

Correlation of Somatostatin Receptor Expression by Qualitative and Quantitative Analysis of ^{18}F -FDG PET and Tumor Grading in Neuroendocrine Tumors and Their Association With Treatment Response to PRRT: A Prospective Observational Cross-Sectional Study

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Abstract

Background:

Although peptide receptor radionuclide therapy (PRRT) has become an established treatment for advanced neuroendocrine tumors (NETs), treatment response varies considerably among patients. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) reflects tumor glucose metabolism and biological aggressiveness and may provide prognostic information beyond conventional histopathological grading.

Objective:

To evaluate the correlation between pretreatment FDG PET/CT maximum standardized uptake value (SUVmax), tumor grade, and treatment response following PRRT in patients with metastatic or unresectable NETs.

Materials and Methods:

This prospective observational cross-sectional study included 50 histopathologically confirmed NET patients undergoing ^{177}Lu -DOTATATE/DOTANOC PRRT. Pretreatment FDG PET/CT was performed, and SUVmax was measured for representative lesions. Histopathological grading was determined using mitotic count and Ki-67 proliferation index. Patients were followed after PRRT and evaluated for symptomatic, biochemical, and objective imaging responses.

Results:

Among 41 patients with available histological grading, 19 (46%) had Grade 1, 17 (42%) Grade 2, and 5 (12%) Grade 3 tumors. Mean pretreatment SUVmax increased with increasing proliferation index and was highest in tumors with Ki-67 >20%. Patients with high SUVmax demonstrated poorer objective treatment responses. Low proliferation index was generally associated with better symptomatic and imaging outcomes, whereas patients with both high proliferation index and high SUVmax demonstrated the poorest treatment outcomes.

Conclusion:

Pretreatment FDG PET/CT SUVmax is a useful imaging biomarker of tumor aggressiveness and treatment response following PRRT. Combining metabolic imaging with histopathological grading may improve risk stratification.

Recommendation:

Pretreatment FDG PET/CT may be considered as a complementary tool for risk assessment and individualized treatment planning in patients undergoing PRRT.

Keywords: Fluorodeoxyglucose positron emission tomography/computed tomography; Maximum standardized uptake value; Peptide receptor radionuclide therapy; Ki-67 proliferation index; Neuroendocrine tumors.

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Introduction

Neuroendocrine tumours (NETs) are a broad category of tumours that originate from neuroendocrine cells found in the lungs, pancreas, gastrointestinal tract, and other organs. A subpopulation of NETs has rapid growth, early metastases, and poor prognosis, despite the fact that many of them have indolent clinical behaviour. Currently, the primary technique for determining tumour aggressiveness and directing treatment choices is histopathological grading based on mitotic count and Ki-67 proliferation index (1). Even tumours with the same histological grade exhibit significant heterogeneity, underscoring the need for more prognostic indicators. Using 18F-fluorodeoxyglucose (18F-FDG), positron emission tomography/computed tomography (PET/CT) has become a crucial functional imaging technique for assessing tumour metabolism (2).

Biologically aggressive tumours are characterised by higher glucose utilisation, and enhanced FDG uptake is linked to increased proliferative activity, dedifferentiation, and unfavourable clinical outcomes. FDG PET/CT offers supplementary information about tumour biology and metabolic activity, in contrast to somatostatin receptor imaging, which shows receptor expression and appropriateness for peptide receptor radionuclide therapy (PRRT) (3). FDG-positive NETs have been linked to shorter progression-free and overall survival, according to earlier research. Despite exhibiting variable degrees of FDG avidity, patients with metastatic NETs often undergo PRRT, and research on the prognostic importance of pretreatment SUVmax in predicting treatment response is still ongoing (4).

Prior to treatment, identifying individuals with metabolically aggressive disease may help with risk assessment, optimise treatment planning, and enhance clinical results. The current study assessed pretreatment 18F-FDG PET/CT SUVmax in patients receiving PRRT for metastatic or incurable

NETs and investigated its correlation with proliferation index and histological tumour grade (5). In order to determine the therapeutic value of FDG PET/CT as a prognostic imaging biomarker in neuroendocrine tumours, the study also evaluated whether metabolic activity measured by FDG PET/CT might predict symptomatic, biochemical, and objective imaging responses following PRRT (6).

Therefore, the present study aimed to evaluate pretreatment 18F-FDG PET/CT SUVmax in patients with metastatic, recurrent, or unresectable neuroendocrine tumors undergoing peptide receptor radionuclide therapy (PRRT) and to assess its correlation with the Ki-67 proliferation index and histopathological tumor grade. The study also

aimed to determine whether pretreatment metabolic activity measured by 18F-FDG PET/CT was associated with symptomatic, biochemical, and objective imaging responses following PRRT.

Materials and Methods

Study Design

This was a **prospective observational cross-sectional study** conducted among patients with histopathologically confirmed metastatic, recurrent, or unresectable neuroendocrine tumors (NETs) who were referred for peptide receptor radionuclide therapy (PRRT). A total of 50 patients who fulfilled the predefined eligibility criteria were included in the study. Histopathological grading was confirmed by review of available pathology records and pathology slides, including assessment of the Ki-67 proliferation index.

Study Setting

The study was conducted at the **Radiation Medicine Centre, Bhabha Atomic Research Centre, Mumbai**, a specialized tertiary-care nuclear medicine facility providing diagnostic and therapeutic nuclear medicine services. The centre provides molecular imaging and radionuclide-based therapeutic services, including somatostatin receptor imaging and peptide receptor radionuclide therapy for patients with neuroendocrine tumors. Patients with metastatic, recurrent, or unresectable NETs referred for PRRT were evaluated using appropriate nuclear medicine imaging and clinical assessment before treatment.

Study Population

The study included 50 patients with histopathologically confirmed metastatic, recurrent, or unresectable NETs who were referred for ¹⁷⁷Lu-DOTATATE or ¹⁷⁷Lu-DOTANOC PRRT. Histopathological grading was confirmed by review of pathology slides, including the Ki-67 proliferation index.

Inclusion Criteria

Patients were included if they met the following criteria:

- Histologically confirmed neuroendocrine tumor.
- Metastatic or unresectable disease.
- Eligibility for PRRT.
- Availability of pretreatment 18F-FDG PET/CT.
- Adequate clinical follow-up.

Exclusion Criteria

Patients were excluded if they had:

- Incomplete PET imaging.
- Missing histopathological grading.
- Loss to follow-up.

PET/CT Imaging

Whole-body **¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT)** was performed according to the institutional protocol before PRRT. The maximum standardized uptake value (SUVmax) was measured in representative tumor lesions and was used as the quantitative measure of tumor metabolic activity.

PRRT

Patients underwent **¹⁷⁷Lu-DOTATATE or ¹⁷⁷Lu-DOTANOC** therapy according to institutional guidelines. Patients were followed clinically and radiologically after each treatment cycle.

Response Assessment

Treatment response was assessed using three parameters:

1. **Symptomatic response**
 2. **Biochemical response**, based on serum Chromogranin-A levels
 3. **Objective imaging response**, based on changes in lesion size and SUVmax.
- Patients were categorized as having partial response, stable disease, or progressive disease according to the available clinical and imaging assessments.

Bias

Potential sources of selection and information bias were addressed by applying predefined inclusion and exclusion criteria consistently to all patients. Standardized institutional protocols were used for 18F-FDG PET/CT imaging and SUVmax assessment. Histopathological grading was based on available pathology records and review of pathology slides, including the Ki-67 proliferation index. Treatment response was assessed using predefined symptomatic,

biochemical, and objective imaging parameters. Patients with incomplete PET imaging, unavailable histopathological grading, or inadequate follow-up were excluded according to the predefined exclusion criteria.

Study Size

A total of **50 patients** were included in the study.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were expressed as frequencies and percentages. Associations between SUVmax, tumor grade, proliferation index, and treatment response were evaluated using appropriate statistical tests. Statistical significance was defined as **$p < 0.05$**

Results

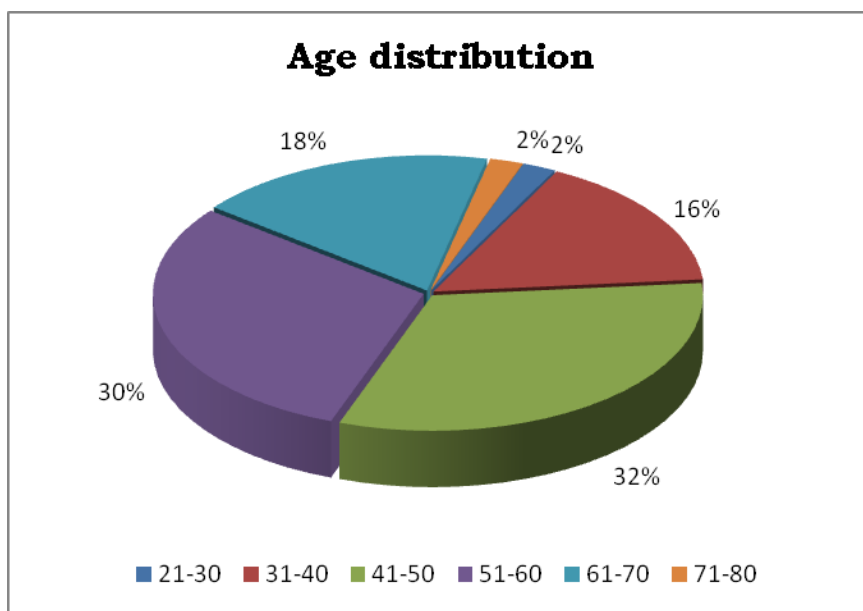
During the study period, patients with histopathologically confirmed metastatic, recurrent, or unresectable neuroendocrine tumors who were referred for PRRT were assessed for eligibility. Patients meeting the predefined inclusion criteria were enrolled in the study, while those with incomplete PET imaging, missing histopathological grading, or inadequate follow-up were excluded. A total of **50 patients were included in the final analysis.**

The study population comprised 50 patients. The largest proportion of patients belonged to the 41–50-year age group, followed by the 51–60-year age group. The age-wise distribution of the patients is presented in Table 1 and Figure 1.

Table1: Distribution of cases according to age group

Age group	Number of cases
21-30	1
31-40	8
41-50	16
51-60	15
61-70	9
71-80	1

Fig 1: Distribution of cases according to Age group



Among the 50 patients, 37 were male, and 13 were female, indicating a male predominance. The distribution of patients according to gender and age group is presented in Table 2 and Figures 2a and 2b.

Table 2: Distribution of cases according to Gender

Age Group	No of Patients	
	Male	Female
21-30	1	0
31-40	4	4
41-50	11	5
51-60	12	3
61-70	8	1
71-80	1	0
Total	37	13

Fig 2a: Distribution of patients according to Gender

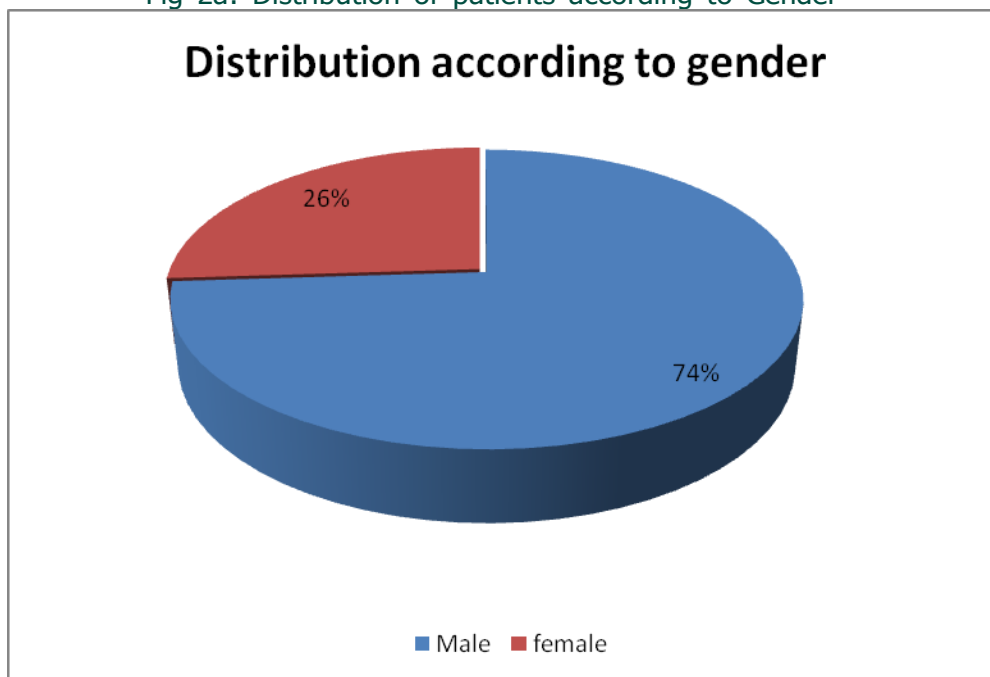
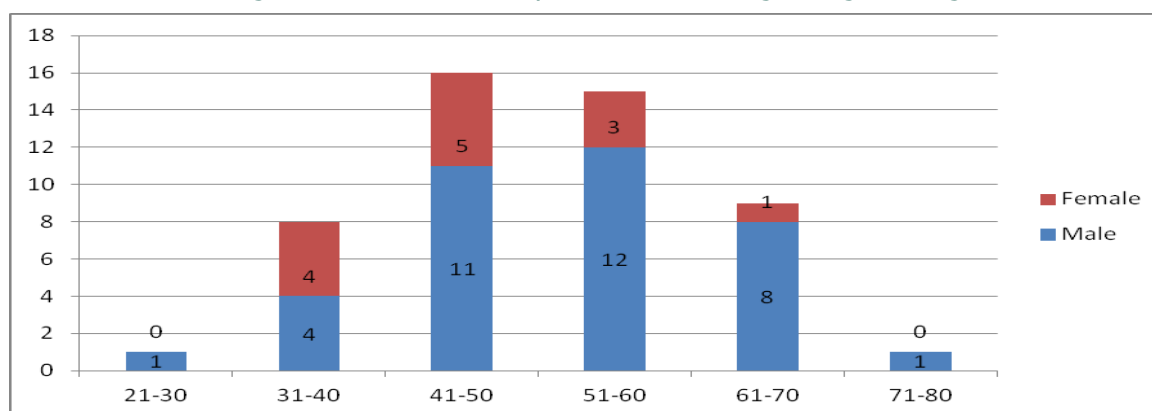


Fig 2b: Distribution of patients according to age and gender



Gastroenteropancreatic neuroendocrine tumour (GEP-NET) constituted the majority of cases (58%), with a few cases under Thoracic Neuroendocrine Tumours (12%) and a case of Medullary carcinoma of the thyroid. The remaining cases were metastatic neuroendocrine tumours with unknown primary (28%). Among the GEP-NET, the pancreas was the

most common primary site. Small intestine was the next common site of primary neoplasm. Gastroenteropancreatic neuroendocrine tumors constituted the majority of cases, followed by tumors with an unknown primary site and thoracic neuroendocrine tumors. The distribution of patients according to diagnosis is presented in Table 3 and Figure 3

Table 3: Distribution of cases according to Diagnosis

Diagnosis	No of Cases
GEP- NET	29
THORACIC NET	6
MCT	1
UNKNOWN PRIMARY	14

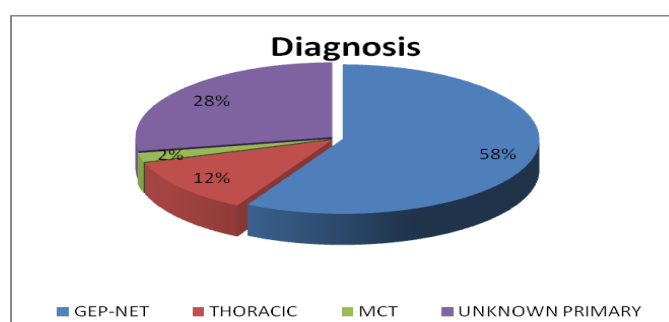


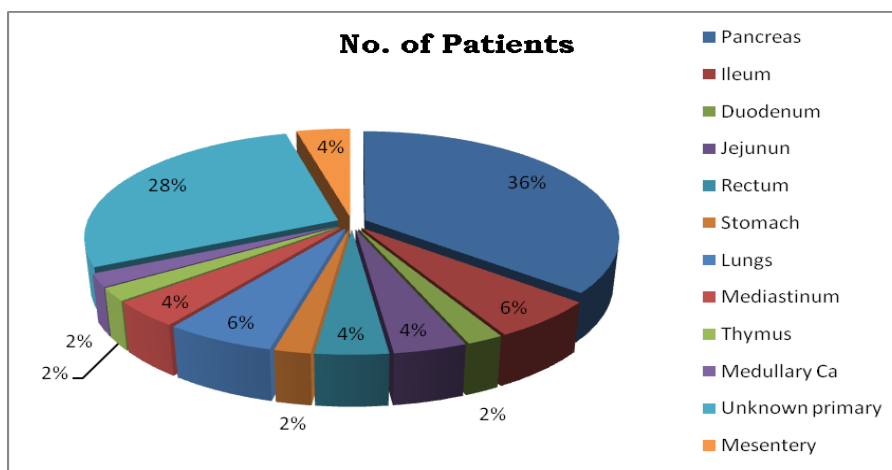
Fig 3: Distribution of cases according to Diagnosis

The pancreas was the most common primary site of neuroendocrine tumors, followed by the ileum and other gastrointestinal and thoracic sites. Fourteen patients had an unknown primary site. The distribution according to the site of the tumor is presented in Table 4 and Figure 4.

Table 4: Distribution of cases according to the site of NET

Site of NET	No of Cases
Pancreas	18
Ileum	3
Duodenum	1
Jejunum	2
Rectum	2
Stomach	1
Lungs	3
Mediastinum	2
Thymus	1
Medullary carcinoma	1
Unknown primary	14
Mesentery	2

Fig 4: Distribution of cases according to the site of NET



Histopathological grade was available for 41 cases, of which 19 were G1 tumours. G2 constituted 17 cases, and 5 cases were of G3. All the primary cases with G3 histopathology were in the pancreas. Histopathological grading was available for 41 patients. Grade 1 tumors were the most frequent, followed by Grade 2 and Grade 3 tumors. The distribution of patients according to tumor grade is presented in Table 5 and Figure 5.

Fig 5: Distribution of cases as per the grade of NE

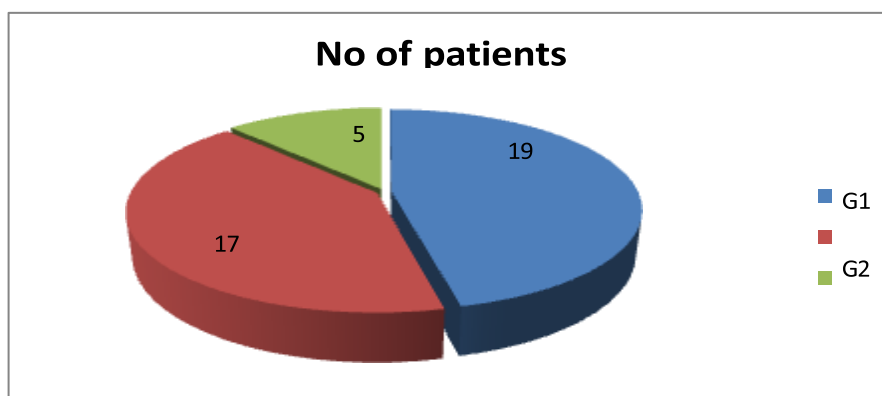


Table 5: Distribution of cases as per the grade of NET

Grade	G1	G2	G3
Number of cases	19	17	5

The distribution of patients according to proliferation index showed that the largest group had a proliferation index of <3%, followed by the 3–10% group. Smaller numbers of patients had proliferation indices of 11–20% and >20%. The distribution is presented in Table 6 and Figure 6.

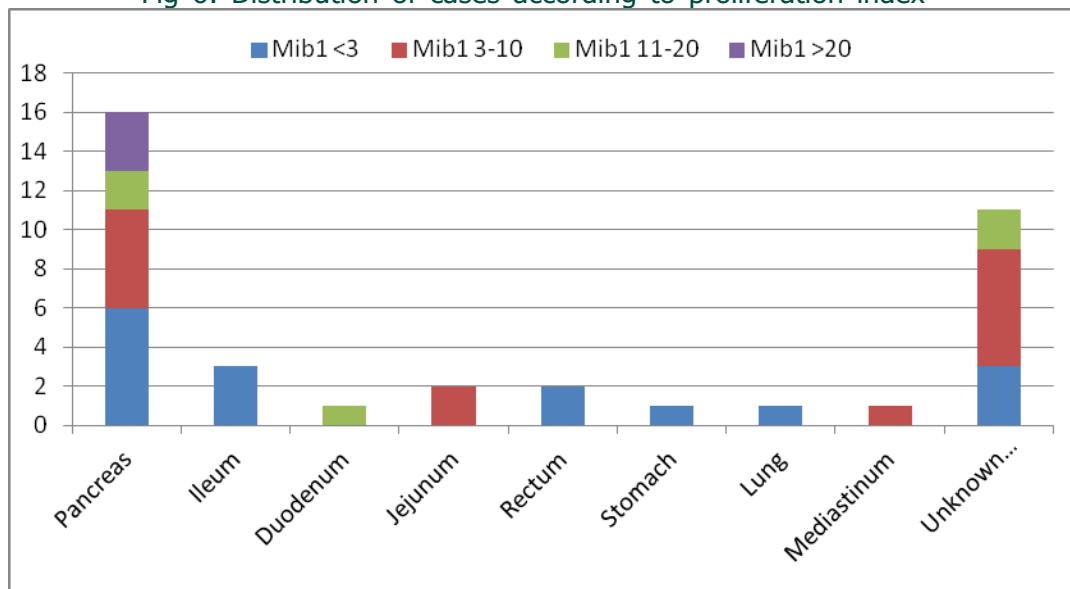
Table 6: Distribution of cases according to proliferation index

Site of NET	Proliferation index %			
	<3	3-10	11-20	>20
Pancreas	6	5	2	3
Ileum	3			
Duodenum			1	
Jejunum		2		
Rectum	2			
Stomach	1			
Lung	1			
Mediastinum		1		
Unknown primary	3	6	2	
Total	16	14	5	3

Proliferation index was not available for 2 cases with a primary tumour in the pancreas, 2 cases with unknown primary, one each of mediastinum, thymus, medullary carcinoma, lung and ileum. Cases were grouped into four categories according to the proliferation index: <3%, 3-10%, 11-20% and >20%. 16 cases had a low proliferation index, 19 had an

intermediate proliferation index, and 3 cases showed a high proliferation index. Those with an intermediate proliferation index were again split into two groups with 3-10% and 11-20% proliferation index to look for any difference in behavior in terms of the HYNIC TOC lesion index, SUVmax, and response to PRRT.

Fig 6: Distribution of cases according to proliferation index

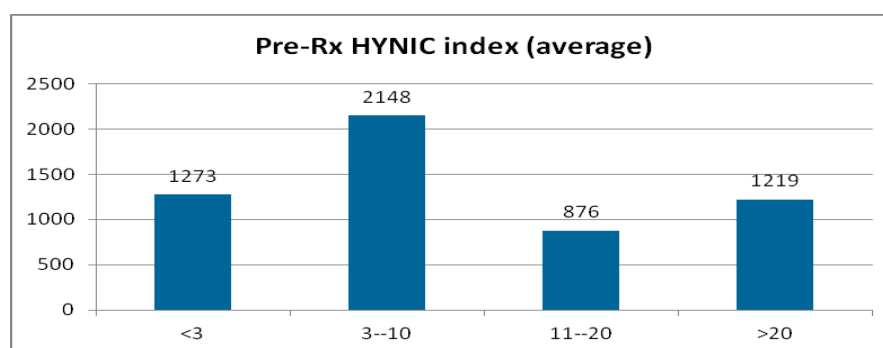


The average pretreatment ^{99m}Tc -HYNIC-TOC lesion index varied across the proliferation-index groups. In contrast, the average pretreatment ^{18}F -FDG SUVmax showed an increasing trend with increasing proliferation index, with the highest average SUVmax observed in the >20% group. These findings are presented in Table 7 and Figures 7a and 7b.

Table 7: Comparison of proliferation index, average pre-therapy ^{99m}Tc -HYNIC TOC lesion index and average pre-therapy ^{18}F -FDG SUVmax of lesions (n=30)

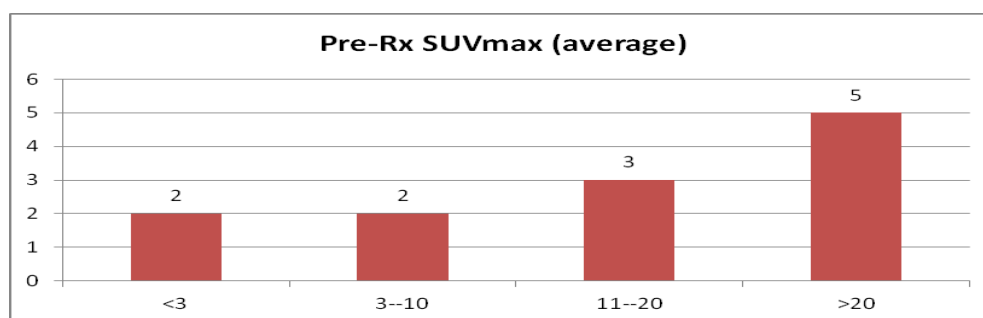
Proliferation Index	Average pre-Rx HYNIC Index	Average preRx SUVmax
<3	1273	5.6
3-10	2148	6.4
11-20	876	6.1
>20	1219	10.7

Fig 7a: Comparison of proliferation index and average pre-therapy ^{99m}Tc -HYNIC TOC lesion index (n=30)



Heterogeneity of the lesions causes variable ssr expression, hence the HYNIC TOC uptake.

Fig 7b: Comparison of proliferation index and average pre-therapy ^{18}F -FDG SUVmax of lesions (n=30)



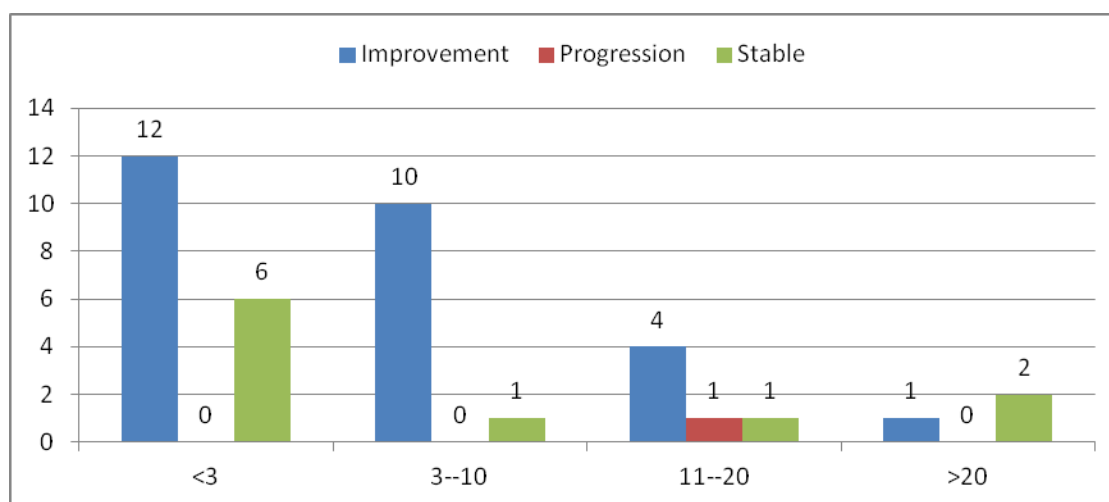
All the cases included in the study were referred for PRRT, and all of them had positive SSTR expression in the tumour. The average pre-therapy HYNIC TOC lesion index was highest in the group of cases with 3-10% proliferation index and was the lowest in the group with 11-20% proliferation index. Average pre-treatment lesion SUVmax showed an increasing trend with the increase in proliferation

index. Treatment response varied across the different proliferation-index groups. Lower proliferation-index groups generally showed more favorable symptomatic and objective imaging responses, whereas higher proliferation-index groups demonstrated a greater frequency of progressive disease. The findings are presented in Table 8 and Figures 8a–8c.

Table 8: Proliferation index vs. response

Prol. Index	Symptomatic response			Biochemical response			Objective(scan) response		
	Improvement	Progression	stable	Partial	Progression	stable	Partial	Progression	stable
<3	12 (66.6%)	0	6 (33.3%)	4 (22.2%)	11 (61.1%)	3 (16.6%)	6 (42.8%)	2 (14.3%)	6 (42.8%)
3-10	10 (90.9%)	0	1 (9.1%)	4 (36.4%)	4 (36.4%)	3 (27.2%)	4 (30.7%)	5 (38.5%)	4 (30.7%)
11-20	4 (66.6%)	1 (16.6%)	1 (16.6%)	3 (50.0%)	2 (33.3%)	1 (16.6%)	1 (16.6%)	4 (66.6%)	1 (16.6%)
>20	1 (33.3%)	0	2 (66.6%)	1 (50.0%)	1 (50.0%)	0	0	2 (66.6%)	1 (33.3%)

Fig 8a: Proliferation index vs. symptomatic response



Symptomatic response was available in 18 cases in the <3% proliferation index group. There was no case with progression of symptoms in this group. 12 (66.66%) out of 18 cases showed improvement in symptoms after treatment. The remaining 6 cases (33.33%) showed no change in symptoms after treatment. In those cases with a proliferation index of 3-10%, 10 out of 11 cases (90.90%) showed improvement in symptoms, and the remaining one patient didn't have a significant change in symptoms.

In the group with a 11-20% proliferation index, 4 out of 6 patients (66.66%) had a good symptomatic

response. Of the remaining 2 patients, one had worsening symptoms, and the other didn't have much improvement in symptoms. Among the cases with a proliferation index >20%, 1 out of 3 (33.3%) showed symptomatic improvement. There was no improvement in symptoms for the remaining two cases (66.6%).

Symptomatic improvement was more in the cases with low proliferation index (<10%). High proliferation index was associated with worsening of symptoms, even though the number of cases was less.

Fig 8b: Proliferation index vs. biochemical response



Biochemical response was available in 18 cases with a proliferation index of <3%; 4 cases (22.22%) showed good biochemical response, 11 (61.11%) had progression, and 3 (16.6%) were stable. In the group of cases with a proliferation index of 3-10%, 4 out of 11 cases (36.4%) had improvement, 4 (36.4%) had progression, and 3 (27.2%) had stable disease. In the group of cases with a proliferation index of 11-20%, 3 (50%) out of 6 showed improvement, 2

(33.3%) showed progression, and 1 case (16.6%) showed stable disease. In those cases where the proliferation index was high (>20%), 1 out of 2 cases showed improvement; the other case showed progression.

The biochemical response showed progression in 61.11% of cases with a <3% proliferation index when compared to 30% in the 3-10% group and 33.3% in the 11-20% group.

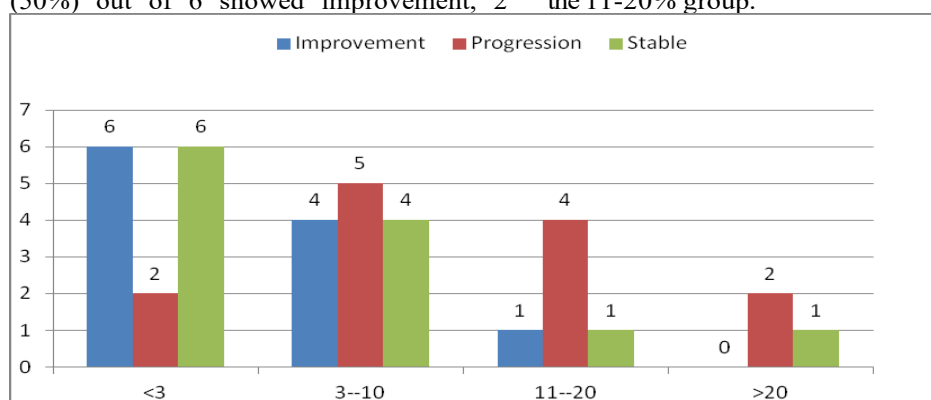


Fig 8c: Proliferation index vs. objective (scan) response

In the 14 cases with a proliferation index <3%, 6 cases (42.85%) showed improvement in the scan, 2 cases (14.28%) showed progression of disease, and 6 cases (42.85%) showed stable disease. Cases with a proliferation index of 3-10% showed improvement in 4 (30.76%) out of 13 cases, progression in 5 (38.46%) cases, and stable disease in 4 (30.76%) cases. In 5 cases in the group with a proliferation index of 11-20%, 1 (16.6%) case showed improvement,

4 (66.6%) cases showed progression, and 1 (16.6%) case showed stable disease. In the fourth group of cases with a proliferation index >20%, 2 (66.6%) out of 3 showed progression, and 1 case (33.3%) showed stable disease. Scans didn't show any improvement in the cases with a proliferation index above 11%

Improvement or stable disease was more common in cases with a low proliferation index (<10%) when

compared to those cases with a higher proliferation index (>10%), where the rate of progressive disease was high.

The lesion SUVmax ranged from 2.28 to 18.5 g/ml in the cases included in this study. Average SUVmax was 11.0065. The values <5, 5-10, and >10 were chosen as low, intermediate, and high SUVmax, arbitrarily. Cases were grouped according to the proliferation index and

¹⁸F-FDG SUVmax, and the treatment response was assessed in each group. Cases showing concordance were grouped into two:

with low proliferation index and low SUVmax
with high proliferation index and high SUVmax

Those cases where there was no concordance were grouped into 4 categories:

with low proliferation index and high SUVmax

with high proliferation index and low SUVmax

with moderate proliferation index (3-10%)

with moderate proliferation index (11-20%)

Cases showing concordance between proliferation index and

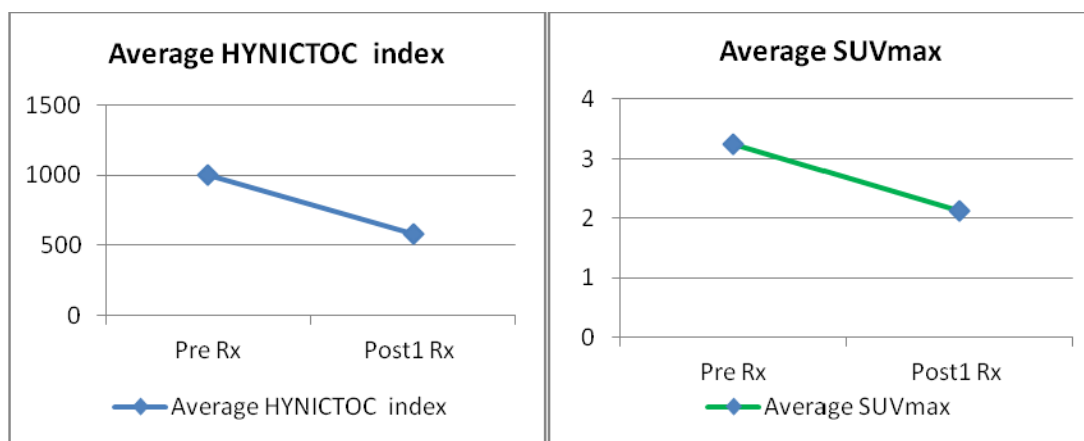
¹⁸F-FDG SUVmax

Patients with a low proliferation index and low ¹⁸F-FDG SUVmax generally demonstrated favorable symptomatic and imaging outcomes. The average SUVmax decreased following treatment, while most patients showed symptomatic improvement or stable disease on imaging. The findings are presented in Tables 9a–9c and Figures 9a–9b

Table 9a: Cases with low proliferation index low ¹⁸F-FDG SUVmax (n=8)

	PreRx	Post 1
Avg HYNIC TOC index	998	577.8
Avg SUVmax	3.25	2.124

Fig 9a: Cases with low proliferation index and low ¹⁸F-FDG SUVmax



The low proliferation index cases with low SUVmax showed a fall in the average SUVmax in the post-therapy scans.

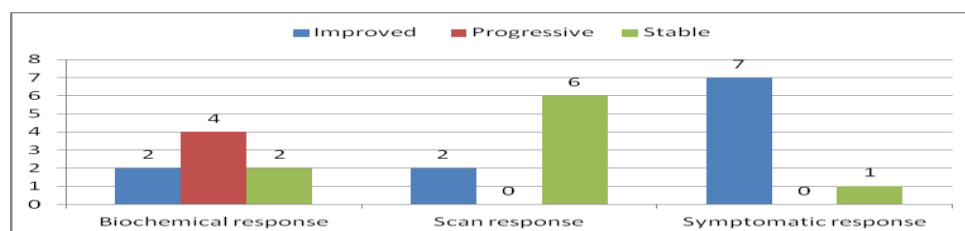
Table 9b: Cases with low proliferation index and low ^{18}F -FDG SUVmax

Proliferation index %	^{18}F -FDG SUVmax-Pre Rx	Response		
		Biochemical	Scan	Symptomatic
1	No lesion	Improvement	Stable	Improvement
2	No lesion	Progressive	Stable	Improvement
1-2	No lesion	Progressive	Stable	Improvement
2	No lesion	Progressive	Stable	Improvement
1-2	4.82	Stable	Improvement	Improvement
<2	4.05	Progressive	Stable	Improvement
1-2	No lesion	Improvement	Stable	Improvement
<2%	5.77	Stable	Improvement	asymptomatic from beginning

Table 9c: Low proliferation index low ^{18}F -FDG SUVmax -summary

Total:8 cases	Improvement	Progression	Stable
Biochemical	2	4	2
Scan	2	0	6
Symptomatic	7	0	1

Fig 9b: Cases with low proliferation index and low ^{18}F -FDG SUVmax



In this group with low proliferation index and low-grade FDG uptake, biochemical response showed improvement in 2 (25%) out of 8 cases, progressive disease in 4 (50%) cases, and stable response in 2 (25%) cases. Scan showed improvement in 2 (25%) out of 8 cases and stable disease in 6 (75%) of cases. Symptomatic response showed improvement in 7 (87.5%) out of 8 cases, and 1 case showed stable symptoms.

in Tables 10a–10b and Figures 10a–10b.

In this group, scan findings and symptomatic response showed improvement or stable disease. Biochemical response showed progression in 50% of cases. Patients with both high proliferation index and high ^{18}F -FDG SUVmax demonstrated progressive disease on follow-up imaging. The average post-treatment SUVmax increased compared with the pretreatment value. The findings are presented.

Table 10a: Cases with high proliferation index, high ^{18}F -FDG SUVmax (n=2)

	PreRx	Post 1
Avg HYNIC TOC index	1179	1114
Avg SUVmax	16.1	18.84

The high proliferation index, high SUVmax cases showed a rise in the average SUVmax in the post-treatment scans. The average HYNIC TOC lesion index showed a fall in the post-treatment scan.

Fig 10a: Cases with high proliferation index, high ^{18}F -FDG SUVmax

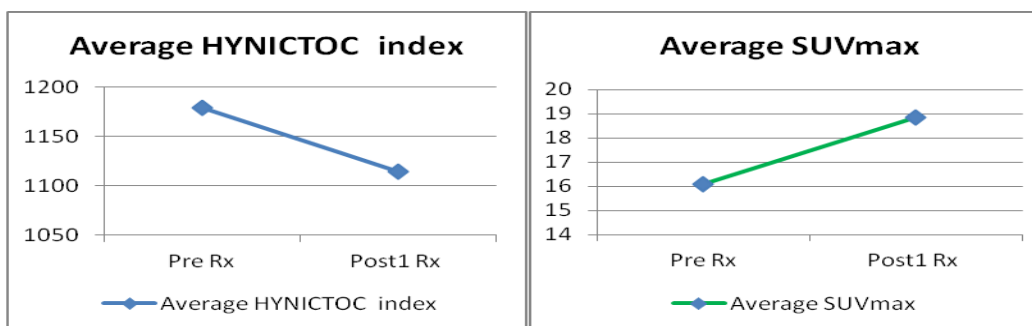
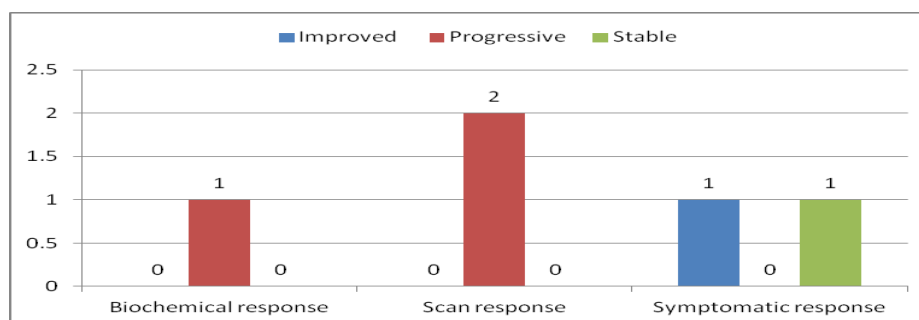


Table 10b: Cases with high proliferation index and high ^{18}F -FDG SUVmax - response

proliferation index	SUVmax -Pre Rx	Response		
		Biochemical	Scan	Symptomatic
>20	18.5	No follow-up	Progressive	Improved
>30	13.6	Progressive	Progressive	Stable

Fig 10b: Cases with high proliferation index, high ^{18}F -FDG SUVmax – response



In two cases with high proliferation index and high ^{18}F -FDG SUVmax, the scan findings showed progressive disease. The chromogranin-A levels were not available in one case, and the other case had rising levels of chromogranin-A, indicating progressive disease. There was improvement of symptoms in one case, and it was stable in the other case.

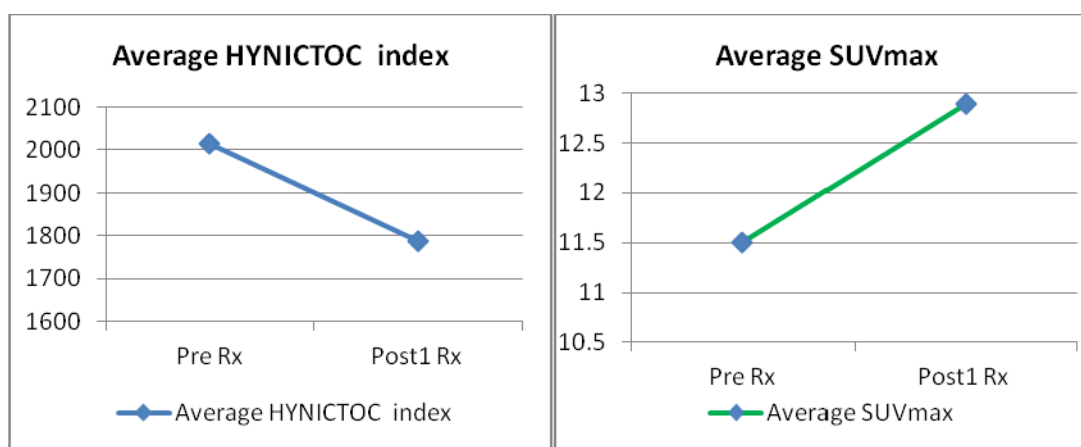
The scan showed progressive disease in the two cases in the group. Patients had stable symptoms or improvement.

Cases not showing concordance between proliferation index and FDG uptake
Patients with a low proliferation index but high ^{18}F -FDG SUVmax showed heterogeneous treatment responses. Biochemical progression was observed in most patients, whereas objective imaging showed improvement in most cases. The findings are presented in Tables 11a–11c and Figures 11a–11b

Table 11a: Cases with low proliferation index, high ^{18}F -FDG SUVmax (n=4)

	PreRx	Post 1	Post 2
Avg HYNIC TOC index	2016	1787	935.5
Avg SUVmax	11.5	12.89	--

Fig 11a: Cases with low proliferation index, high ^{18}F -FDG SUVmax



The low proliferation index, high SUVmax group showed a rise in the average lesion SUVmax in the

post-treatment scans. Average HYNIC TOC lesion index showed a fall.

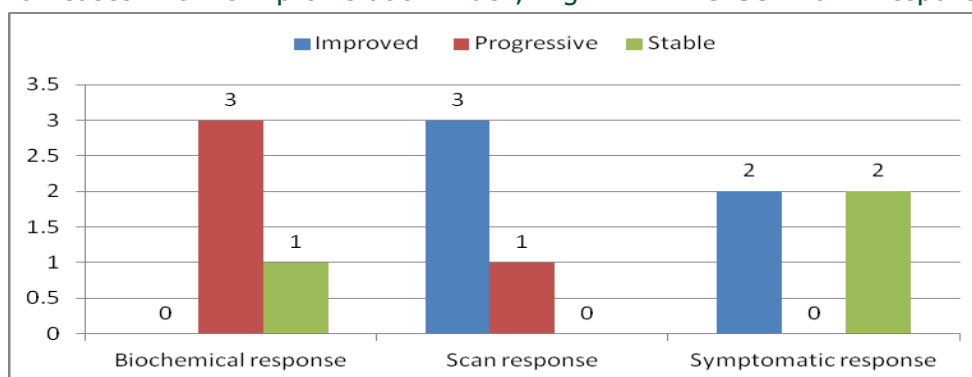
Table 11b: Cases with low proliferation index, high ^{18}F -FDG SUVmax - response

Proliferation index	% ^{18}F -FDG SUVmax-Pre Rx	Response		
		Biochemical	Scan	Symptomatic
1	10.1	progressive	Improvement	Improvement
<2	16.8	Progressive	Progression	Stable
1	7.08	Stable	Improvement	Improvement
2	16.2	progression	Improvement	Stable

Table 11c: Cases with low proliferation index, high ^{18}F -FDG SUVmax - summary

Total:4 cases	Improvement	Progression	Stable
Biochemical	0	3	1
Scan	3	1	0
Symptomatic	2	0	2

Fig 11b: Cases with low proliferation index, high ^{18}F -FDG SUVmax - response



In cases with low proliferation index and high FDG uptake, biochemical response showed progression in 3 (75%) out of 4 cases, and one case showed stable disease. Scan showed improvement in 3 (75%) out of 4 cases, and one case showed progression of disease. Improvement of symptoms was found in 2 (50%) out of 4 cases; the remaining 2 cases didn't show much change in symptoms. In this group, 3 out of 4 cases showed progression in biochemical response, and 1 out of 4 cases showed progression on the scan. There was no progression of symptoms.

Case with high proliferation index, low ^{18}F -FDG SUVmax

In this group, there was only one case, and there was no FDG uptake in the lesion. Only one patient had a high proliferation index with low ^{18}F -FDG uptake. This patient demonstrated biochemical improvement and stable disease on imaging and remained asymptomatic. The findings are presented in Table 12.

Table 12: Case with high proliferation index, low ^{18}F -FDG SUVmax

proliferation index	SUVmax-Pre Rx	Response		
		Biochemical	Scan	Symptomatic
>20	no lesion	Improvement	Stable	Stable (asymptomatic)

Only one case was found in this group. Biochemical response showed improvement. Scan showed stable disease. Patient was asymptomatic from the beginning

Discussion

In patients receiving peptide receptor radionuclide therapy (PRRT) for metastatic or incurable neuroendocrine tumours (NETs), the predictive importance of pretreatment ^{18}F -FDG PET/CT SUVmax was assessed. The results confirm the significance of FDG PET/CT as a crucial functional biomarker in the treatment of NETs by showing that enhanced metabolic activity on FDG PET/CT is linked to higher tumour proliferative activity and worse therapeutic

outcomes (7). In line with the usual distribution of patients referred for PRRT, the study revealed that most patients had well-differentiated tumours (Grades 1 and 2), while Grade 3 tumours made up only a tiny percentage of cases. Additionally, according to the epidemiological trend shown in tertiary referral centres, pancreatic NETs were the most prevalent primary tumours (8, 9).

The study's key finding was that the mean SUVmax gradually increased as the Ki-67 proliferation index

increased. While tumours with low proliferation indices showed comparatively poor FDG absorption, tumours with a proliferation index of more than 20% showed the highest metabolic activity (10). This result confirms the well-established biological connection between glucose metabolism and tumour aggressiveness, according to which less differentiated and quickly growing tumours have more glycolytic activity and, as a result, more FDG build-up (11). The complementary relevance of molecular imaging in assessing tumour biology is shown by the overlap in SUVmax values among intermediate-grade tumours, which suggests that metabolic behaviour cannot be anticipated exclusively by histological grading (12).

The predictive usefulness of FDG PET/CT was further demonstrated by treatment response analysis. Following PRRT, patients with proliferation indices below 10% typically demonstrated better clinical improvement and a higher percentage of stable disease or partial response, while those with proliferation indices above 10% had a higher incidence of progressing illness on follow-up imaging (13). The worst objective response was also seen in patients whose pretreatment SUVmax was greater than 10, indicating that high metabolic activity is linked to PRRT resistance. Crucially, a number of patients with low histological grades but high SUVmax also showed poor outcomes, suggesting that FDG PET/CT can detect physiologically aggressive tumours that histopathological grading could miss (14, 15). These results highlight metabolic imaging's additional prognostic usefulness in improving risk classification above and beyond traditional pathological evaluation (16).

The comparison of concordant and discordant groups based on proliferation index and FDG uptake was another significant discovery. Following PRRT, patients with both low proliferation index and low SUVmax typically had favourable clinical and imaging outcomes, while those with both high proliferation index and high SUVmax continued to advance despite treatment (17). Variable responses were seen in discordant cases, especially those with low proliferation index but high SUVmax. This suggests that metabolic activity may represent underlying tumour heterogeneity that is not reflected by Ki-67 alone. These findings are in favour of combining pretreatment ^{18}F -FDG PET/CT with histopathological grading to enhance patient selection, prognostic evaluation, and customised treatment planning for PRRT patients (18).

Limitations

This study was conducted at a single tertiary referral center with a relatively small sample size, which limits the generalizability of the findings. Histopathological grading

and Ki-67 proliferation index were unavailable for a few patients, potentially affecting subgroup analyses. The heterogeneous primary tumor sites and varying biological behavior of neuroendocrine tumors may have influenced the observed treatment responses. Additionally, the study evaluated short-term treatment outcomes, and long-term progression-free and overall survival analyses were not performed.

Conclusion

The current study shows that in patients receiving peptide receptor radionuclide therapy (PRRT) for metastatic or incurable neuroendocrine tumours, pretreatment ^{18}F -FDG PET/CT SUVmax is a useful predictive imaging indicator. Higher tumour grade, a higher proliferation score, and more biological aggressiveness were all linked to increased FDG uptake. While tumours with high pretreatment SUVmax, especially values greater than 10, demonstrated a significantly increased chance of disease progression despite treatment, patients with low FDG avidity showed improved symptomatic and objective responses to PRRT. Significantly, a subgroup of low-grade tumours with poor treatment outcomes was also identified by higher FDG absorption, suggesting that metabolic imaging offers prognostic information beyond traditional histological grading alone. In order to enhance risk classification, maximise patient selection for PRRT, and enable customised treatment planning targeted at improving clinical outcomes, these data justify the incorporation of ^{18}F -FDG PET/CT into the routine pretreatment evaluation of neuroendocrine tumours.

Limitations

This study was conducted at a single tertiary referral center with a relatively small sample size, which **limited** the generalizability of the findings. Histopathological grading and Ki-67 proliferation index were unavailable for a few patients, which limited subgroup analyses. The heterogeneous primary tumor sites and varying biological behavior of neuroendocrine tumors may have influenced the observed treatment responses. Additionally, the study evaluated short-term treatment outcomes, and long-term progression-free and overall survival analyses were not performed.

Generalizability

The findings of this study may be applicable to patients with metastatic, recurrent, or unresectable neuroendocrine tumors undergoing peptide receptor radionuclide therapy in specialized tertiary-care nuclear medicine centers with access to ^{18}F -FDG PET/CT and somatostatin receptor

imaging. However, the single-center setting, relatively small sample size, heterogeneous tumor sites, and incomplete availability of histopathological grading limited the external validity of the findings. Therefore, the results should be interpreted cautiously when applying them to broader neuroendocrine tumor populations and different clinical settings.

Recommendation

Based on the findings of this study, pretreatment 18F-FDG PET/CT may be considered as a complementary imaging tool alongside somatostatin receptor imaging and histopathological grading for risk assessment in patients undergoing PRRT. Patients with high metabolic activity may benefit from closer clinical and imaging follow-up. Further multicenter studies with larger sample sizes and longer follow-up are recommended to validate the prognostic value of 18F-FDG PET/CT SUVmax in predicting PRRT response.

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List of Abbreviations

1. **FDG** – Fluorodeoxyglucose
2. **PET/CT** – Positron Emission Tomography/Computed Tomography
3. **SUVmax** – Maximum Standardized Uptake Value
4. **PRRT** – Peptide Receptor Radionuclide Therapy
5. **NETs** – Neuroendocrine Tumors
6. **GEP-NET** – Gastroenteropancreatic Neuroendocrine Tumor
7. **SSTR** – Somatostatin Receptor
8. **Ki-67** – Ki-67 Proliferation Index
9. **HYNIC-TOC** – Hydrazinonicotinamide-Tyr³-octreotide
10. **MCT** – Medullary Carcinoma of the Thyroid

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this study.

Author Contributions

Harilal P.: Conceptualization, study design, supervision, data collection, data interpretation, and critical revision of the manuscript.

Arun B. R.: Data collection, investigation, data analysis, interpretation of results, and manuscript preparation.

Vivek Matthew James: Methodology, data interpretation, manuscript preparation, and critical revision of the manuscript.

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Data Availability

The data generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, subject to institutional and ethical restrictions.

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