fig-2) (SUVmax:9.6). Considering this new lesion was not consistent with other hepatic metastatic lesions, a CT-

guided biopsy was considered. Subsequently, patient defaulted for more than 6 months and missed his appointments due to pandemic-related lockdown.

At the next visit, he was re-evaluated with dual tracer PET/CT (Fig-3) which showed SSTR expressing multiple (at least 4) hypodense liver lesions in both lobes of the liver, soft tissue mass at splenic hilum. ^{18}F-FDG-avid soft tissue density lesion with irregular margin in the upper lobe of the right lung and similar such new smaller lesion in the apical segment of right lung upper lobe were noted. While hypodense liver lesions and soft tissue lesion at splenic hilum were weakly ^{18}F-FDG-concentrating. Both SSTR avid hepatic lesions and FDG avid lung lesions showed an increase in size and tracer uptake, overall suggestive of disease progression (Fig-3). Considering discordant lung lesions (^{18}F-FDG-avid, non-SSTR-expressing), the possibility of metachronous primary lung malignancy was thought of. The larger right lung lesion was targeted with CT-guided biopsy and was found to harbour primary pulmonary adenocarcinoma on histopathology. On immunohistochemistry, tumor cells are positive for Thyroid Transcription Factor-1(TTF-1), while negative for synaptophysin. The patient was planned for a further PRRT cycle, with a referral to the thoracic oncologist who planned him for mutational analysis. The patient disease course remained symptomless till now for both malignancies.

DISCUSSION

The present report emphasizes the importance of dual tracer PET/CT examinations and their adequate analysis to decode the disease pathology. One report, also have reported utility of discordance in dual tracer PET/CT in diagnosis of triple negative breast carcinoma in a patient of NEN *4*. Few also have shown diagnosis of primary lung NEN in the scenario of metastasis with unknown primary *(5)*. This molecular PET imaging technique enables us to understand the tumor biology of the lesions non-invasively and can provide added benefits as demonstrated in this case.

In the presented case, dual tracer PET/CT findings raised suspicion for the noted lung lesion early in the disease course. This has potential to provide the patient with adequate lead time where curative intent would be feasible.

Conclusion

In summary, the case underscores the value of correlation of discordant findings in dual-tracer PET/CT in patients of NEN including biopsy where indicated. The attending physicians should be familiar to its variants and differentials while interpreting these studies.

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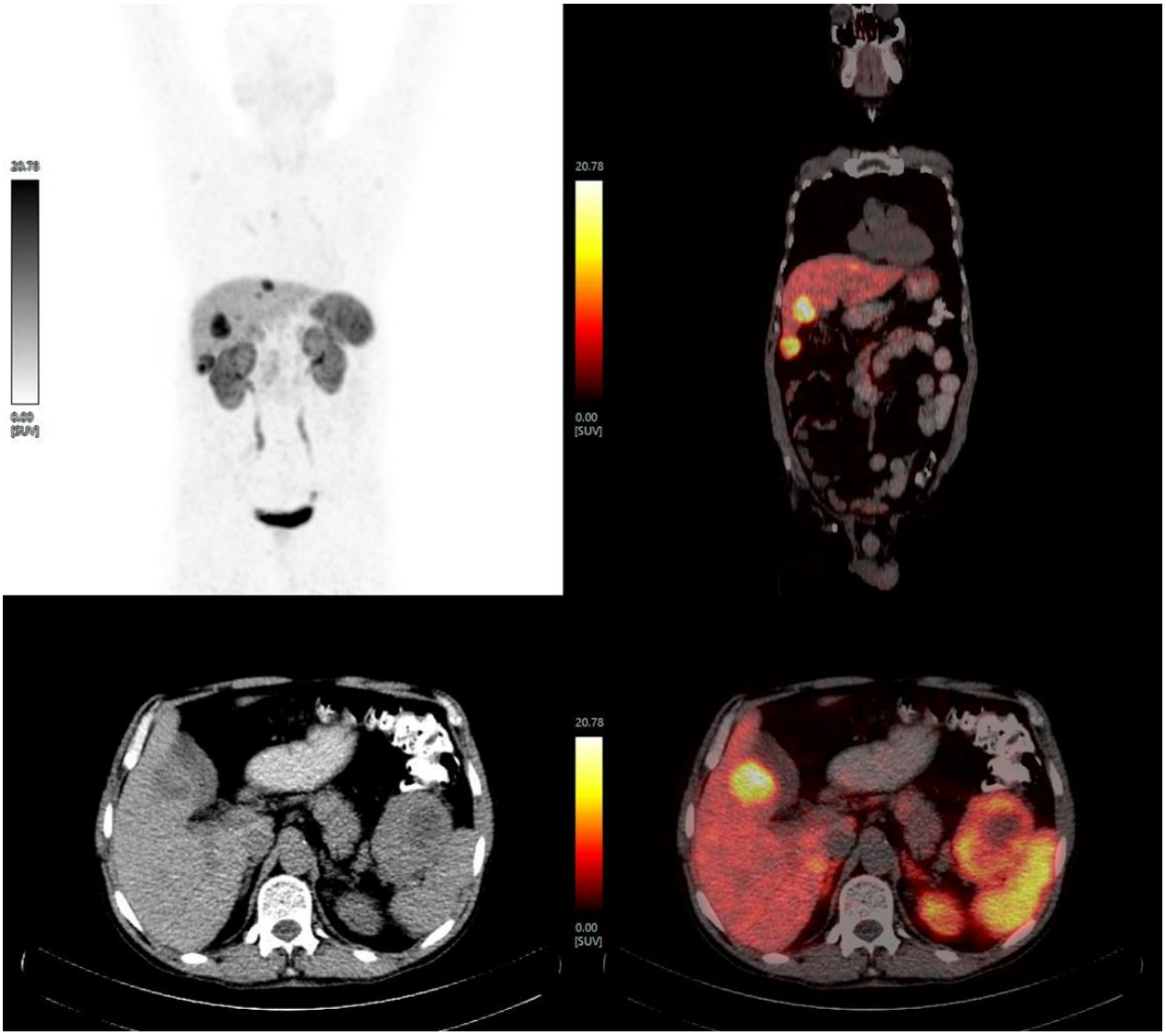

Figure-1: Baseline ^{68}Ga-DOTATATE PET/CT (MIP, fused coronal, transaxial slices) showing SSTR expressing multiple hepatic metastases (Liver segment V lesion)

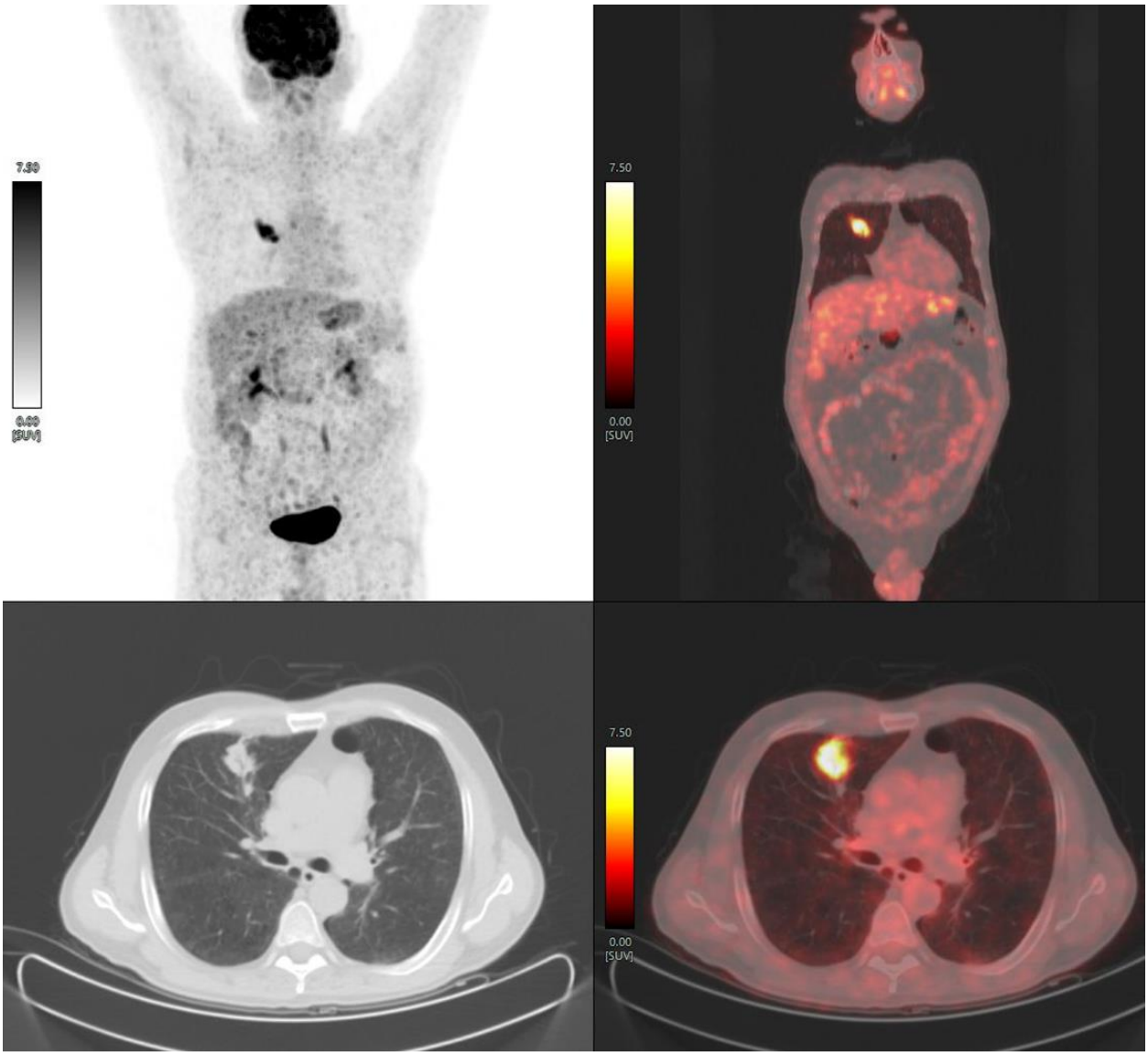

Figure-2: ^{18}F-FDG-PET/CT (post-2 cycles PRRT) (MIP, fused sagittal and transaxial slices) showing FDG concentrating (SUVmax:9.6) ill-defined lung opacity in upper lobe of right lung.

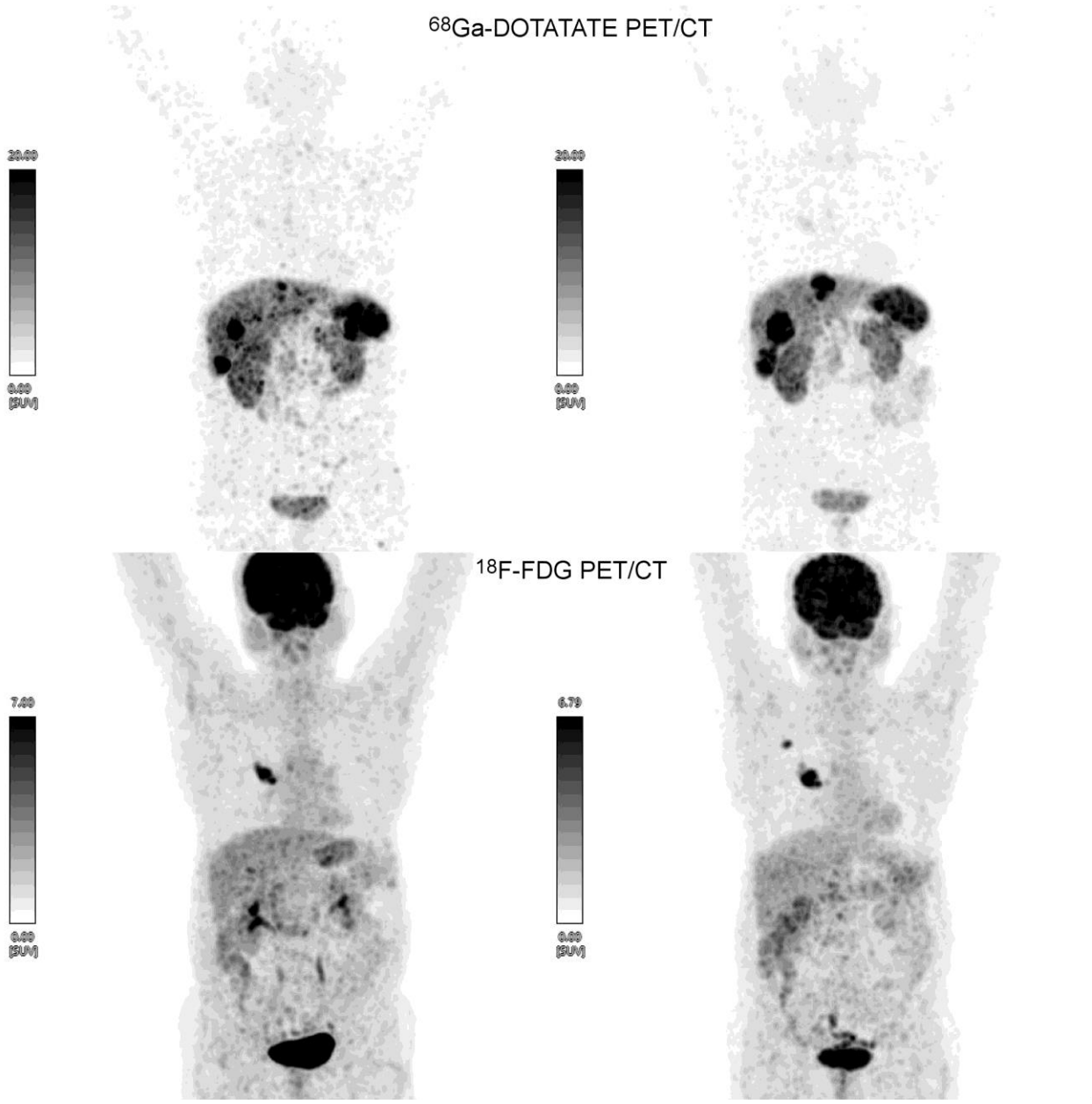

Figure-3: Follow-up dual tracer PET/CT MIP images undertaken 6 months apart (right panel later) showing disease progression in terms of increase in size and number of SSTR expressing hepatic lesions on ^{68}Ga-DOTATATE PET/CT (upper panel) and increase in size and number of FDG avid lung lesions on ^{18}F-FDG PET/CT (lower panel).

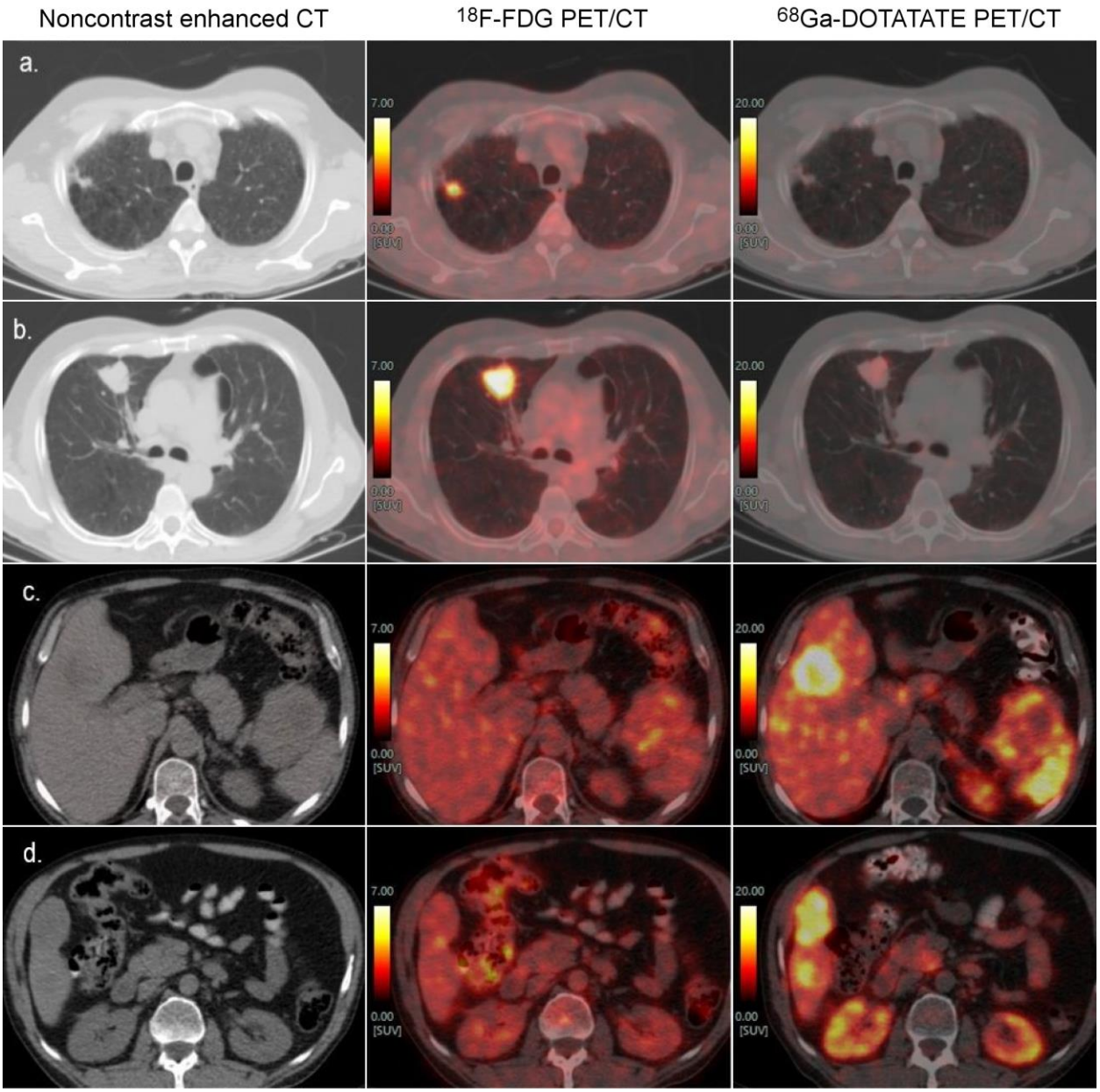

Figure-4: Follow-up dual tracer PET/CT (non-contrast CT, ^{18}F-FDG fused transaxial images and ^{68}Ga-DOTATATE fused transaxial images) showing FDG avid (SUVmax:10.9) and non-SSTR expressing (SUVmax:4.7) lung lesions in right upper lobe (a. and b.); non-FDG concentrating (SUVmax:2.8) and highly SSTR-expressing hypodense segment V lesion in the liver (SUVmax:29.4) and nodal mass at splenic hilum (c.) and similar non-FDG concentrating (SUVmax:2.4) highly SSTR-expressing hypodense segment VI lesion in the liver (SUVmax: 26.5).