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ORIGINAL ARTICLE

Role of ^{18}FDG PET/CT in patients treated with ^{177}Lu-DOTATATE for advanced differentiated neuroendocrine tumours

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Abstract
Purpose The prognostic value of FDG PET for neuroendocrine tumours (NETs) has been reported. In this study we evaluated the role of FDG PET in predicting response and progression-free survival (PFS) after ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (Lu-PRRT) in patients with advanced well-differentiated grade 1/2 NETs.
Methods We retrospectively evaluated 52 patients with progressive advanced NETs overexpressing somatostatin receptors and treated with Lu-PRRT with a cumulative activity up to 27.7 GBq divided into five courses. According to WHO 2010/ENETS classification, patients were stratified into two groups: those with grade 1 tumour (Ki-67 index ≤2 %, 19 patients), and those with grade 2 tumour (Ki-67 index >3 % to <20 %, 33 patients). On the basis of the FDG PET scan, 33 patients were classified as PET-positive (PET+) and 19 as PET-negative (PET−).
Results FDG PET was positive in 57 % of patients with grade 1 NET and in 66 % of patients with grade 2 NET, and the rates of disease control (DC, i.e. complete response + partial response + stable disease) in grade 1 and grade 2 patients were 95 % and 79 %, respectively (P=0.232). In PET− and PET+ patients, the DC rates were 100 % and 76 % (P=0.020) with a PFS of 32 and 20 months, respectively (P=0.033). Of the PET+ patients with grade 1 NET, 91 % showed disease control, whereas about one in three PET+ patients with grade 2 NET (32 %) progressed after Lu-PRRT (DC rate 68 %).
Conclusion These results suggest that FDG PET evaluation is useful for predicting response to Lu-PRRT in patients with grade 1/2 advanced NETs. Notably, none of PET− patients had progressed at the first follow-up examination after Lu-PRRT. Grade 2 NET and PET+ (arbitrary SUV cutoff >2.5) were frequently associated with more aggressive disease. PET+ patients with grade 2 NET, 32 % of whom did not respond to Lu-PRRT monotherapy, might benefit from more intensive therapy protocols, such as the combination of chemotherapy and PRRT.

Keywords FDG PET · Neuroendocrine tumours · PRRT · ^{177}Lu-DOTATATE

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Introduction

Neuroendocrine tumours (NETs) are a relatively rare and heterogeneous group of neoplasms arising from neuroendocrine cells widely distributed throughout the body, and are characterized in about 30 % of patients by a clinical syndrome due to hormonal overproduction. At the same time they have a highly variable biological and a behaviour that is still not well defined, which may, in some cases make them difficult to

diagnose [1, 2]. Different classification systems are based on the site of origin, extent and degree of differentiation, the presence of distant metastases and hormone production capacity [3, 4]. At present, the most accepted classification system is the World Health Organization (WHO) classification released in 2000 and 2004, and subsequently integrated in 2006–2007 by the European Neuroendocrine Tumor Society (ENETS) to overcome difficulties in its application [5]. The basis for such an integration is that the malignant potential is inherent to each form of NET. The ENETS classification was proposed to try to define the biological behaviour on the basis of grading (Ki-67 and mitotic index) and staging (developed on the TNM template). Theoretically, this new classification system allows an efficient prognostic stratification of patients.

Nevertheless, even with these recent integrations, the histopathological classification of NETs is still limited by an intrinsic bias: the tissue obtained from a single metastasis does not necessarily reflect the behaviour in the whole lesion and in all the sites. Furthermore, more than one sample is seldom available in routine clinical practice. More accurate prognostic factors are desirable to select patients for treatment with more aggressive therapies. While its diagnostic sensitivity is low, ^{18}F-FDG PET has demonstrated prognostic value in several forms of cancer, including NETs and, therefore, seems promising for the determination of tumour aggressiveness in this class of disease [6–8].

NETs overexpress somatostatin receptors (SSTRs) particularly the subtype 2 [9]. SSTR overexpression is the basis for the use of radiolabelled somatostatin analogues in the diagnosis and treatment of NETs. Peptide receptor radionuclide therapy (PRRT) with ^{90}Y- and ^{177}Lu-labelled peptides has been used in the treatment of NETs for over 15 years, and achieves objective responses in approximately 30 % of patients [10, 11]. However, the correct position of PRRT in the therapeutic algorithm of NETs remains to be assessed.

Despite the fact that a high SSTR expression is roughly a predictor of response to PRRT [12, 13], the positivity of ^{111}In-pentetreotide scintigraphy (OctreoScan®) or PET with ^{68}Ga-DOTA peptides does not represent per se a prognostic parameter in terms of progression-free survival (PFS).

In the present study, we investigated the role FDG PET/CT in predicting the response rate and PFS after Lu-PRRT in patients affected by grade 1 and grade 2 NETs.

Materials and methods

Patient identification

We retrospectively evaluated 52 patients (28 men, 24 women; mean age 61 years) with NETs of various origins (29 pancreas, 12 gastrointestinal, 1 lung, 10 unknown), all with unequivocal disease progression on morphological imaging according to Southwest Oncology Group (SWOG) criteria [14] (Table 1). All patients had histological confirmation of NETs according to the ENETS criteria [5], including Ki-67 index, and positive ^{111}In-pentetreotide scintigraphy (OctreoScan) or PET/CT with ^{68}Ga-DOTA peptides, that were performed according to EANM guidelines [15–19]. All the included patients underwent a PET/CT scan with ^{18}F-FDG before being treated with five cycles of PRRT with ^{177}Lu-DOTATATE.

FDG PET/CT imaging

PET/CT scans were carried out using either of two hybrid PET/CT scanners (Biograph Sensation 16 Siemens or Discovery LS GE Medical Systems) after intravenous administration of 5.3 MBq/kg of ^{18}F-FDG. The glucose analogue ^{18}F-FDG was supplied and quality controlled by Advanced Accelerator Application (Ivrea-Meldola, Italy). Patients were required to fast for at least 6 h before administration of ^{18}F-FDG to improve image quality, and patients with serum glucose <140 mg/dl were selected for the procedure. After approximately 50 min from intravenous injection patients were placed in a supine position on the tomography bed with their arms raised above their head. PET data were acquired from head the base of the pelvis in two-dimensional mode, with 4 min acquisition time for every bed position.

Analysis was performed on digital transaxial PET/CT images and fused images. Any focal FDG uptake with

Table 1 Patient characteristics, grading and FDG PET/CT findings

Characteristic	Value
Total no. of patients	52
Age (years)	
Mean	61
Range	26–81
Gender	
Male	28
Female	24
Primary tumour site	
Pancreas	29
Gastrointestinal tract	12
Lung	1
Unknown	10
Liver involvement	44 (84.6 %)
Grade	
1	19
2	33
FDG PET positivity	
Positive	33
Negative	19

SUV 2.5 or more as an arbitrary cutoff value was reported as positive for malignancy (PET+). Diffuse uptake not related to pathological findings on conventional radiological images was indicated as nonmalignant uptake and therefore reported as negative (PET−).

Therapy protocol

Patients selected for treatment with Lu-PRRT had any previous medical treatment suspended, except for cold somatostatin analogues, for at least 4 weeks. Blood chemistry parameters to receive the treatment were within the limits defined in the protocol (white blood cell count >2,500/μl, absolute neutrophil count >1,500/μl; haemoglobin >10 g/dl; platelets >100,000/μl, bilirubin <2.5 mg/dl, creatinine <2 mg/dl, ECOG performance status ≤2). All patients provided informed consent after the delivery and discussion of detailed information for inclusion in the study.

According to our phase II protocol for PRRT with ^{177}Lu-DOTATATE, two different levels of cumulative activity were chosen, based on the presence of risk factors for the possible onset of kidney or bone marrow toxicity [20]. These risk factors were: severe hypertension, insulin-dependent diabetes, prior platinum-based chemotherapy and prior treatment with ^{90}Y-DOTATOC (up to 200 mCi cumulative administered activity). The two levels of cumulative activity administered were 18.5 GBq (500 mCi) and 27.7 GBq (750 mCi). All patients were treated with intravenous solution containing amino acids both before and after administration of the radiopharmaceutical to reduce exposure of the kidneys, which are the main critical organs in this type of therapy [21].

Assessment of response and follow-up

The main objective of this study was to evaluate the rates of disease control (DC) and PFS after ^{177}Lu-DOTATATE treatment according to the FDG PET results. DC was defined as complete response (CR) plus partial response (PR) plus stable disease for at least 12 months (SD), evaluated according to SWOG criteria [14]. All patients with SD were in progression before PRRT. CR was defined as complete disappearance of all measurable and evaluable lesions, confirmed after at least 4 weeks; PR was defined as a reduction in the product of major lesion diameters by at least 50 % from baseline, confirmed after at least 4 weeks; progressive disease (PD) was defined as an increase of at least 50 % in the size of all measurable lesions or worse than the previous assessment, or appearance of new lesions; SD was defined as any response not classifiable as CR, PR or PD. The disease assessment included a contrast-enhanced CT scan (or another test, such as MRI) 3 months after PRRT, a PET/CT scan with ^{68}Ga DOTA-peptide or ^{111}In-pentetreotide scintigraphy 6 months after PRRT and then a contrast-enhanced CT scan every 6 months until disease progression occurred.

Statistical evaluation

To determine whether the association between grading or FDG PET results and response to therapy in the sample was likely to reflect a real association between these variables in the population, the chi-squared test was performed. Other parameters, such as Karnofsky performance status (KPS), OctreoScan positivity and the presence of liver metastases, were also taken into consideration.

PFS was computed from the start date of the first cycle to the date of the first observation of progression or death from any cause. Patients without tumour progression at the time of analysis were censored at the date of the last tumour evaluation. PFS curves were obtained using the Kaplan-Meier product-limit estimator (the 95 % CI were calculated), and the PET results (positive and negative) and grading categories were compared using the log-rank test. The statistical significance level was 0.05 and no correction for the multiple significance test was performed. Statistical analyses were carried out with SAS Statistical software (version 9.1, SAS Institute, Cary, NC, USA).

Results

The overall objective responses in the total group of 52 patients were as follows: 3 CR (5.7 %), 8 PR (15.4 %), 33 SD (63.5 %) and 8 PD (15.4 %). The median PFS was 26 months (95 % CI 20–32 months). Based on the frequency distribution in the sample, 19 of the 52 patients were classified as having grade 1 and 33 as having grade 2 NET. Correlating assessment of Ki-67 index and responses seen on PET/CT, of the patients with grade 1 NET, 11 were PET+ (57 %) and 8 were PET− (43 %), and of the patients with grade 2 NET, 22 were PET+ (66 %) and 11 were PET− (34 %; Figs. 1 and 2).

In the patients with grade 1 NET, DC was seen in 18 (95 %) and PD in 1 (5 %), while in the patients with grade 2 NET, DC was seen in 26 (79 %) and PD in 7 (21 %; chi squared 2.35, p=0.232). The median PFS was not reached in patients with grade 1 NET, but was 26 months (95 % CI 13–26 months) in those with grade 2 NET (log-rank test, p= 0.268).

Evaluation the objective responses in relation to the outcome of FDG PET/CT, in the 33 PET+ patients 1 had CR (3.1 %), 6 PR (18.2 %), 18 SD (54.5 %) and 8 PD (24.2 %). The median PFS was 20 months (95 % CI 17–29 months). In the 19 PET− patients, 2 had CR (10.5 %), 2 PR (10.5 %) and 15 SD (79 %). The median PFS was 32 months (95 % CI 26 months to not reached).

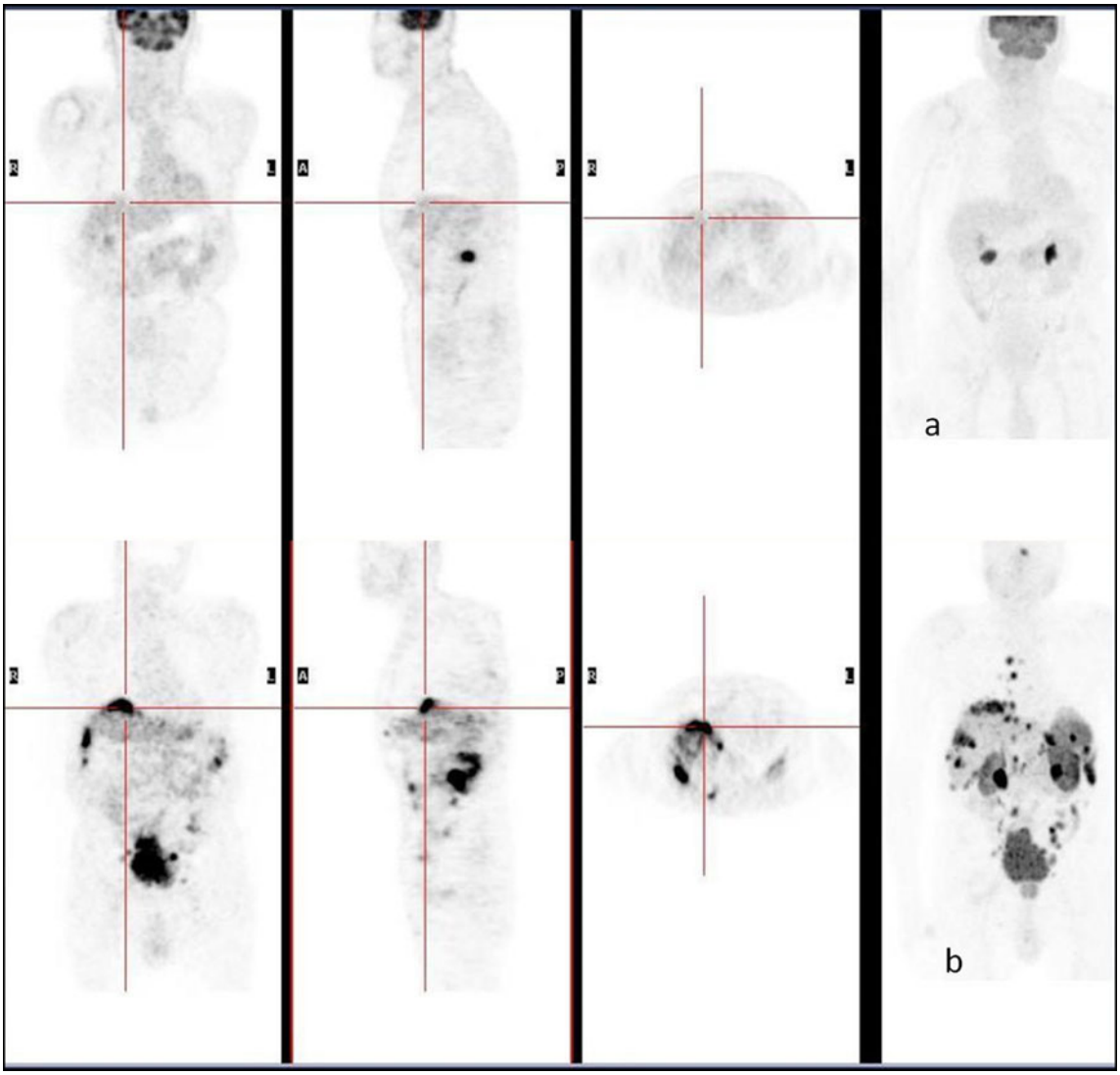

Fig. 1 PET/CT maximum intensity projection (MIP) images in a patient with resected ileal NET (grade 2, Ki-67 index 9 %) and multiple metastatic lesions (**a** ^{18}F-FDG PET/CT, **b** ^{68}Ga-DOTATOC PET/CT)

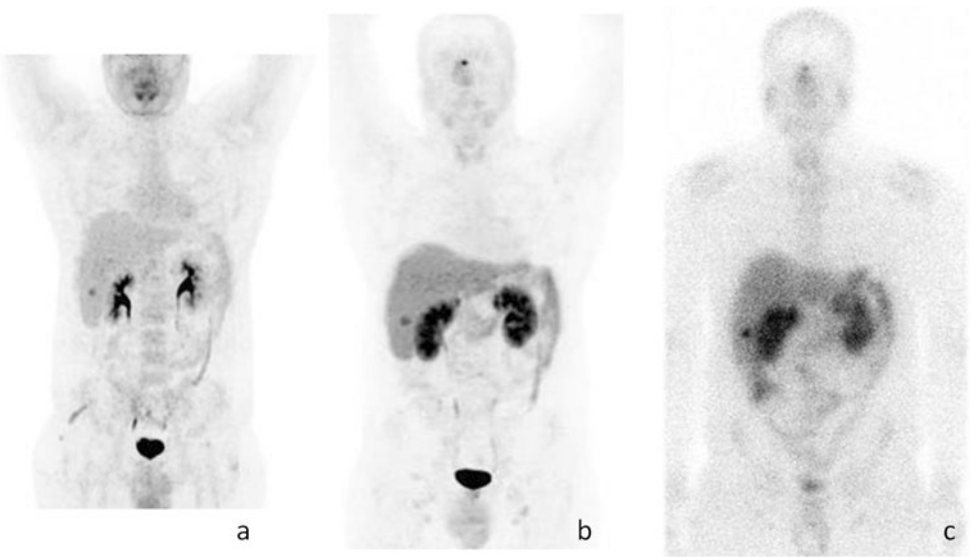

Fig. 2 PET/CT maximum intensity projection (MIP) images in a patient with resected pancreatic NET (grade 1, Ki-67 index 1.5 %) and a single liver lesion (**a** ^{18}F-FDG PET/CT, **b** ^{68}Ga-DOTATOC PET/CT, **c** total body scan after PRRT)

Overall, the DC rate was different in the PET+ and PET− groups. In the PET+ patients, 25 (76 %) showed DC, while in the PET− patients the DC rate was 100 % (chi-squared test, $p=0.020$). None of the PET− patients had progressed at the first follow-up examination 3 months after therapy. The PFS curves in relation to the FDG PET outcomes discriminated two different prognostic courses ($p=0.033$) during the follow-up time (Fig. 3).

Cross-response assessment of the grading and PET results showed that of the 11 PET+ patients with grade 1 NET 10 (91 %) showed DC and 1 (9 %) PD. The median PFS was not reached. Of the 22 PET+ patients with grade 2 NET, 15 (68 %) showed DC and 7 (32 %) PD. The median PFS was 19 months (95 % CI 13–29 months; log-rank test, $p=0.038$; Table 2).

Table 3 shows the results with all the parameters considered for the prediction of DCR and PFS prior to PRRT. Regarding OctreoScan positivity, 18 patients had grade 2 uptake and 34 had grade 3 uptake, according to the so-called Rotterdam scale [10]. In our series, no significant correlation was found between the degree of uptake and the response rate or PFS.

Similar results were observed for KPS, and for the presence of liver metastases. However, when the presence of liver metastases and the PET results were combined, a better outcome was observed in those patients with liver lesions and a negative PET compared to those without liver lesions but with a positive FDG scan in other sites, such as the primary tumour or lymph nodes. The possible effect of SUV was not taken into consideration in this retrospective analysis, since FDG scans were performed with two different PET systems.

Discussion

In recent years, the focus on NETs has produced a significant increase in knowledge, which is reflected in the diagnostic and therapeutic tools for this type of malignancy. NETs are now being recognized earlier, while new treatments and strategies are proposed in guidelines and algorithms [22–24]. In this sense, the recent refinements and integrations in the classification of NETs help discriminating categories of patients with different prognosis [5]. The introduction of SSTR scintigraphy (OctreoScan) in the 1990s was a breakthrough in the diagnosis, staging, restaging and therapy selection of these patients [12, 15, 25]. More recently, PET/CT with ^{68}Ga-DOTA-peptides has increasingly been used and has been demonstrated to affect the therapeutic management in a consistent proportion of patients [17].

Surgery is the only curative treatment, but is feasible only in less than 20 % of patients. In the majority of patients, systemic treatments including biomolecular targeted agents, chemotherapy and PRRT, as well as locoregional treatments, are variably applied and combined [26]. Therefore, in the complex therapeutic algorithm of NETs, in which therapies have to be integrated, the identification of more aggressive

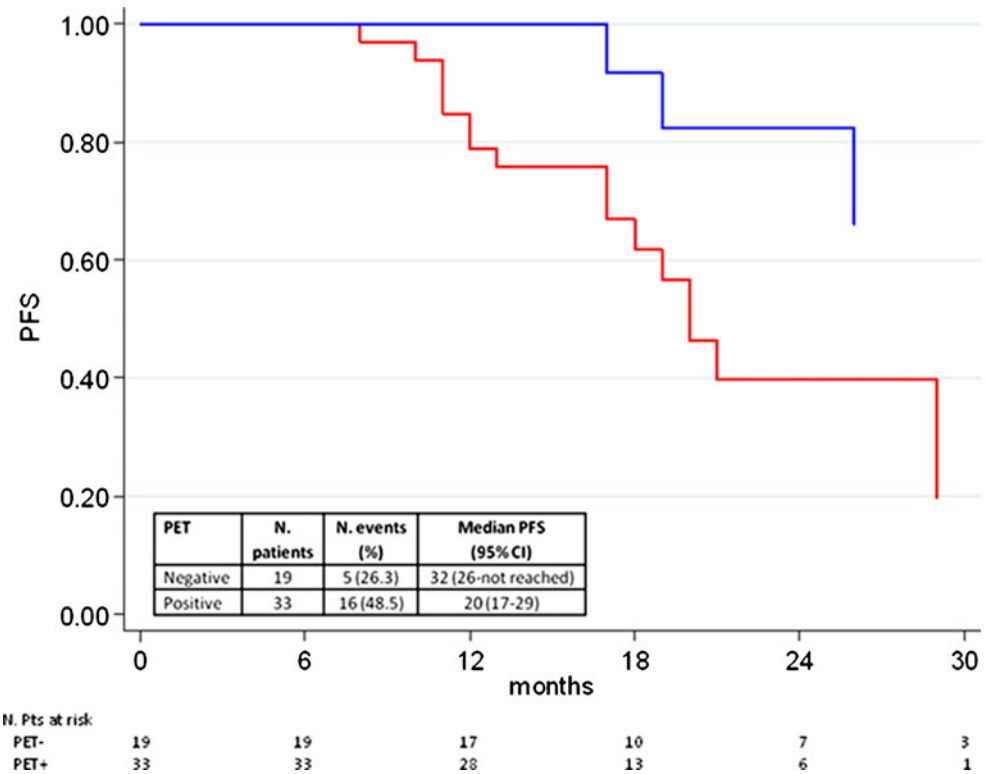

Fig. 3 Kaplan-Meier curved of PFS according to PET responses

Table 2 DC rates according to grade and FDG PET/CT outcomes

	No. of patients	DC rate (%)	PD (%)	PFS months (95 % CI)
Overall	52	84.6	15.4	26 (20–32)
Grade 1	19	95	5	Not reached
Grade 2	33	79	21	26 (19–32)
PET−	19	100	0	32 (26-nr)
PET+	33	76	24	20 (17–29)
Grade 1/PET−	8	100	0	Not reached
Grade 1/PET+	11	91	9	Not reached
Grade 2/PET−	11	100	0	Not reached
Grade 2/PET+	22	68	32	19 (13–29)

forms is crucial. However, specific prognostic factors are still needed to arrive at the best therapeutic strategy in aggressive tumours, within a multidisciplinary approach. Generally, patients are stratified on the basis of the location of the primary lesion, proliferative index, as determined by Ki-67 index, and the presence of distant metastases.

PRRT is an option that is rarely proposed by the referring oncologist as an upfront therapy. Possible reasons are probably the lack of a commercially available product, as well as the lack of randomized phase III trials. A stratification of the patients who are most likely to benefit from this therapy is desirable. The concept of personalized medicine seems crucial for selective therapeutic strategies such as PRRT, for which the presence of a specific target such as the overexpressed SSTR is an indicator of response but does not necessarily affect survival parameters.

In this study, FDG PET/CT was positive in large percentages of both patient groups, those with grade 1 tumours (57 %) and those with grade 2 tumours (66 %). The positivity of FDG PET in many grade 1 tumours, as well as its negativity in some grade 2 tumours indicates the need to better characterize these classes of NETs relative to the intrinsic aggressiveness of the disease in addition to the mere evaluation of morphological features and Ki-67 index. The histopathological characterization of the tumour pertains to the evaluation performed at the time of the biopsy and does not necessarily reflect the entirety of the tumour lesion. Moreover, the morphology and the grading of a lesion do not always correlate with the clinical behaviour, therefore indicating the likely role of other factors. Indeed, NETs show a wide spectrum of morphological appearance and there is often heterogeneity in cellular differentiation within the same tumour mass. The assessment of Ki-67 index is a useful tool in differentiating low-grade and high-grade NETs, but it is usually the result of the evaluation of a specific area within the tumour lesion at a specific time point, and therefore does not necessarily reflect

Table 3 Relevant parameters in the prognostic evaluation of patients with NET

Parameter	DC[a]				PFS		
	No. of patients	No. of events	DC rate %	*p* value	No. of events	Median PFS (95 % CI) (months)	*p* value
Karnofsky performance status							
≤90	21	5	76.2	0.244	11	20 (12–not reached)	0.155
>90	31	3	90.3		10	32 (19–not reached)	
Octreoscan positivity[b]							
2+	18	2	88.9	0.828	6	26 (18–not reached)	0.586
3+	34	6	82.3		14	29 (17–not reached)	
Liver metastasis							
Yes	42	4	90.5	0.035	16	26 (20–32)	0.250
No	10	4	60.0		5	18 (8–not reached)	
Liver metastasis/PET+	26	4	84.6		11	21 (19–not reached)	
Liver metastasis/PET−	16	0	100		5	32 (17–not reached)	
No liver metastasis/PET+	7	4	42.9		5	17 (8–not reached)	
No liver metastasis/PET−	3	0	100	0.395	0	Not reached	0.016

[a] CR + PR + SD.

[b] OctreoScan positivity according to the Rotterdam scale [10].

the current situation in the whole lesion and in all the lesions. In recent years, findings on FDG PET have been shown to affect survival parameters, such as PFS, irrespective of Ki-67 index [7, 8].

FDG PET/CT is a noninvasive, whole-body imaging procedure that can visualize in real time all the metabolically active sites of the disease. Consequently, the derived information helps improve the stratification, and therefore the management, of those patients who are likely to show rapid disease progression, particularly in the wide low-grade spectrum. Our data also confirm the importance of the assessment of Ki-67 index in predicting tumour behaviour and PFS and, ultimately, survival. As to the objective response, grade 1 tumours showed better results than grade 2 tumours, although statistical significance was not reached. However, despite the fact that the difference in results between grade 1 and grade 2 tumours was not statistically significant, stratification according to the PET results did yield a statistically significant difference, since among patients with a negative PET scan Lu-PRRT resulted in a DC rate of 100 %, while among patients with a positive PET scans the DC rate was significantly lower (76 %). This observation was strengthened by the evidence of a statistically significant difference between the PFS in the 19 PET− patients, of whom 26 % showed disease progression after a median follow-up of 20 months, and the PFS in the PET+ patients, of whom 48 % showed disease progression after the same follow-up time. Our results are in line with those of Ezziddin et al. who demonstrated that patients with a high proliferative index are less likely to respond to PRRT and vice versa [27].

FDG PET seems, therefore, to be able to distinguish between more aggressive and less aggressive NETs. This study demonstrated for the first time the prognostic value of FDG PET in patients undergoing PRRT after tumour progression. The duration and quality of the response was found to be superior in patients with a negative FDG PET scan. In this sense, glucose consumption could reflect a different radiosensitivity, related to the activation of proliferating pathways that could render the tumour less prone to respond to PRRT or even more likely to relapse after therapy. Beside the cumulative administered activity, other features, such as radiosensitivity/radioresistance parameters, the number of cycles and the FDG PET result could be involved in the determination of the response.

Stratification according to FDG PET seems to indicate that a different follow-up strategy should be pursued in these patients: the higher aggressiveness of metabolically active tumours is likely to require a more intensive approach, with morphological and functional imaging examinations. On the other hand, the more indolent behaviour of PET− tumours may allow a lighter approach with restaging techniques. Moreover, more aggressive PET+ tumours, especially grade 2 tumours, will probably benefit from more intensive therapeutic approaches such as the combination of PRRT and radiosensitizing chemotherapy, such as capecitabine or another chemotherapeutic agent.

Conclusion

Although the observations reported here should be confirmed in a larger prospective series of patients, it is certainly interesting that this study confirmed the idea of expanding the use of FDG PET/CT to the pretherapy assessment of tumours usually defined as low risk such as SSTR-positive NETs. We should then probably be in a better position to stratify NET patients and modulate the intensity of therapy and follow-up in relation to the degree of risk.

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Conflicts of interest None.

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