



THE DIAGNOSTIC ROLE OF 68GA DOTATATE PET/CT IN THE DETECTION OF NEUROENDOCRINE TUMORS

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Abstract

Aim of work: To detect the overall diagnostic performance of 68Ga-DOTATATE PET/CT in the assessment of recently diagnosed NETs and follow-up the patients after different treatment regimens.

Patients and methods: A prospective analysis of 98 NETs patients, the study includes 50 females and 48 males with ages between 25 to 68 with mean age of 49. The patients were referred either to confirm the diagnosis of suspected NETs (clinically doubtful patients or with laboratory and image-based suspicion), or to initial stage confirmed cases, or for posttherapy assessment. All patients performed 68Ga-DOTATATE PET/CT scans. Any localized or patchy inhomogeneous uptake greater than the background and located outside the normal anatomic structure was considered as DOTATATE avid lesions. Available follow-up DOTATE PET/CT scans for 19 patients were interpreted visually and semiquantitative according to the PERCIST criteria.

Results: In our study, 68Ga-DOTATATE PET/CT was positive in 55 patients (56.1%) and negative in 43 patients (43.9%) The most common primary NETs had gastro-entero-pancreatic localization (GEP tumors) (27/55 patients, 49.2%). Two false positive and two false negative cases were detected giving a PPV & NPP of 96.3% and 95.3% respectively. The overall diagnostic performance of DOTATATE PET/CT showed comparable high values of sensitivity, specificity, and accuracy (96.3%, 95.3%, and 95.9% respectively). Follow-up post-therapy scans for 19 patients (n= 19/55, 34.5%) were interpreted, and a correlation between the Responders (n=10, 52.7%) and Non-responder (n=9, 47.3%) groups regarding SUVmax and MTB of the primary lesions and the metastatic was made. A significant correlation was found between the SUVmax and MTB of the metastatic liver lesions in the responders and Non-responders groups (p value< 0.01).

Conclusions: 68Ga-DOTATATE PET/CT provides whole-body imaging allowing accurate localization of 1ry NETs and detection of avid distant metastatic sites to achieve best therapy planning and disease prognosis.

Keywords: NETs (Neuroendocrine tumor), 68Ga DOTATATE, PET/ CT), MTB (metabolic tumor burden).

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Introduction

Neuroendocrine neoplasms (NENs) arise from the diffuse neuroendocrine cell system and may occur at many different sites throughout the body. Most frequently, these neoplasms occur in the digestive system, followed by the lung. The term NEN encompasses well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NECs represent only about 10%-20% of all NENs [1].

Early investigation of NENs is crucial, the accurate tumor localization is essential since surgery remains the optimal treatment in nonmetastatic disease [2]. Several imaging methods are available including CT, magnetic resonance imaging, ultrasonography, scintigraphy, and positron emission tomography.

Somatostatin receptor-based scintigraphic imaging is widely used. Somatostatin is an endogenous peptide that is secreted by neuroendocrine cells and binds to one of five types of somatostatin receptors (SSTR1- SSTR5), these receptors are present on the cell surface of neuroendocrine cells, providing a unique and specific molecular target for imaging [3]. 68Gallium DOTATATE PET tracer, has an affinity for SSTR type 2 that is 100 times higher than that of 111Inpentetretoid and used as a functional imaging modality for the evaluation of neuroendocrine tumors for all histological grades [4].

Accordingly, our objective in this study was to detect the overall diagnostic performance of 68Ga-DOTATATE PET/CT in the accurate staging of recently diagnosed NETs and follow-up the patients after different treatment regimens. Also, evaluating

the significance of semiquantitative measurements (including SUVmax & TLG) in the initial and follow-up 68Ga DOTATATE PET/CT scans for NETs patients.

Patients and Methods

In our prospective study, all the procedures had been approved by the ethical and scientific committee of our institution's clinical oncology and nuclear medicine department. Between May 2020 and October 2021, the study was conducted on 98 patients referred from the clinical oncology department to perform 68Ga DOTATATE PET/CT scans either; i) to confirm the diagnosis of suspected NETs (clinically doubtful patients or with laboratory and image-based suspicion), ii) to initial stage confirmed cases or iii) to detect the response to therapy after surgical or systemic treatments.

The patient's medical records were thoughtfully reviewed for collecting detailed clinical information including age, gender, methods of diagnosis, detailed pathology, all imaging findings, and treatment protocols.

Inclusion criteria were Adults >18 years, patients with suspected or pathologically proved NETs, also post-treated NETs patients either surgically or by medical systemic treatment regimens. The exclusion criteria included patients with known double primary malignancies other than NETs.

68Ga DOTATATE PET/CT

All patients were instructed to fast for at least 2 to 4 hours. Whole-body 68Ga DOTATATE PET/CT study was obtained using ingenuity 64 Multislice Philips PET/CT scanner (PET/CT, Philips Healthcare). Scanning started 45-60min after intravenously administered 3MBq/kg of body weight 68Ga DOTATATE, well hydration status prior to and post tracer injection was ensured. First, low-dose, CT images were acquired and used for attenuation correction of the PET images followed by PET scanning from mid femur to the base of the skull was performed in five or six bed positions, with 2min per bed position. Full-dose contrast-enhanced CT of the neck, chest, abdomen, and pelvis was also performed.

68Ga DOTATATE PET/CT image analysis

Three experienced nuclear medicine physicians and A radiologist interpret the PET/CT scan. On visual bases, any anomalous localized or patchy inhomogeneous uptake greater than the background and located outside the normal anatomic structure was considered as DOTATATE avid lesions. The CT pictures were updated to reflect the CT revisions.

The semiquantitative assessment, including SUVmax & TLG, and the size of the primary tumor and the metastatic lesions were measured for each patient. volumetric regions of interest (ROIs) were manually determined on the attenuation-corrected emission images throughout the axial planes for the lesions that were identified as areas of focally

increased uptake. Another ROI was drawn over the normal liver parenchyma. Formulas used to calculate the maximal SUVmax and the TLG included:

- SUVmax = maximum activity concentration in the neoplasm (kBq/mL) injected dose (MBq) /body weight (kg)
- TLG= Metabolic tumor volume (MTV) x SUVmean

68Ga DOTATATE PET/CT image interpretation

Pathologically elevated tracer uptake that could not be attributed to normal physiologic activity was considered as positive study. True positive 68Ga DOTATATE PET/CT was recorded when the PET/CT and histopathology have been agreed upon and lesions regression/progression is noted in follow-up PET/CT. False positive 68Ga DOTATATE PET/CT was interpreted when the positive PET/CT uptakes did not meet any of the prior criteria, or in patients who had uptake and were confirmed pathologically to be inflammatory or benign in nature. True negative 68Ga DOTATATE PET/CT was interpreted when both histopathology and PET/CT were negative and the Negative PET/CT scans were matched with the clinical and imaged-based follow-up of the patients. False Negative 68Ga DOTATATE PET/CT as considered when there were lesions detected in other imaging modalities or confirmed by histopathology as NETs, yet with negative PET/CT scans.

Follow-Up 68Ga DOTATATE PET/CT

The available follow-up PET/CT scans including the quantitative parameters (size, number of avid lesions, SUVmax, and TLG) were interpreted according to the PERCIST criteria. The percentage change in SUVmax levels and the metabolic tumor burden MTB in all notable lesions in the initial and follow-up studies were computed using the following formula: (Follow-up values - Initial values) ÷ (Initial values) X 100. The MTB is equal to the sum of the total TLG for all the avid lesions.

Statistical Analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 28. Numerical data were summarized using medians and ranges. Categorical data were summarized as numbers and percentages. Estimates of the frequency were done using numbers and percentages. Numerical data were explored for normality using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Comparison between two related groups of non-normally distributed numeric variables was done by Wilcoxon test. All tests were two-tailed & Probability (p-value) ≤ 0.05 is considered significant. Figures were performed using Graph pad prism version 8.0.1.

Results

Patient's characteristics and clinical presentation

This prospective study was conducted on 98 patients with confirmed or suspected NETs, including 50 females and 48 males with a mean age of 44 years (range 25-68 years) (Table 1). ⁶⁸Ga- DOTATATE PET/CT scan was performed to all patients. 35 of the 98 patients (35.7%) were pathologically confirmed as NETs (7/35 patients were referred for initial staging and 28/35 patients were examined after surgical resection and referred for suspected recurrence or metastatic workup). For the rest of the 63 patients (64.3%), NETs were doubtful either clinically (32 patients presented with suspected symptoms), laboratory (11 patients presented with elevated tumor markers) or imaged-based (20 patients' previous imaging was performed and revealed suspected lesions) (32.6%, 11.2%&20.4% respectively) (Figure 1). In the 32 clinically suspected patients the most frequent presentation was found to be hypoglycemic attacks (14.3%) and resistant hypertension (6.1%) (Table 1).

⁶⁸Ga-DOTATATE PET/CT scan qualitative and semiquantitative assessment

The ⁶⁸Ga-DOTATATE PET/CT scan was positive for NETs in 55 patients (56.1%) and negative in 43 patients (43.9%). As for the positive scans, 17/55 patients (30.9%) presented with DOTATATE avid lesions confined only to the primary site while 38/55 scans (69.1%) showed metastatic avid lesions (Table 2). The most common primary NETs had gastro-entero-pancreatic localization (GEP tumors) (27/55 patients, 49.2%), and the remaining sites of primary NETs (11/55 patients, 20%) were located as followed; 4 in adrenal glands, 3 in the lungs, 1 medullary thyroid NET and 3 in other sites (Table 2) (Figure 2).

The most common Iry NETs lesions were located in the pancreas and had a measured mean size of 5.7cm (range1.4-12.0 cm), the mean SUVmax was 20.1 (range 2.5-92) and mean TLG was180.6 (range 9.7-655.0). 38 patients presented with DOTATE AVID metastatic disease, the liver was the most common metabatic site noted, the metastatic hepatic lesions has mean size of 3.28 cm (range0.70-11.0), the mean SUVmax was 27.26 (range 5.0-102.0) and mean TLG was536.13 (range 18-5559) (Table 3).

Correlation between the two most commonly detected Iry DOTATATE avid NET lesions

(including pancreatic and GIT NETs) according to size, SUVmax and TLG was performed and no significant difference was found between the measurements (P value >0.05).

Diagnostic performance results of ⁶⁸Ga-DOTATATE PET/CT in detecting NETs

The overall diagnostic performance of ⁶⁸Ga-DOTATATE PET/CT showed comparable high values of sensitivity, specificity, and accuracy (96.3%,95.3%, and 95.9% respectively) (Table 4). There were two cases considered as false positive DOTATE avid lesions that were confirmed pathologically to be of benign inflammatory nature and also two false negative cases by ⁶⁸Ga- DOTATE scan and biopsy confirmed the presence of small-sized NET lesions. PPV & NPP was 96.3% and 95.3% respectively (Figure 3 and 4).

Follow-up ⁶⁸Ga-DOTATATE PET/CT and response assessment:

Follow-up post-therapy scan was performed within 6 months to 1.5 years duration for 19 patients with initially positive DOTATE scan (n= 19/55, 34.5%) to detect any new events and assessed the efficacy of therapy. The Iry NET lesions were located as follows; 14 GIT, 2 lungs, 2 MTC, and one ovarian NETs. Surgical resection was done in 2 /19 patients and another 2 received PPRT (LU-177 DOTATAE). For the rest of the 15 patients, systemic (long-acting SSRT) treatment regimens were used (Figure 5).

According to PERCIST criteria, complete metabolic remission was achieved in 2 of the 19 patients (10.5%), partial response in 8 (42.1%), stable disease in 2 patients (10.5%) and progression detected in 7 patients (36.8%).

The follow-up patients were then divided according to their response into 2 groups, Responders (n=10, 52.7%); including patients achieved regression and resolution and, Non-responders (n=9, 47.3%; including patients with stable disease and progressed patients. Correlation between the Responders and Non-responder groups regarding SUVmax and MTB of the primary lesions and the metastatic sites (including liver, lymph nodes, and bones) was performed; A significant correlation was found between the SUVmax and MTB of the metastatic liver lesions in both groups (p value< 0.01) (Table 5).

Table 1: Demographic data of the whole cohort (n=98) and symptoms of clinically suspected NETs patients(n=32)

Clinical data (n = 98)	No.	%
Gender		
Male	48	49.0%
Female	50	51.0%
Age (years)		
Range	(25-68)	
Mean ± SD)	43.95± 10.07	
Symptoms (n = 32)		
Hypoglycemia	14 14	14.3
Resistant HTN	6	6.1
Bleeding per rectum	3	3.1
Diarrhea	3	3.1
Fever	2	2.0
Abdominal pain	2	2.0
Hematemesis	1	1.0
Loss of weight	1	1.0

Table 2: Identification of NETs by ⁶⁸Ga-DOTATATE PET/CT scan

	No	%
DOTATATE PET/CT	(n=98)	(100%)
Positive	55	56.1%
Negative	43	43.9%
Positive scans	(n=55)	(100%)
Confined to 1ry site	17	30.9%
Metastatic	38	69.1%
1ry site Localization: GEP tumors	(n=55)	(100%)
Pancreas GIT	27	49.2
	15	
	12	
Adrenal	4	7.3
Lung	3	5.5
Thyroid	1	1.8
Others	3	5.5
Metastasis of resected 1ry	17	30.9

Table 3: Primary lesions size and uptake of patients' group(N=55)

Site of primary	Mean ± SD	Range (Min.-Max.)
Pancreas		
SUVmax	20.1(± 23.9)	2.5-92.0
SUVmean	9.3(± 8.8)	1.5-30.2
TLG	180.6(± 191.1)	9.7-655.0
GIT		
SUVmax	25.9(± 22.5)	4.4-72.3
SUVmean	7.4(± 6.8)	2.5-24.0
TLG	290.9(± 433.0)	13.7-1137.0

Table 4: Diagnostic indices of 68Ga-DOTATATE PET/CT Scanning for Primary NETs in patients' group

Iry NET	True +	False -	True -	False +	Sensitivity %	Specificity %	NPV %	PPV %	Accuracy %
	53	2	41	2					
Total +					96.3	95.3	95.3	96.3	95.9
Total -	55		43						

Table 5: Median values of MTB and SUVmax of the primary sites and metastatic sites.

Responders (n=10)				Non-responders (n=9)		p-value
		Median	Range	Median	Range	
No. of lesions		14	(1-45)	6	(2-40)	0.732
Primary lesions						
SUVmax		34	(5.7-72)	10	(4.7-39)	0.456
MTB		753	(13-891)	243	(1.5-860)	0.335
Metastatic lesions						
Liver	SUVmax	70	(20-102)	14.5	(0-53.8)	0.00*
	MTB	1869	(692-3301)	59	(0-2669)	0.01*
LN's	SUVmax	3	(3-16.5)	3.3	(1.5-15)	1.0
	MTB	1	(1-10)	1.4	(1-25)	0.455
Bone	SUVmax	9	(2.2-10)	6.6	(0-15.3)	1.0
	MTB	4.9	(2.6-5.8)	3.9	(0-8.6)	0.876
			Total			
SUVmax		141.5	(5.7-470)	68	(12.3-300)	0.429
	MTB	1928	(13-6630)	299	(13.4-4778)	0.642

* P <0.05 describes significant difference between two tests.

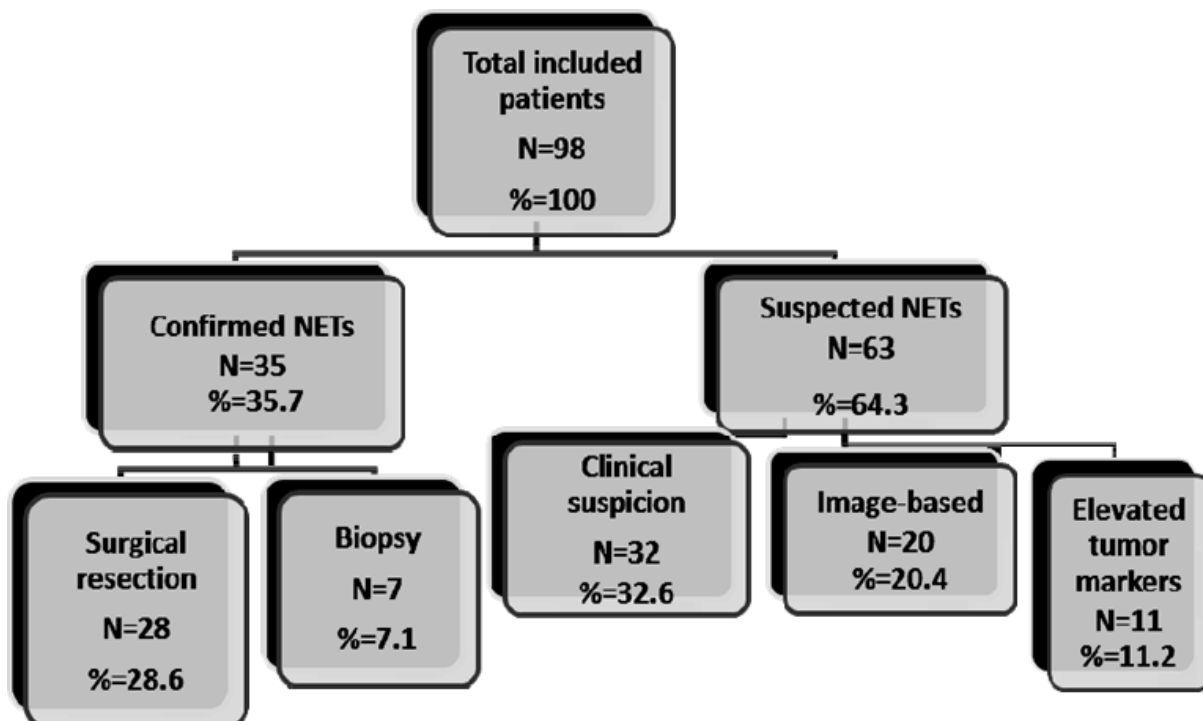


Fig. 1: Patient's presentation in our study (n=98)

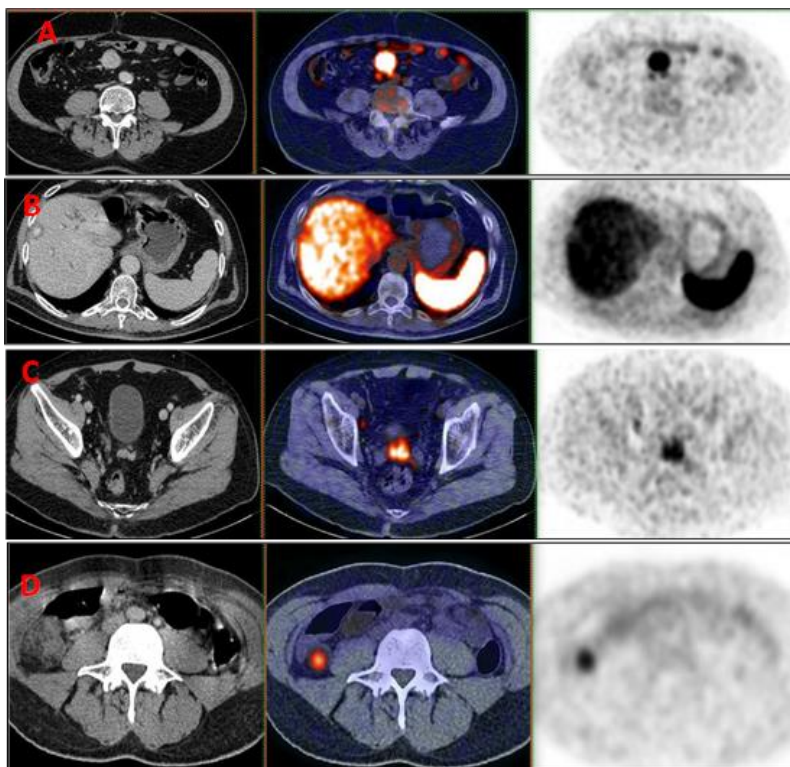


Fig. 2: A 47 years old male patient complained of abdominal pain for 4 months duration had imaged-based suspicion of NETs (by abdominal ultrasound and CT). ^{68}Ga DOTATATE PET/CT
A) showed avid mesenteric node **B)** DOTATATE avid hepatic lesions, **C)** DOTATATE avid pelvic peritoneal lesion, **D)** DOTATATE avid 1ry colon NET.

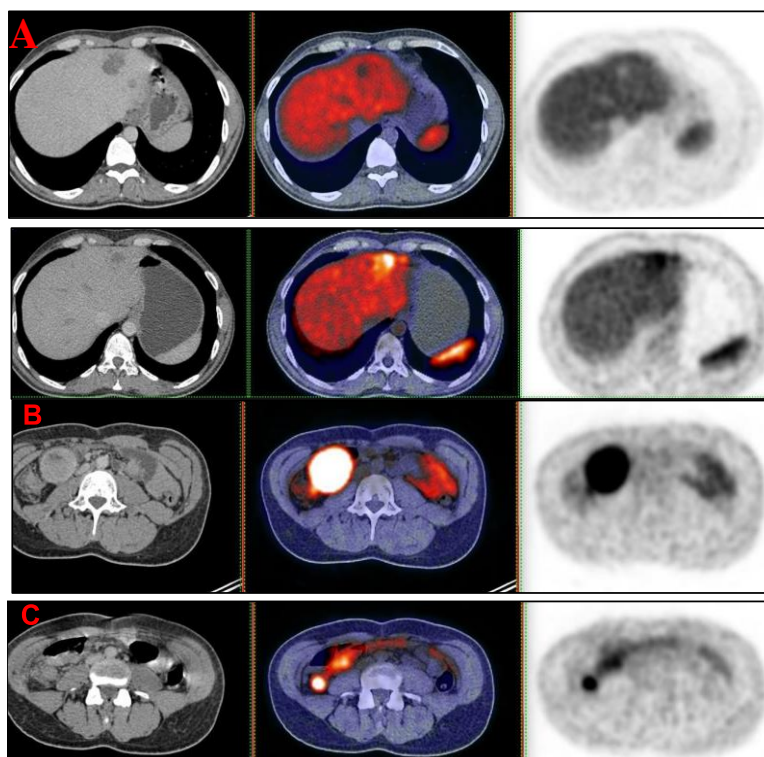


Fig. 3: A 57-year-old male patient complained of bleeding per rectum and had imaged-based suspicion of NETs (by abdominal CT). ^{68}Ga -DOTATATE PET/CT precisely localized the 1ry and the metastatic sites **A)** hepatic avid lesions, **B)** right lumbar enhancing mass, **C)** terminal ileum lesion (1ry site).

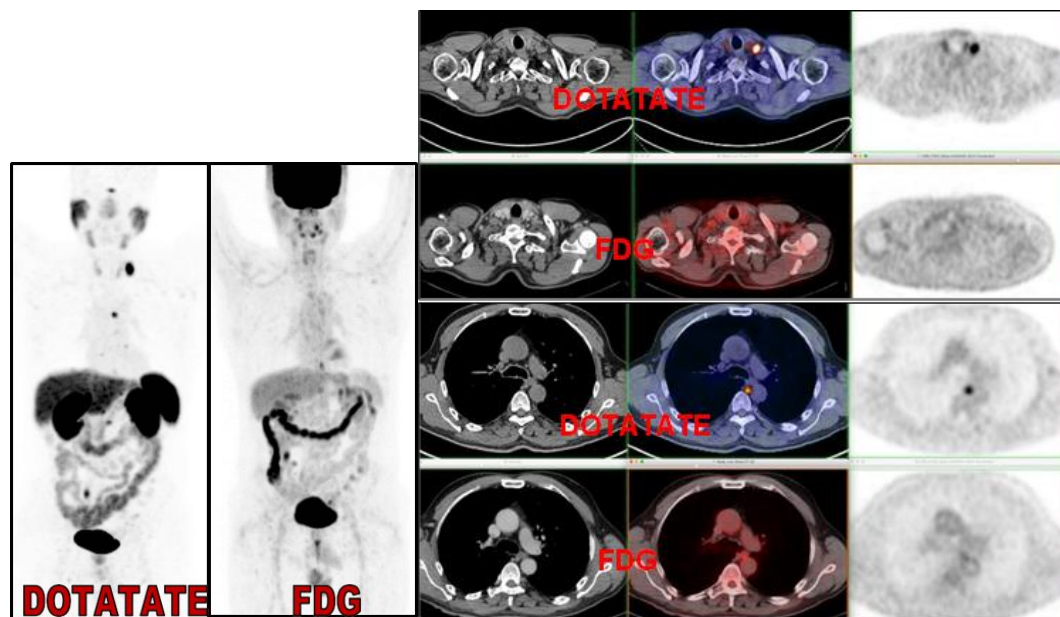
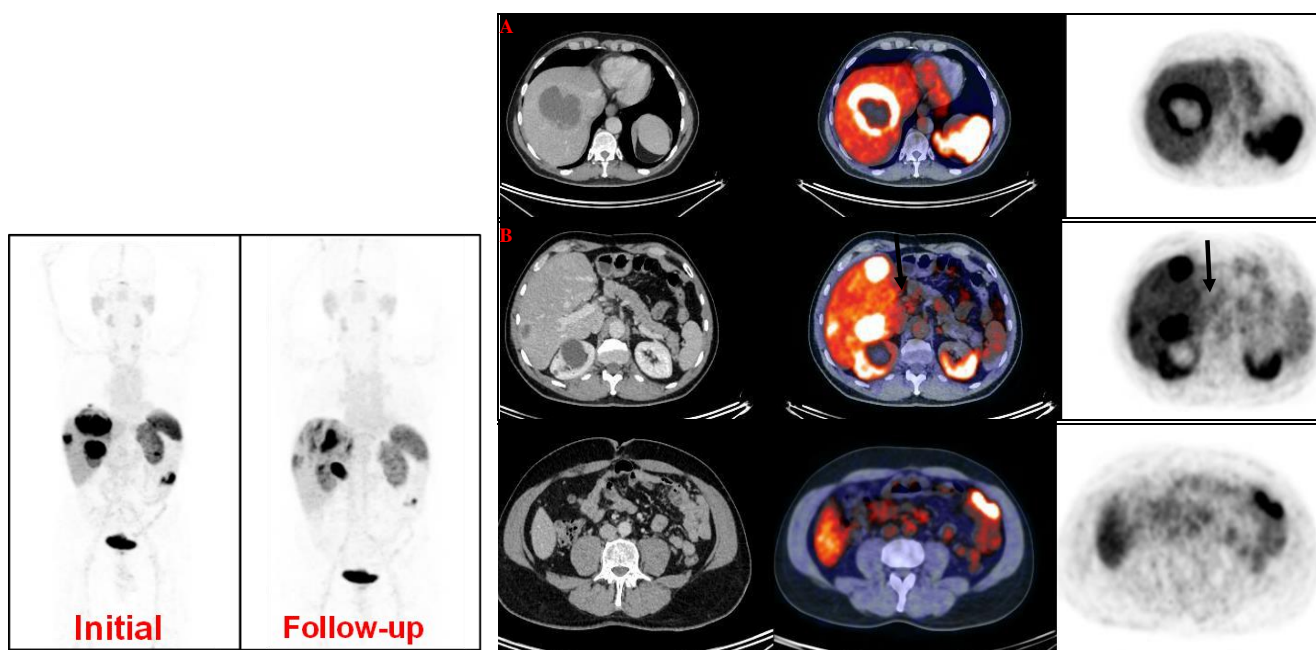


Fig. 4: Complementary ^{68}Ga -DOTATATE PET/CT was performed after a negative ^{18}F FDG PET/CT for a 64 years old male patient with a history of resected small bowel carcinoid tumor and clinically suspected recurrent NETs. (MIP and Fused images showed DOTATATE avid lymph nodal deposits)



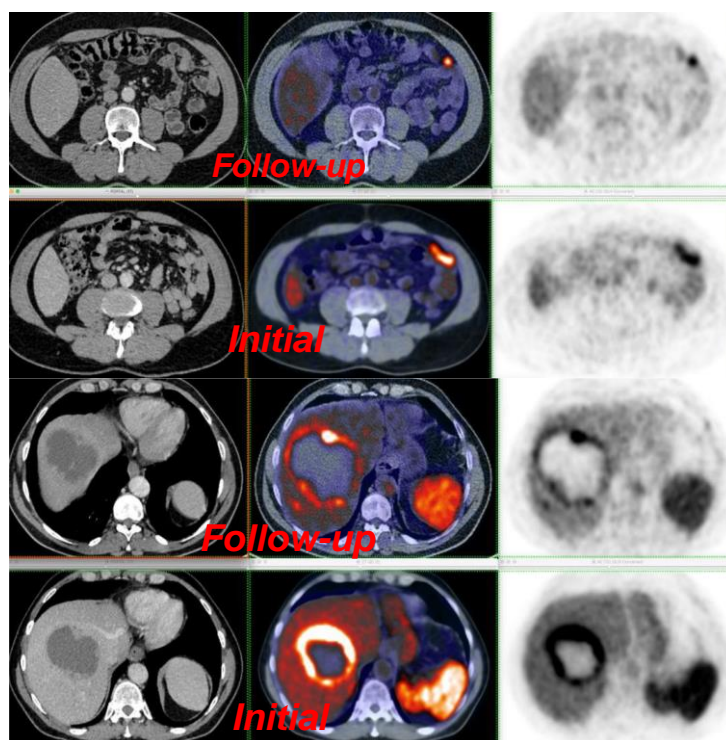


Fig. 5: ^{68}Ga - DOTATATE PET/CT to exclude the recurrence of a 65-year-old male patient with known GIT NET. **A)** Showed DOTATATE avid hepatic lesion, **B)** showed DOTATATE avid porta-hepatis node, **C)** DOTATATE avid peritoneal lesion. The patient received 2 cycles of ^{177}Lu DOTATATE therapy. Post-therapy PET/CT revealed regression of the previously detected DOTATATE avid lesions.

Discussion

Neuroendocrine tumors (NETs) are a kind of tumor with a variety of biological characteristics that arise from cells throughout the diffuse endocrine system [5]. NETs account for about 0.5% of all newly diagnosed malignancies. The incidence, which is on the rise, possibly due to improved awareness, is approximately 5.86/100,000 per year [6]. Tumor localization is critical since surgery is still the best therapeutic option for non-metastatic disease, the CT, MRI, ultrasonography, scintigraphy, and positron emission tomography are among the imaging techniques available for assessment of NETs [7]. The newest somatostatin receptor-based imaging modality uses the positron emitter ^{68}Ga to label various somatostatin analogs. In the current study we aimed to evaluate the diagnostic role of ^{68}Ga -DOTATATE PET/CT in the detection of neuroendocrine tumors.

We conducted a prospective study on 98 patients with confirmed or suspected NETs. Patients were referred between May 2020 and October 2021, ^{68}Ga -DOTATATE PET/CT scan was performed to all patients. The study included 98 patients (50 females and 48 males) with mean age of 44 years (range 25-68 years). The current study was younger than reported in many studies in literature such as

Poeppel et al., who reported mean age 56 ± 19 years old, and males were double the number of females [8], and Deppen et al., [9], who reported mean age 53.4 ± 11 years and predominance of females compared to males (63% versus 37%) among his included patients [9]. In our study, 56.1% (n=55) showed positive scan features for NETs, 30.9% (n=17) presented with DOTATATE avid lesions confined to the primary site and 69.1% (n=38) showed metastatic avid lesions. Prevalence of metastases at the time of presentation was higher than reported in a population-based study that assessed the number of patients who were presented initially with metastatic disease which was 38%, with incidence of 0.63-0.69 per 100,000 per year [10].

In the present study, the most common primary NETs localization 49.2% were gastro- enteropancreatic (GEP-NET), whereas 30.9% the primary NETs sites were resected, and patients presented with positive scan for metastatic lesions, the remaining sites of primary NETs were located as followed; 4 in adrenal glands, 3 in the lungs, 1 medullary thyroid NET and 3 in other sites. These findings are consistent with evidence in literature that stated GEP-NET as the commonest site for

neuroendocrine tumors comprising 55–70% of all NETs [11-14].

The main outcome in the current study was detection the overall diagnostic performance of 68Ga-DOTATATE PET/CT. It showed sensitivity, specificity, and diagnostic accuracy of (96.3%, 95.3% & 95.9%, respectively) with two false positive cases and two false negative cases. Our findings were comparable to Wild et al., [15], who assessed the diagnostic indices of DOTATATE PET/CT in 18 patients diagnosed with NET, only one case was false-negative. The lesion-based sensitivity of DOTATATE PET was 85.5% [15]. Another study by Haug, CindeaDrimus et al. 2012, showed that 68Ga-DOTATATE PET/CT identified NET in 29 of the 36 cases and excluded the presence of a NET in 61 of the 68 non-NET patients, indicating a sensitivity of 81% and specificity of 90% [16]. The 68Ga-DOTATATE scan showed one false-positive results in a study conducted by Deppen et al., and one false-negative case. It showed 96%; sensitivity 93% specificity and 94% overall accuracy [9]. These findings were also matched with our study. An excellent systematic review and meta-analysis of 68Ga-DOTATATE by Geijer and Breimer demonstrated pooled sensitivity and specificity for these imaging agents of 93% and 96% respectively, with overall diagnostic accuracy of 97.6% [17].

In our study, 34.5% performed follow-up post therapy DOTATATE PET/CT scan that showed complete metabolic remission in 10.5%, partial response in 42.1%, stable disease in 10.5% and progression detected in 36.8%. We almost agreed with Ortega et al., who reported a response rate of 78% including patients with complete and partial response [14]. Other studies have reported lower response rates compared to our study including Brabander, Teunissen et al. who showed complete and partial response of 15–35% [18]. And Yau et al., who showed a response rate 11%, disease stability in 58%, and progression in 31% [19].

-based bone marrow assessment, which may incorrectly interpret insignificant BMI as relevant independent prognostic factor,

In an attempt to assess the significance of the semiquantitative analysis of DOTATE PET/CT The follow-up patients were then divided according to their response into 2 groups in the current study Responders (n=10, 52.7%); including patients achieved regression and resolution and, Non-responders (n=9, 47.3%); including patients with stable disease and progressed patients. Correlation between the Responders and Non-responder groups regarding SUVmax and MTB of the primary lesions and the metastatic sites (including liver, lymph

nodes, and bones) was performed and a significant correlation was found between the SUVmax and MTB of the metastatic liver lesions in both groups. No related results in the literature were found to assist our findings. Semiquantitative data including the SUVmax may play a crucial role in post-therapy assessment reflecting the proliferative and metabolic activity of NET patients pre ad post different treatment regimens, therefore, further research is required to make a decisive conclusion.

Conclusion:

68Ga-DOTATATE PET/CT is a reliable whole-body imaging providing a very accurate assessment of early diagnosed NETs. It allows accurate localization of 1ry NETs and detection of avid distant metastatic sites. Semi-quantitative methods including SUVmax and TLG can be used for diagnosis and follow-up of NET patients after different therapy regimens, An overall comparable high sensitivity, specificity, and diagnostic accuracy of DOTATE PET/CT was concluded in our study patients. Our findings stress on the necessity for more prospective trials with larger sample sizes and longer follow-up durations to support the usage of 68Ga-DOTATATE PET/CT in clinical routine diagnosis and follow-up of NETs.

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