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Original Article

Implications of fluorodeoxyglucose uptake in low-intermediate grade metastatic neuroendocrine tumors from peptide receptor radionuclide therapy outcome viewpoint: A semi-quantitative standardized uptake value-based analysis

ABSTRACT

Dual tracer positron emission tomography (PET) imaging approach (with ^{68}Ga-DOTATATE PET-computed tomography (CT) for somatostatin receptor and 18-fluorodeoxyglucose (^{18}FDG) PET-CT for glucose transporter receptor) plays a vital role in baseline differentiation, treatment decision-making, and prognostic assessment of neuroendocrine tumors (NETs). The aims of this study were to observe and compare the clinical behavior of low-/intermediate-grade NETs depending on their baseline FDG metabolism (calculated through pre-peptide receptor radionuclide therapy [PRRT] FDG standardized uptake value [SUV]) and to determine its prognostic importance in predicting extent of therapeutic response (post-PRRT) in terms of symptomatic, biochemical, and scan parameters along with the long-term impact on progression-free survival (PFS) and overall survival (OS). Fifty-nine patients with low ($\leq$2%) and intermediate (3–20% Mib-1/Ki-67 index) grade metastatic NET were selected for this retrospective analysis and divided into three groups: Group 1 consisted of patients having low-grade FDG uptake at baseline, predefined as SUV_{max} <5 (n = 13); Group 2 consisted of those having intermediate-grade FDG uptake at baseline, SUV_{max} 5–10 (n = 34), and Group 3 consisted of patients having high-grade FDG uptake at baseline, defined as SUV_{max} >10 (n = 12). The trend of FDG avidity was studied from the baseline till the time of analysis and the overall outcomes were compared in terms of symptomatic response (Karnofsky and ECOG performance score), biochemical response, scan response (anatomical and metabolic, RECIST 1.1 and PERCIST 1.0), PFS and OS. Patients in Groups 1 and 2 showed highest proportion of symptomatic complete response, biochemical partial response, and stable disease on scan. These patients also demonstrated better PFS and OS and lowest hazard ratio compared to patients in the Group 3. An important finding was a substantial fraction of the complete metabolic responders (CMRs) across the groups, achieved CMR within first 2 cycles of PRRT (85% of Group 1, 51% of Group 2, and 47% of Group 3). In conclusion, most of the patients of low-/intermediate-grade NET having low-to-moderate baseline tumor FDG metabolism ($SUV_{max} \leq 10$) showed favorable symptomatic response with good biochemical and anatomical disease control and were associated with prolonged PFS and OS, compared to that of those having high-grade baseline tumor FDG metabolism ($SUV_{max} > 10$).

Keywords: ^{177}Lu-DOTATATE, fluorodeoxyglucose-positron emission tomography/computed tomography, neuroendocrine tumor, peptide receptor radionuclide therapy, survival, treatment response, tumor grade

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INTRODUCTION

Neuroendocrine tumors (NETs) are tumors arising from peptide and amine producing cells which are diffusely distributed throughout the body. NETs are indolent tumors

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and patients are usually asymptomatic till late; however, by the time NETs are detected; majority of patients have progressed to a stage IV disease. NETs are classified into three grades based on proliferative index: Mib-1/Ki 67 index according to WHO (2017) criteria.[1] Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE has become a preferred treatment modality for patients of metastatic/advanced and inoperable well-differentiated NETs (G1 and G2: According to WHO classification of NET 2017[1] classified based on proliferative index-Ki-67/MiB-1 (%) and mitotic rate).

The definitive treatment is surgical;[2] however, in cases of inoperable or metastatic disease, PRRT has emerged as the treatment modality of choice. The pretreatment requisites of PRRT are a definitive histopathological diagnosis of NET (preferably with low-to-intermediate proliferative index) with good somatostatin receptor (SSTR) expression (at least equal to or greater than that of normal liver, Krenning score 2 or more) demonstrated on SSTR-based molecular imaging.

Dual tracer positron emission tomography (PET) imaging approach[3] with ^{68}Ga-DOTATATE (for SSTR expression) and 18-fluorodeoxyglucose (^{18}FDG) (for glucose transporter [GLUT] receptor to assess metabolic behavior) plays a vital role in baseline assessment followed by response evaluation and has well established benefits in therapeutic decision-making. The Grade 1 and Grade 2 NETs, which are the well and moderately differentiated respectively, show more SSTR expression as compared to the poorly differentiated (Grade 3) lesions. On FDG PET- computed tomography (CT), the trend is opposite with poorly differentiated/high-grade (G3) NETs usually showing high-grade or intense FDG uptake with low-grade SSTR expression (low DOTANOC/DOTATATE uptake and poor differentiation) and carry poor prognosis as compared to the well-differentiated tumors which show otherwise.[4] Hence, FDG uptake is often used as an important prognostic marker in these patients.

Furthermore, the baseline metabolic activity (FDG uptake) of low- and intermediate-grade tumors has prognostic implications; those with high-FDG metabolic activity show a poor response to PRRT alone in contrast to non-FDG avid tumors. In clinical practice, the attending physicians come across a number of patients having low-/intermediate-grade NETs (Ki 67 index ≤20%) showing high FDG avidity in spite of their low-/intermediate-proliferation characteristics, contradicting the expected functional imaging findings. The premise of the study was that it would be worthwhile to observe and analyze the tumor behavior in these groups of patients including studying the treatment outcome in a large volume PRRT setting.

MATERIALS AND METHODS

A total of 59 patients (35 males and 24 females) were retrospectively studied. Among these, 15 patients have undergone resection of the primary tumor and in 12 patients the site of the primary tumor was not known (unknown primary) [Table 1]. All patients had tumor uptake on the ^{68}Ga-DOTATATE (Krenning score 2 or more) and ^{18}FDG uptake (demonstrated on molecular imaging with PET CT scan) preceding the therapy. None of the patients had received prior treatment with other radiolabeled somatostatin analog(s) [Table 1].

PRRT was administered following the standardized regimen with mixed amino acid infusion protocol for renal protection.[5]

The inclusion criteria for this study analysis were as follows:
1. Biopsy proof of NET (either from the primary or the metastatic site)
2. Mib index/Ki 67 ≤20%
3. SSTR expression seen on molecular imaging (Krenning score 3 and above)
4. GLUT expression on FDG PET-CT scan
5. Received at least 3 cycles of PRRT.

We also retrospectively compared the metabolic behavior of the tumor on FDG PET-CT scan post PRRT with the baseline scan and studied the trend of FDG uptake in the lesions.[5]

Table 1: Demographic data

Total	59 Patients
Age	
Range	25-78 years
Mean	47.89 years
Sex	
Males	35
Females	24
MIB index	
G1 (</=2%)	27
G2 (3-20%)	22
Primary	
Pancreas	18 (30.51%)
Unknown	12 (20.34%)
Ileum	06 (10.17%)
Lung	06 (10.17%)
Duodenum	05 (08.47%)
Rectum	04 (06.78%)
Mesentry	02 (03.39%)
Stomach	02 (03.39%)
Jejunum	01 (01.69%)
Retroperitoneum	01 (01.69%)
Thymus	01 (01.69%)
Presacral mass	01 (01.69%)

The patients were divided into three groups based on their baseline metabolic activity, that is, standardized uptake values on ^{18}FDG WB PET-CT scan: Group 1 comprised of 13 patients who had baseline SUV_{max} <5; Group 2 included 34 patients having baseline SUV_{max} 5–10, and Group 3 comprised of 12 patients having baseline SUV_{max} >10.

The response to PRRT was analyzed and compared among the patients in the above-mentioned groups. The standard protocol for response evaluation using 3 scale response evaluation criteria:[6,7] symptomatic, biochemical, and scan (anatomical and metabolic) outcomes was followed. Symptomatic response evaluation was done in terms of Karnofsky/ECOG[8] performance score, biochemical response evaluation was done by assessing the percent decrease in the tumor markers (serum Chromogranin A and 24 h Urinary 5-HIAA), and anatomical/metabolic scan response evaluation was done using the RECIST 1.1 and PERCIST 1.0 guidelines. The response was documented as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) in accordance with the established guidelines for each category.

RESULTS

Post-PRRT response was assessed in all the three groups of patients with low-/intermediate-grade NETs and the following observations were derived.

Symptomatic response

Most of the patients with low-to-moderate baseline tumor metabolism (SUV_{max} up to 10 on FDG PET-CT; Groups 1 and 2) showed complete symptomatic response (CR). Among them, patients with tumor showing low-grade baseline FDG metabolism, SUV_{max} <5 (Group 1) showed highest symptomatic response, and CR was achieved in 85% of patients succeeded by those with moderate baseline FDG metabolism, SUV_{max} 5-10 (Group 2), where symptomatic CR was achieved in 68% of patients. About 8% of the patients showing low (Group 1) and 30% of those showing moderate (Group 2) baseline tumor FDG metabolism achieved PR. <3% of the patients in Group 2 showed symptomatically SD and none progressed except for one patient in Group 1 who showed symptomatic progression [Figure 1].

Patients with high baseline tumor metabolism SUV_{max} >10 (Group 3) showed a trend that subtly favored symptomatic progression with 33% patients showing symptomatic progression (PD). This was closely followed by symptomatic CR in 25%, PR in 25%, and SD in 17% [Figure 1].

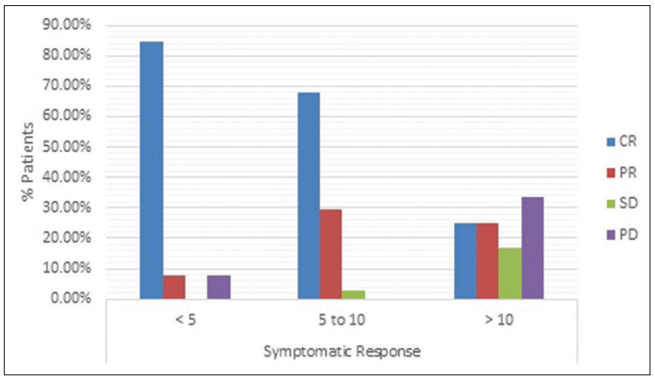

Figure 1: Post peptide receptor radionuclide therapy symptomatic response in three subgroups of patients of metastatic neuroendocrine tumors categorized based on fluorodeoxyglucose standardized uptake values

Biochemical response

Most of the patients with low-to-moderate baseline tumor metabolism (SUV_{max} up to 10 on FDG PET CT; Groups 1 and 2) showed CR and PR; however, the observed trend subtly favored partial biochemical response (PR) in both the groups with 54% in Group 1 and 47% in Group 2. CR was observed in 23% of the patients in Group 1 and in 32% patients in Group 2. <10% of patients in both these groups belonged to SD. As compared to the symptomatic response, larger proportion of patients showed biochemical progression with 12% of patients progressing in Group 1 and 15% in Group 2 [Figure 2].

Compared to these, most of the patients with high baseline tumor metabolism, SUV_{max} >10 (Group 3), showed biochemical progression with PD in 68% of patients. This was followed by biochemically SD in 17%, and less than 10% of the patients showed CR and PR [Figure 2].

Scan response

Anatomical response

Most of the patients with low-to-moderate baseline tumor metabolism (SUV_{max} up to 10 on FDG PET-CT; Groups 1 and 2) showed stable anatomical disease as per RECIST 1.1 guidelines with SD in 54% patients of Group 1 and in 59% patients of Group 2. About 37% patients in Group 1 showed PR and <10% progressed on scan, whereas in Group 2, PR was observed in 16% of patients and 23% progressed anatomically (in terms of size of lesion) [Figure 3].

Compared to these, most of the patients with high baseline FDG metabolism, predefined as SUV_{max} >10 (Group 3), showed anatomical progression with PD in 58% of patients. This was followed by SD in 33% and only <10% of patients showing PR. None of the enrolled patients showed anatomical CR except for a single patient in Group 2, who showed CR [Figure 3].

Metabolic response

Metabolic response was analyzed in terms of complete metabolic response (CMR) within first 2 cycles of PRRT and that attained after 3 or more cycles of PRRT. Most of the patients with low baseline tumor metabolism (SUV_{max} <5; Group 1) showed complete metabolic response with 62% of patients achieving CR in total, out of which 54% (85% of complete metabolic responders) achieving CR within first 2 cycles of PRRT. Among patients with moderate baseline tumor metabolism (SUV_{max} 5-10; Group 2), 47% showed CR and 24% (51% of complete metabolic responders) achieved CR within first 2 cycles of PRRT. Patients with high baseline tumor metabolism (SUV_{max} >10, Group 3) showed CMR in 17% of patients and of them 8% (47% of complete metabolic responders) achieved CR within first 2 cycles of PRRT [Figure 4].

Survival analysis

The OS curve was estimated for the total cohort of patients using the Kaplan–Meier product-limit method; point estimates and corresponding 95% confidence intervals (CI) were calculated for annual survival rates. The above shows that total 59 patients and 14 events/death has occurred in them [Figure 5].

The estimated mean survival was 79.33 months with 95% CI between 68.37 and 90.29 months in patients with low baseline tumor metabolism (SUV_{max} <5; Group 1), 72.74 months with CI between 63.96 and 81.53 months for moderate baseline tumor metabolism (SUV_{max} 5–10; Group 2), and 35.52 months with CI between 23.2 and 43.84 months for high baseline tumor metabolism (SUV_{max} >10; Group 3) [Figures 5 and 6].

Progression-free survival

The estimated mean progression-free survival (PFS) was 70.67 months with CI between 56.79 and 84.54 months for patients with low baseline tumor metabolism (SUV_{max} <5; Group 1), 69.24 months with CI between 59.77 and 78.71 months for moderate baseline tumor metabolism (SUV_{max} 5-10; Group 2), and 26.83 months with CI between

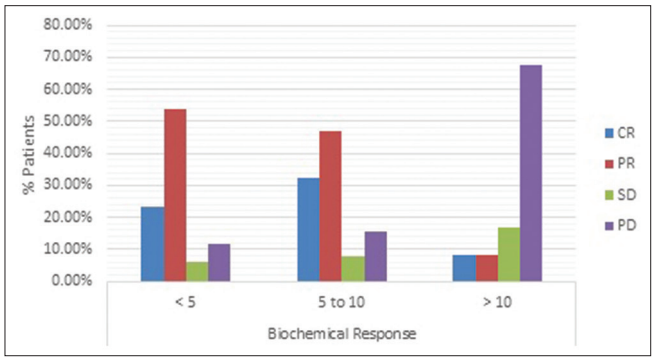

Figure 2: Post peptide receptor radionuclide therapy biochemical tumor marker response in three subgroups of patients of metastatic neuroendocrine tumors categorized based on fluorodeoxyglucose standardized uptake values

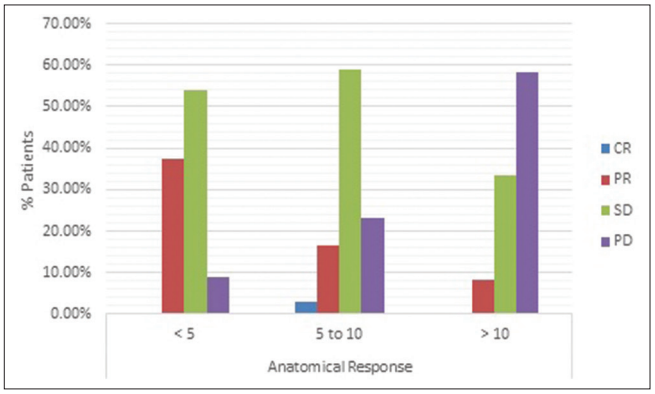

Figure 3: Post peptide receptor radionuclide therapy anatomical scan response in three subgroups of patients of metastatic neuroendocrine tumors categorized based on fluorodeoxyglucose standardized uptake values

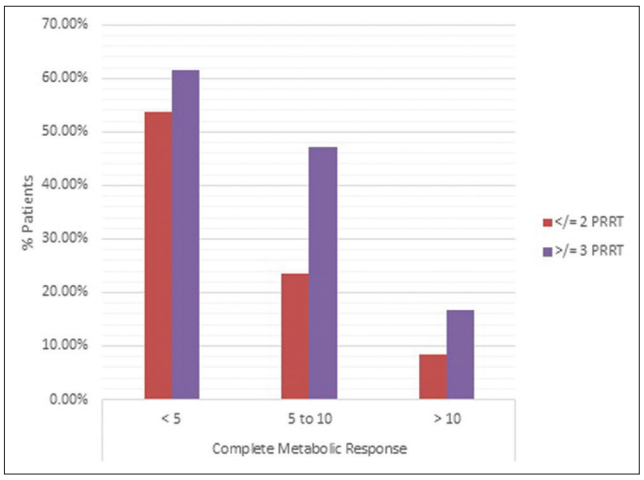

Figure 4: Post peptide receptor radionuclide therapy metabolic scan response in three subgroups of patients of metastatic neuroendocrine tumors categorized based on fluorodeoxyglucose standardized uptake values

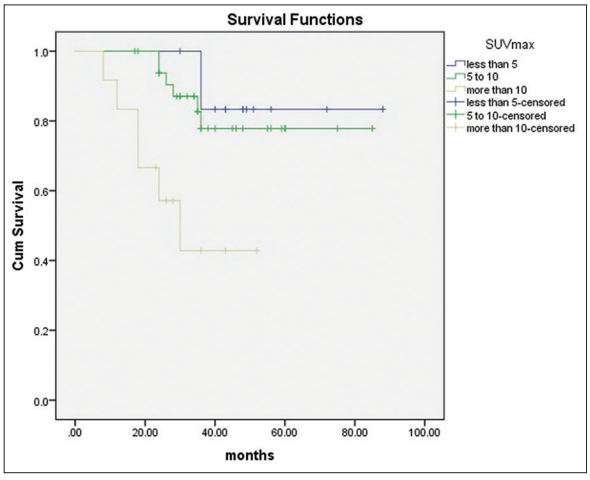

Figure 5: Overall survival curve for the total cohort of patients using the Kaplan–Meier product-limit method

17.07 and 36.59 months for high baseline tumor metabolism (SUV_{max} >10; Group 3) [Figures 7 and 8].

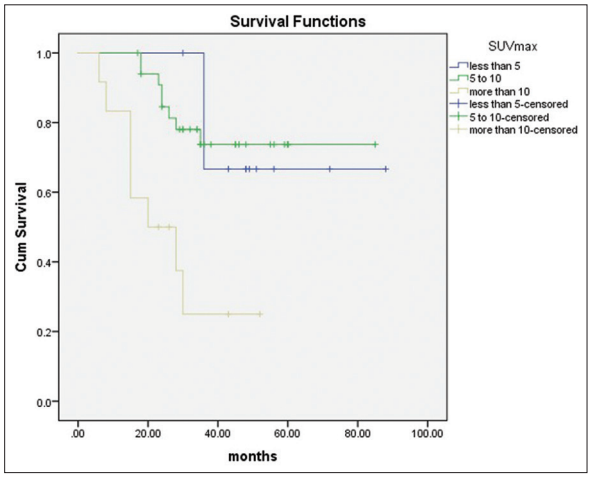

Figure 6: Progression-free survival curve for the total cohort of patients using the Kaplan–Meier product-limit method

DISCUSSION

SSTR-based imaging with ^{68}Ga-DOTATATE PET CT is most sensitive and specific modality of disease assessment in NET and for deciding on therapeutic intervention. ^{18}F-FDG forms an important adjunct to determine metabolic activity of the tumor and corresponds with the histological grade of tumor. High FDG uptake in tumor is associated with low level of tumor differentiation and hence low-SSTR expression.[9] Recent studies with larger number of patients tried to assess the synchronicity between tumor grade, glucose metabolism, and survival attributes in NET and inferred that high histological grades are associated with intense glucose metabolism,[4] aggressive tumor biology and higher risk of progression and death.[10] Hence, FDG avidity of the tumor has been considered to be of important prognostic value in predicting early progression and survival.[11]

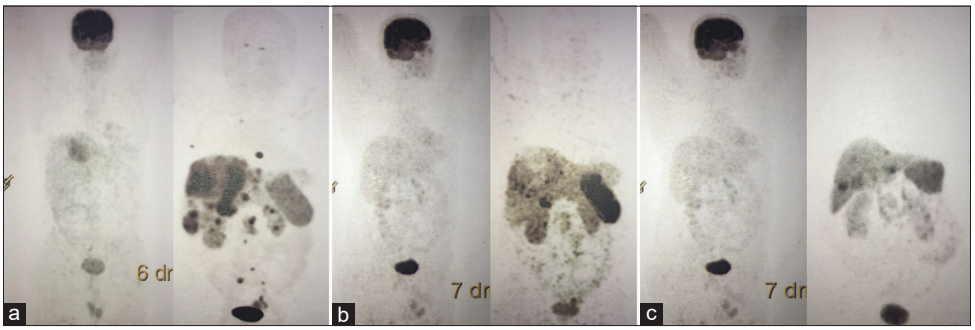

Figure 7: (a-c) ^{18}F-fluorodeoxyglucose and ^{68}Ga-DOTATATE positron emission tomography computed tomography at baseline and post second and sixth cycle of peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE. A 53-year-old-male, diagnosed in 2015 with metastatic neuroendocrine tumor (Grade II)* of unknown primary to liver and skeleton, had received 7 doses of long acting octreotide depot injections (before peptide receptor radionuclide therapy), with progressive disease and had low-grade fluorodeoxyglucose uptake (SUV_{max}: 4.69) on dual tracer positron emission tomography-computed tomography. A complete metabolic resolution on fluorodeoxyglucose positron emission tomography-computed tomography scan after second cycle of peptide receptor radionuclide therapy was observed and significant reduction in disease burden on ^{68}Ga-DOTATATE positron emission tomography computed tomography scan at the end of sixth cycle. Patient is being asymptomatic with normal tumor marker assay and is on biannual follow-up at present

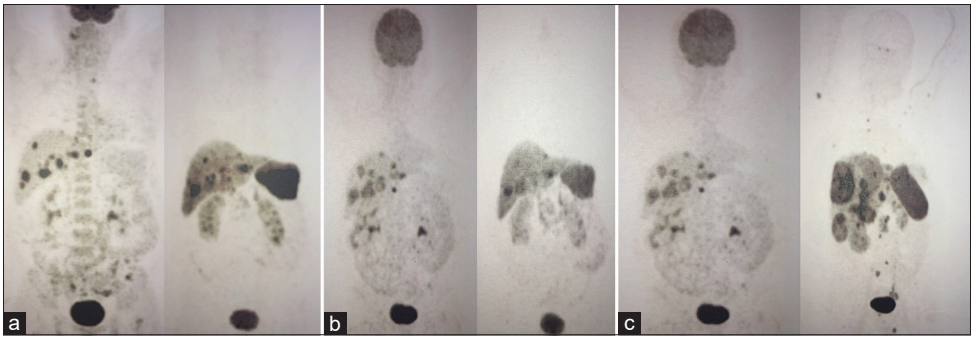

Figure 8: (a-c) Figure 7 (a-c), ^{18}F-fluorodeoxyglucose and ^{68}Ga-DOTATATE positron emission tomography computed tomography at baseline and post second and sixth cycle of peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE of another patient of *Grade 2 neuroendocrine tumor with liver and skeletal metastases, postresection of primary followed by local RT and chemotherapy and subsequently one dose of long-acting octreotide depot injection. Baseline positron emission tomography computed tomography scans show high grade metabolic activity as evident by relatively intense fluorodeoxyglucose uptake in liver and skeletal metastatic sites (SUV_{max} 14.98). Interim fluorodeoxyglucose and SSTR positron emission tomography computed tomography scans showed some response. However, the positron emission tomography computed tomography scans post sixth cycle of peptide receptor radionuclide therapy showed obvious disease progression. Tumor markers showed increasing trend and the patient complained of pain in abdomen and skeletal sites. Peptide receptor radionuclide therapy was withheld and the patient was referred to medical oncology facility

There has been a shift of the global consensus in management of NET toward a more personalised approach with the concept of dual tracer imaging with ^{68}Ga-DOTATATE and ^{18}F-FDG PET-CT scans.[6,12,13] The dual tracer imaging in NET is one of the most important criteria in devising the most appropriate and personalized therapeutic strategy and also for changing the on-going therapy protocol, particularly in cases of progression.[6,12,13]

Owing to the dynamic nature of tumor biology, the one-time diagnosis with histopathology may not suffice for the patients to be effectively stratified in the long run and the administered therapy could, in future be rendered ineffective. Moreover, the histopathological sections sampled may not represent the most aggressive part of the tumor. These challenges and limitations mandates that there should be a continuous track of tumor biology that has obvious prognostic and strategic advantages. SSTR imaging with ^{68}Ga-DOTATATE PET CT and metabolic behavior assessment with ^{18}F-FDG PET CT are useful modalities for noninvasive evaluation of the natural course of disease.

High FDG uptake of the tumors has been described in literature to strongly correlate with the low overall survival (OS) and one study showed that SUV_{max} >9 on FDG PET-CT is associated with early disease progression.[9] This reflected aggressive tumor biology and in such tumors, monotherapy with ^{177}Lu-PRRT alone has guarded benefits.[14] For such patients devising more aggressive therapy protocols, such as combining pharmacotherapy (with sandostatin analogs octreotide and lanreotide, interferons, and everolimus), chemotherapy (streptozocin, cisplatin, and etoposide), and radio sensitizers (capecitabine and temozolomide) with PRRT would be worthwhile. Another similar study indicated that uptake on FDG PET-CT is an independent prognostic factor in evaluating NET.[15]

In this study, we have evaluated the patients of low-/intermediate-grade (G1/G2) NET by stratifying them according to their baseline FDG uptake as low (SUV_{max} <5), moderate (SUV_{max} 5-10), and high (SUV_{max} >10). The patients with NETs having low-to-moderate baseline tumor metabolism (SUV_{max} up to 10 on FDG PET CT) showed excellent symptomatic response, with good biochemical control of the disease after PRRT suggesting therapeutic benefits. Most of the patients in these groups showed stable anatomical disease post-PRRT. However, there was significant difference in rate of achieving complete metabolic response (CMR) and the tumors with low baseline metabolism clearly scored over those with moderate baseline tumor metabolism and attained CMR within one or two PRRT cycles. The OS and PFS curves were placed close together for these two groups suggesting comparable survival outcomes post PRRT. The curve of PFS for tumors with moderate baseline metabolism is better than those with low baseline tumor metabolism could be due to statistical variation as there were less patients in Group 1 than Group 2.

The patients having high baseline tumor metabolism (SUV_{max} >10 on FDG PET-CT) showed higher percentage of symptomatic, biochemical, anatomical, and metabolic progression of the disease compared to the first two groups and, hence, were associated with unsatisfactory therapeutic outcomes post PRRT, reflected by the significantly low OS and PFS.

This retrospective study has certain inherent limitations, mainly because of small number of patients in the subgroups, due in part to the heterogeneity observed in the NETs, primary site of the tumor, different types of treatment before and during follow-up. The use of ^{177}Lu-based PRRT protocol (which due to lesser β energy and the range is somewhat less potent than its ^{90}Y based congener, especially in the larger lesions) could be another confounding factor; however, the positive points were a uniform examination and treatment protocol (with ^{177}Lu-DOTATATE) adopted in a single-center of the patients of Grade 1 and Grade 2 NET in the study.

CONCLUSION

This study illustrated that low-/intermediate-grade (G1/G2) metastatic NETs which show significant hypermetabolism at diagnosis, characterized by intense baseline FDG uptake (SUV_{max} >10) were associated with poor therapeutic benefits with PRRT alone and a substantial fraction of these patients can show disease progression, lowering the OS and PFS and, hence, are phenotypically similar to high grade (G3) tumors.

On the other hand, low-/intermediate-grade (G1/G2) NETs having low-or-moderate baseline tumor metabolism (SUV_{max} up to 10) were associated with favorable therapeutic outcomes post-PRRT with significantly prolonged survival benefits and delayed time to progression.

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Conflicts of interest
There are no conflicts of interest.

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