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Clinical Usefulness of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in the Diagnostic Algorithm of Advanced Entero-Pancreatic Neuroendocrine Neoplasms

Maria Rinzivillo,[a] Stefano Partelli,[d] Daniela Prosperi,[c] Gabriele Capurso,[a] Patrizia Pizzichini,[c] Elsa Iannicelli,[b] Elettra Merola,[a] Francesca Muffatti,[d] Francesco Scopinaro,[c] Orazio Schillaci,[e] Matteo Salgarello,[f] Massimo Falconi,[d] Gianfranco Delle Fave,[a] Francesco Panzuto[a]

[a]Digestive and Liver Disease Unit, ENETS Center of Excellence, and Departments of [b]Radiology and [c]Nuclear Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; [d]Division of Pancreatic Surgery, Pancreas Translational and Clinical Research Center, San Raffaele Scientific Institute, Vita e Salute University, Milan, Italy; [e]Department of Nuclear Medicine, University of Tor Vergata, Rome, Italy; [f]Department of Nuclear Medicine, Ospedale Sacro Cuore Don Calabria, Negrar, Italy

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. ^{18}F-fluorodeoxyglucose positron emission tomography • Neuroendocrine tumors • Prognosis • Clinical usefulness • Diagnosis

Abstract

Background. The role of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in the diagnostic algorithm of entero-pancreatic neuroendocrine neoplasms (EP NENs) is unclear because most available data derive from heterogeneous populations in terms of tumor biology and disease status at time of examination. The aim of this study was to determine the ability of ^{18}F-FDG PET to identify patients with more aggressive disease among those with advanced EP NENs.

Subjects, Materials, and Methods. Patients with advanced EP NENs and known disease status (progressive disease [PD] or stable disease [SD]) according to imaging procedures, who received ^{18}F-FDG PET and computed tomography scans during a time frame of 1 month, were included.

Results. A total of 93 patients, including 69 patients with pancreatic NENs and 24 patients with small-intestine NENs, were included. At the time of study entry, 64 patients (68.8%) had PD, and the remaining 29 patients (31.2%) had SD. A total of 62 patients (66.7%) had positive ^{18}F-FDG PET, whereas ^{18}F-FDG PET was negative in the remaining 31 patients (33.3%). Overall, ^{18}F-FDG PET sensitivity and specificity to detect PD were 90.6% and 86.2%, respectively, resulting in a diagnostic accuracy of 89.2%. A positive ^{18}F-FDG PET was significantly associated with PD at the time of study entry ($p < .0001$ at multivariate analysis). Although a higher proportion of ^{18}F-FDG PET-positive examinations were observed in patients with higher tumor grade ($p = .01$), 53.8% of patients with grade 1 neuroendocrine tumors (NETs) had positive ^{18}F-FDG PET, and 37.5% of patients with grade 2 NETs had negative ^{18}F-FDG PET. Overall survival was significantly shorter in ^{18}F-FDG PET-positive patients (median: 60 months) in comparison with ^{18}F-FDG PET-negative patients (median not reached; $p = .008$).

Conclusion. ^{18}F-FDG PET has a high diagnostic accuracy to identify progression of disease with unfavorable clinical outcome in patients with advanced EP NENs. Knowledge of disease status and G grading are key factors for physicians to better select patients for whom ^{18}F-FDG PET is clinically useful. ***The Oncologist*** 2018;23:186–192

Implications for Practice: The findings of the present study may help physicians dealing with advanced neuroendocrine neoplasms to select patients for whom ^{18}F-fluorodeoxyglucose positron emission tomography is useful to predict poor clinical outcome.

Introduction

Entero-pancreatic neuroendocrine neoplasms (EP NENs) are rare tumors arising from neuroendocrine cells in the pancreas and in the intestinal tract. Although their incidence is low (6.9 cases per 100,000), their prevalence is relatively high (48 cases per 100,000) due to patients' long survival [1].

Several factors affect their prognosis, including the specific primary tumor site, histological features, tumor grading according to the World Health Organization (WHO) classification, degree of differentiation, and tumor burden [2, 3]. The major prognostic factor is Ki67, which is the basis of the WHO classification and the European Neuroendocrine Tumor Society (ENETS) G-grading system [4–8].

Noninvasive functional imaging with 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) has been

Correspondence: Francesco Panzuto, M.D., Ph.D., Digestive and Liver Disease Unit, Sapienza University of Rome, ENETS Center of Excellence – Roma, Sant'Andrea Hospital, via di Grottarossa, 1035-39, 00189 Roma, Italy. Telephone: 00390633775605; e-mail: fpanzuto@ospedalesantandrea.it Received June 14, 2017; accepted for publication September 26, 2017; published Online First on November 8, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0278

proposed as an alternative to tissue sampling for the determination of the aggressiveness of tumors [9] and has shown prognostic value in several kinds of cancer other than NENs. In fact, it is commonly used for initial diagnosis, as well as to assess treatment efficacy in patients with pulmonary cancer [10], Hodgkin's lymphoma [11, 12], gastrointestinal stromal tumors [13], and colorectal cancer [14].

18F-FDG PET is not routinely used in NENs, because they are generally slow growing and, accordingly, have a low glycolytic activity, which may result in low diagnostic accuracy. However, previous studies on small groups of patients with EP NENs suggest that 18F-FDG PET might be of value for detecting more aggressive tumors with high proliferative Ki67 index [15, 16]. A role for 18F-FDG PET, alone or in combination with 68Ga PET, has also been proposed, with conflicting results, in some series of NENs with a more aggressive clinical course [17–21].

However, due to the heterogeneity of the findings reported in the above studies and the lack of data focused on its diagnostic accuracy according to disease behavior (progressive disease [PD] or stable disease [SD]), the role of 18F-FDG PET in the diagnostic algorithm of patients with advanced EP NENs is still to be established.

Therefore, the present study aimed at investigating the ability of 18F-FDG PET to identify, among patients with advanced EP NENs, disease progression and cases with more aggressive and unfavorable clinical outcomes.

Subjects, Materials, and Methods

Study Design

All consecutive patients with advanced, unresectable, histologically proven diagnosis of EP NENs, seen at the two participating centers (Sant'Andrea Hospital Center, Rome, and San Raffaele Hospital-Negrar Hospital, Milan and Negrar) from January 2011 to January 2016, were evaluated as candidates for this study. Inclusion criteria were (a) known disease status (PD or SD assessed by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.0 criteria [22]) according to computed tomography (CT) scan or magnetic resonance imaging (MRI) and (b) ^{18}F-FDG PET and CT scans performed within a 30-day interval (indication to perform ^{18}F-FDG PET was given at each center based on specific clinical scenarios). All patients with familial syndromes (multiple endocrine neoplasia type I, von Hippel-Lindau) were excluded. Data were prospectively collected according to a shared protocol on NEN patients' management and thus retrospectively analyzed.

Patients in whom the primary tumor site was unknown were also included if they were believed to belong to the small bowel due to the presence of a carcinoid syndrome and reliable histological and immunohistochemical criteria, after other common primary sites had been ruled out by conventional imaging procedures (CT or MRI, as appropriate, and ^{68}Ga PET TC), as previously reported by other authors [23].

The diagnosis of EP NENs was based on conventional histological findings [24]. All cases were classified according to the World Health Organization 2010 classification [25] and were staged using the TNM staging system [26, 27]. Follow-up was performed by both participating centers according to the ENETS standard of care [28] by CT or MRI every 3–6 months depending on the clinical scenario. In addition, assessment of somatostatin receptors expression was performed in all patients, as suggested by ENETS guidelines [29], by ^{68}Ga PET CT examination. Disease status (PD or SD) at the time of study entry was assessed by comparing CT scan performed at the time of ^{18}F-FDG PET examination and previous CT or MRI performed within the previous 6 months. At the time of study entry, as well as during subsequent follow-ups, the disease status was assessed according to RECIST version 1.0 criteria [22]. The research protocol was approved by the local ethics committee, and full informed consent was obtained from all patients.

Imaging Protocols

All examinations were carried out by highly experienced nuclear medicine physicians at each center. ^{18}F-FDG PET CT studies were performed on hybrid PET/CT systems (Philips Medical Systems, Cleveland, OH [at the Sant'Andrea Hospital Rome Center] and Siemens mCT Biograph, Germany [at the San Raffaele Milan-Negrar Hospital Center]) after patients received an adequate dose of FDG (2.96 mBq/kg and 3.7 mBq/kg at the Rome and Milan-Negrar Centers, respectively).

In all cases, patients fasted for at least 6 hours before starting the study; blood glucose level was measured before injection and was less than 160 mg/dL in all patients. PET images were recorded for 3 minutes per bed position, from head to midthigh, 1 hour after intravenous injection. Low-dose CT scans for attenuation correction and anatomic location were performed using a continuous spiral technique on a 64-slice helical CT scanner with the following parameters: 120–140 kV, 90–100 mA, 0.5–0.8-second tube rotation, 5 mm thickness. After acquisition attenuation, corrected PET images were fused with CT images and displayed in maximum intensity projections along the axial, sagittal, and coronal orthogonal planes.

Imaging Analysis

^{18}F-FDG PET images were reviewed by nuclear medicine physicians, well experienced in the field of NENs, who were unaware of the patients' clinical data. The reviewers were asked to classify the scans as positive or negative after visual and qualitative evaluation. Each examination was considered to be positive when a focal uptake was higher than the liver radioactivity and negative in the absence of high-uptake foci. The sites of known physiologic uptake, that is, kidney, ureter, bladder, and muscle-skeletal symmetrical uptake, were not mentioned to avoid misinterpretations. The maximum standardized uptake value (SUV_{max}), a parameter used to achieve a semiquantitative evaluation of the ^{18}F-FDG PET uptake, was calculated, but no quantitative or semiquantitative parameters were considered for the reviewers' qualitative assessment.

Data Analysis

The diagnostic ability of ^{18}F-FDG PET to correctly identify disease status was evaluated by assessing the proportion of cases in which it correctly identified the disease status (positive ^{18}F-FDG PET in patients with documented PD, negative ^{18}F-FDG PET in patients with documented SD). A 2 $\times$ 2 table was used to assess ^{18}F-FDG PET sensitivity and specificity.

Progression-free survival (PFS) was defined as the interval between radiological examinations and time of PD or patient death, if it occurred before documented PD. PFS, as well as overall survival (OS) analyses, were performed using the Kaplan-Meier method, and the results were compared by using the log-

Table 1. General features of the 93 evaluated patients

Characteristics	*n* (%)
Gender	
Male	41 (44.1)
Female	52 (55.9)
Primary tumor site	
Pancreas	69 (74.1)
Small intestine	24 (25.9)
Tumor staging[a]	
Stage III	9 (9.7)
Stage IV[b]	84 (90.3)
Grading[c]	
NET G1	26 (28)
NET G2	48 (51.6)
NEC G3	19 (20.4)
Median Ki67 (25th–75th IQR)	7% (3–17)
^{68}Ga PET positive	87 (93.5)
Median SUV^{68}_{max}Ga PET (25th–75th IQR)	22 (16–44)

[a]According to the European Neuroendocrine Tumor Society TNM staging system.
[b]Metastasis site: liver ($n = 93$, 100%), lung ($n = 15$, 16.1%), bone ($n = 7$, 7.5%).
[c]According to the World Health Organization 2010 classification/ENETS G-grading system.
Abbreviations: G1, grade 1; G2, grade 2; G3, grade 3; IQR, interquartile range; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PET, positron emission tomography; SUV_{max}, maximum standardized uptake value.

rank test. Multiple regression was used to determine the association between selected clinical and imaging variables and the presence of documented PD at the time of study entry, which was considered as a dependent variable. The analysis of risk factors for prediction of PD during follow-up was performed by univariate and multivariate analysis using a Cox proportional hazard model. Risk factors were expressed as hazard ratio (HR). The multivariate model was constructed by the "enter" method, after including all variables that had resulted significant at the univariate analysis. The distribution of continuous variables was reported as median and interquartile range [IQR; 25th to 75th percentiles]. Comparison between subgroups was performed by Fisher exact test or chi-square test, as appropriate. All p values $<.05$ were considered significant. The statistical analysis was performed using a dedicated software (MedCalc16.4.3; MedCalc Software, Ostend, Belgium, www.medcalc.be).

Results

Included Patients

Of 142 patients with advanced EP NENs initially reviewed for potential eligibility, 93 (median age 60 years, IQR 50–68 years), with a median overall follow-up of 39 months (IQR 15–50 months) were included in the final analysis. The remaining 49 patients were excluded because of the following reasons: ^{18}F-FDG PET and CT scan were performed with a time frame >1 month ($n = 34$); follow-up data were not available ($n = 13$); Ki67 value was unknown ($n = 2$).

The median interval between patients' initial diagnosis with EP NENs and enrollment into the study was 13 months (IQR 6–85 months). Patients' general features are summarized in Table 1.

Table 2. ^{18}F-FDG-PET diagnostic accuracy

^{18}F-FDG PET findings	Progressive disease ($n = 64$) *n* (%)	Stable disease ($n = 29$) *n* (%)
^{18}F-FDG PET positive ($n = 62$)	58 (90.6)	4 (13.8)
^{18}F-FDG PET negative ($n = 31$)	6 (9.4)	25 (86.2)

Overall diagnostic accuracy was 89.2% (83/93) as a result of the sum of patients with positive ^{18}F-FDG PET and progressive disease (58/64) and patients with negative ^{18}F-FDG PET and stable disease (25/29).
Abbreviation: ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

Table 3. ^{18}F-FDG PET findings according to G grading categories

^{18}F-FDG PET findings	NET G1 ($n = 26$): *n* (%)	NET G2 ($n = 48$): *n* (%)	NEC G3 ($n = 19$): *n* (%)
^{18}F-FDG PET positive ($n = 62$)	14 (53.8)	30 (62.5)	18 (94.7)
^{18}F-FDG PET negative ($n = 31$)	12 (46.2)	18 (37.5)	1 (5.3)

Chi-square test $p = .01$.
Abbreviations: ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; NET G1, neuroendocrine tumors with Ki67 $\leq 2\%$; NET G2, neuroendocrine tumors with Ki67 3%–20%; NEC G3, neuroendocrine carcinomas with Ki67 $>20\%$.

The most frequent medical treatments that patients had received before the study entry were somatostatin analogues, 69 patients (74.1%); everolimus, 18 patients (19.3%); peptide receptor radionuclide therapy (PRRT), 18 patients (19.3%); and systemic chemotherapies, 6 patients (6.5% [capecitabine and temozolomide, 4 patients; cisplatin and etoposide, 1 patient; capecitabine and oxaliplatin, 1 patient]). A total of 8 patients (8.6%) had undergone liver disease cytoreduction (surgical debulking, 4 patients; chemoembolization, 4 patients), and the primary tumor had been previously resected in 43 patients (46.2%). A total of five patients (5.4%) did not receive any treatments before entering the study due to a recent diagnosis; however, the disease status was also known in these patients given the availability of previous radiological examination to assess the tumor behavior.

According to RECIST 1.0 criteria, 64 patients (68.8%) had PD, as documented by radiological imaging procedures, whereas the remaining 29 patients (31.2%) had SD at the time of study enrollment.

^{18}F-FDG PET Results and Association with Disease Status at Study Entry

A total of 62 patients (66.7%) had a positive ^{18}F-FDG PET, median SUV_{max} being 6 (IQR 4–8.2), whereas ^{18}F-FDG PET was negative in the remaining 31 patients (33.3%). As far as the primary tumor site was concerned, ^{18}F-FDG PET was positive in 47 patients with pancreatic NENs (68.1%) and in 15 patients (62.5%) with intestinal NENs ($p = .449$).

Disease status was correctly identified by ^{18}F-FDG PET in 83 of 93 patients, thus resulting in a diagnostic accuracy of 89.2% (Table 2). The sensitivity and specificity of ^{18}F-FDG PET to

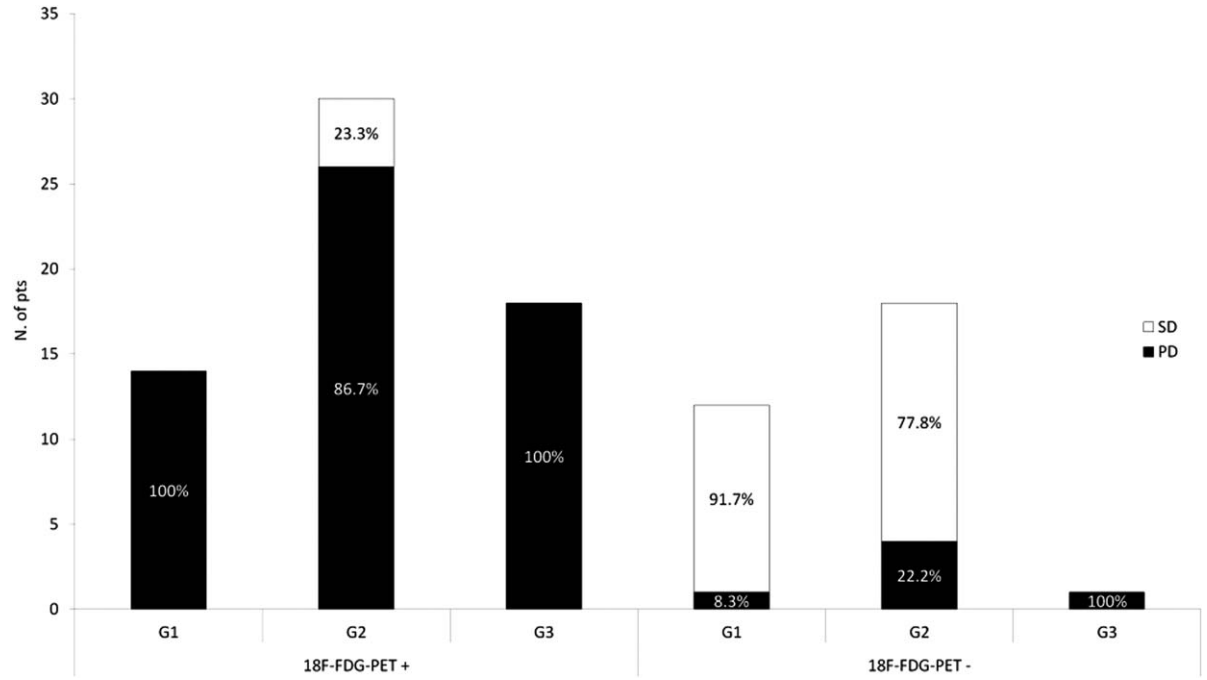

Figure 1. Relationship between ^{18}F-FDG PET findings and disease status at time of diagnosis, according to the G grading system.
Abbreviations: ^{18}F-FDG PET+, ^{18}F-fluorodeoxyglucose positron emission tomography positive; ^{18}F-FDG PET−, ^{18}F-fluorodeoxyglucose positron emission tomography negative; G1, grade 1 (Ki67 $\leq$ 2%); G2, grade 2 (Ki67 = 3%–20%); G3, grade 3 (Ki67 $>$ 20%); PD, progressive disease; SD, stable disease.

identify the disease status correctly were 90.6% and 86.2%, respectively.

As far as the relationship between ^{18}F-FDG PET findings and tumor grading was concerned, a statistically significant higher proportion of ^{18}F-FDG PET-positive examinations were observed in patients with higher tumor grade ($p = .01$; Table 3; Fig. 1).

A positive ^{18}F-FDG PET was significantly associated with PD at the time of study entry, as confirmed by univariate and multivariate regression analysis (Table 4), thus confirming the high ability of ^{18}F-FDG PET to predict tumor aggressiveness in these patients.

^{18}F-FDG PET Results and Association with Clinical Outcome

After the ^{18}F-FDG PET examination, patients received the following therapies during a median follow-up time of 25 months (IQR 15–36): somatostatin analogues, 70 patients (75.2%); everolimus, 35 patients (37.6%); PRRT, 31 patients (33.3%); systemic chemotherapies, 12 patients (12.9% [capecitabine and temozolomide, 11 patients; cisplatin and etoposide, 1 patient]); and sunitinib, 5 patients (5.3%).

Overall, median PFS was 22 months. PFS was significantly longer in patients with a negative ^{18}F-FDG PET in comparison with ^{18}F-FDG PET-positive ones, the median PFS being 50 and 9 months, respectively ($p < .0001$; Fig. 2).

A total of 30 patients died during follow-up, resulting in a mortality rate of 32.2%. Median OS was 60 months. A significantly longer OS was observed in ^{18}F-FDG PET-negative patients in comparison with ^{18}F-FDG PET-positive patients, median OS being not reached and 60 months, respectively ($p = .008$; Fig. 3).

At univariate analysis, the predictors for increased risk of death during follow-up were Ki67 (HR 1.02 for each increasing unit) and ^{18}F-FDG PET positivity (HR 3.19; $p = .001$ and $p = .013$, respectively). Both variables were also confirmed to be independent predictors for poor clinical outcome by multivariate analysis ($p = .009$ and $p = .037$, respectively).

Table 4. Variables associated with progressive disease at the time of study entry

Variable	Coefficient	SE	*p* value
Univariate analysis			
Pancreatic primary	0.141	0.110	.202
Tumor grading[a]	0.198	0.067	.004
Ki67	0.007	0.002	.003
^{18}F-FDG PET positive	0.741	0.067	<.0001
^{68}Ga PET positive	−0.121	0.215	.573
Multivariate analysis			
Model 1			
^{18}F-FDG PET positive	0.717	0.070	<.0001
Tumor grading[a]	0.058	0.047	.225
Model 2			
^{18}F-FDG PET positive	0.712	0.068	<.0001
Ki67[b]	0.003	0.001	.052

[a]According to World Health Organization 2010 classification/ENETS G-grading system.
[b]Continuous variable.
Abbreviations: ^{18}F-FDG PET, ^{18}F-fluourodeoxyglucose positron emission tomography; ^{68}Ga PET, ^{68}Ga positron emission tomography; SE, standard error.

Discussion

The possible clinical usefulness of ^{18}F-FDG PET in EP NENs has been extensively investigated over the last few years. Although the overall ^{18}F-FDG PET utility in aggressive NENs has already been investigated by other studies, conflicting results have been reported, possibly due to the heterogeneity of the

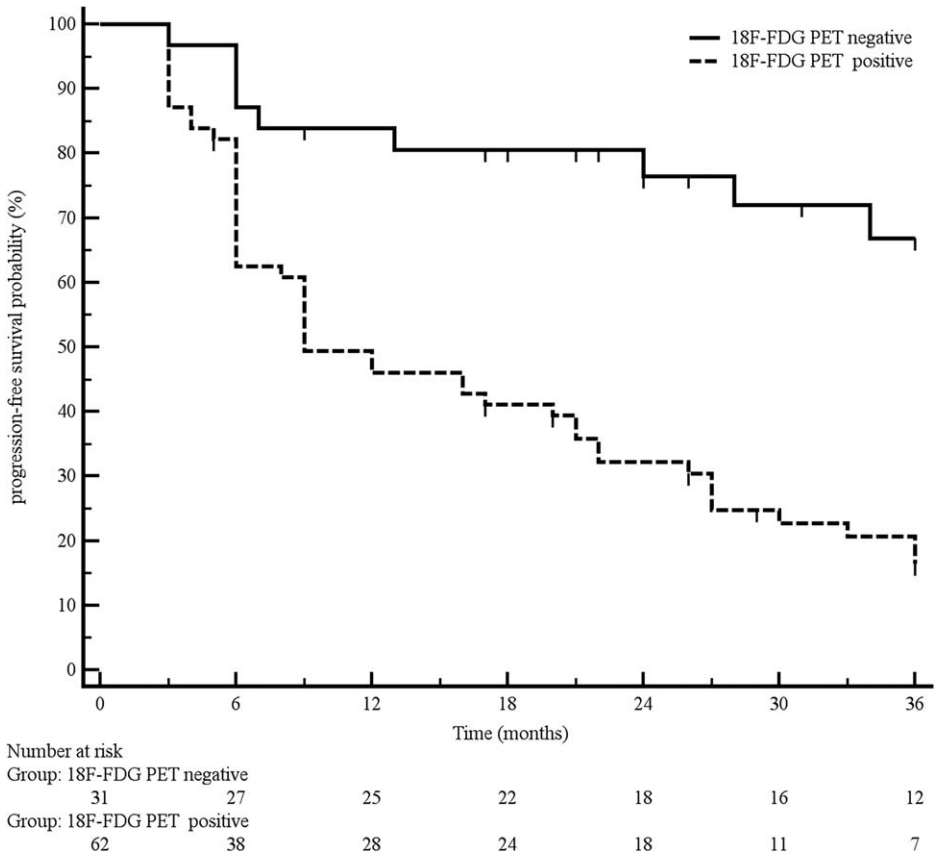

Figure 2. Progression-free survival according to ^{18}F-FDG PET findings.
Abbreviation: ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

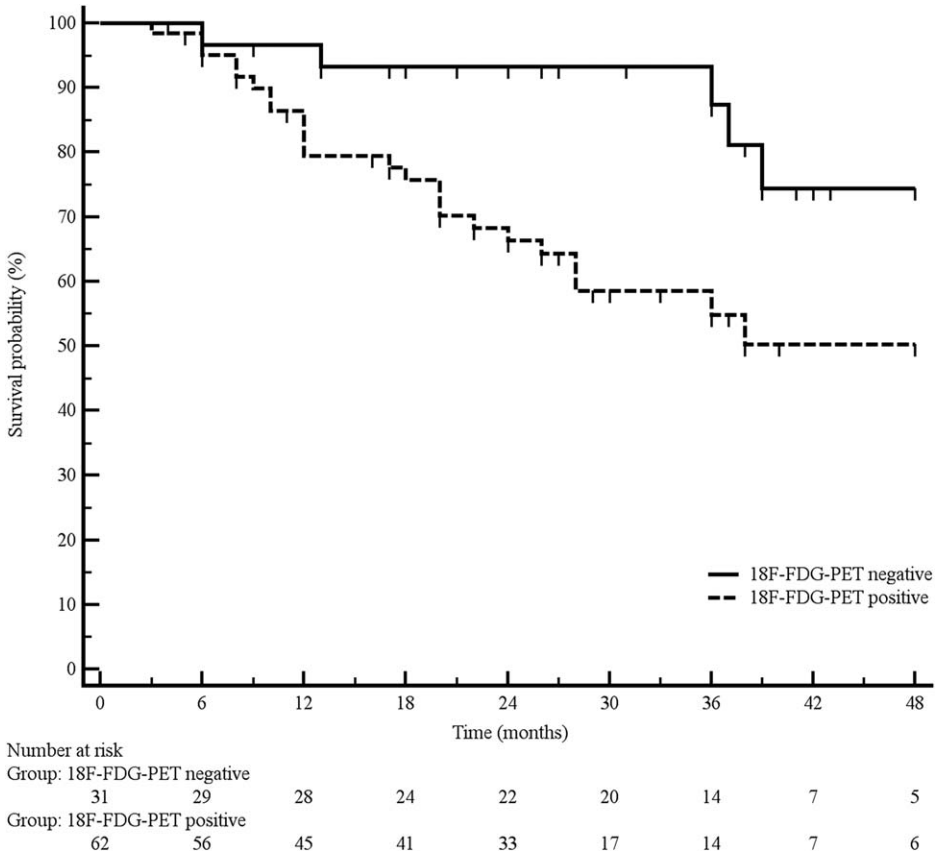

Figure 3. Overall survival according to ^{18}F-FDG PET findings.
Abbreviation: ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

enrolled populations in most of those studies, which have rarely focused on the relationship between ^{18}F-FDG PET findings and tumor behavior at the time of the examination.

Ezziddin et al. [30] investigated the predictive ability of ^{18}F-FDG PET on PFS and OS, suggesting that patients should be stratified according to the metabolic expression into three risk categories based on the glycolytic activity. In that study, the metabolic grade inversely correlated with survival stratification, thus proving to be a strong independent predictor for poor clinical outcome. However, the possible correlation with histological grading was not evaluated. Furthermore, the methodology proposed to identify the risk categories has not been validated so far.

A proposal to correlate ^{18}F-FDG PET findings with the WHO classification was made by Binderup et al. [18], who observed, over a relatively short follow-up period (11.5 months), that ^{18}F-FDG PET SUV_{max} correlated with patients' risk of death. An increased incidence of ^{18}F-FDG PET positivity was reported in tumors with increased Ki67, suggesting a possible correlation between the two parameters. However, that study was performed in a heterogeneous population of patients (digestive and bronchial NENs). Furthermore, the Ki67 proliferative index was not available for all patients, and the ^{18}F-FDG PET expression did not correlate with the disease status (PD or SD).

Similar findings were also reported by other studies [19, 20], which generally showed that ^{18}F-FDG PET positivity correlated with poor survival in NENs. Again, although the messages from these studies agree with that reported by the present work, they were usually performed in small, heterogeneous series of patients, including those with NENs arising both from the digestive system and from the lung.

In the present paper, a larger and homogeneous series of patients with advanced EP NENs with known disease status and Ki67 at the time of study enrollment was investigated in order to assess the relationship between ^{18}F-FDG PET findings and disease status and to try to better place this examination in the diagnostic algorithm of these patients.

As already mentioned, in the present study, disease status (SD or PD) was assessed according to RECIST version 1.0 criteria, which suggest evaluating tumor response basing on conventional CT or MRI techniques [22]. However, additional useful information on disease status during follow-up might be provided by using ^{68}Ga PET CT, given its ability to detect new metastatic lesions in progressive tumors [31].

The recent updated European Neuroendocrine Tumors Society guidelines, indeed, do not recommend the use of ^{18}F-FDG PET in EP NENs unless a grade 3 grading is present [32, 33]. This recommendation might be challenged by some of our findings.

In the present study, the association between ^{18}F-FDG PET positivity and the presence of PD was significantly stronger, compared with that of the G grading system or Ki67 analyzed as continuous variables, as confirmed by the multiple regression models summarized in Table 4. This figure highlights the role of this examination as a noninvasive, accurate tool able to identify unfavorable disease behavior that might be an alternative to Ki67, which, as is well known, is considered to be the strongest prognostic factor for these patients, as reported in both pancreatic and intestinal NENs [4–8, 34, 35].

Interestingly, a consistent proportion of patients with grade 1 neuroendocrine tumors (NETs) (53.8%) also had positive ^{18}F-FDG PET, and 37.5% of patients with grade 2 NETs had negative ^{18}F-FDG PET (Fig. 1). This finding suggests that ^{18}F-FDG PET findings do not depend on G grading alone, because it may also be positive in tumors with low proliferative activity. On the contrary, it significantly correlated with the disease behavior at the time of examination, again suggesting consideration of tumor behavior instead of Ki67 as the major factor influencing ^{18}F-FDG PET findings.

Guidelines from both the National Comprehensive Cancer Network and the European Neuroendocrine Tumor Society [36, 37] propose to consider a "watch and wait" strategy in the therapeutic algorithm of nonfunctioning, low-grade NENs with limited tumor burden and known stable disease. However, if disease behavior is unknown (i.e., in newly diagnosed patients), positive ^{18}F-FDG PET may be helpful to identify those patients with significant risk of progression, avoiding unsafe observation before beginning antitumor therapy.

Conclusion

Although the present study is affected by some limitations, which, however, may be considered intrinsic to most studies investigating EP NENs (i.e., retrospective data analysis and heterogeneous, nonstandardized, therapeutic approaches received by the patients), we believe that some useful clinical messages might be drawn: (a) Because ^{18}F-FDG PET findings strongly correlate with disease behavior, they may provide useful information to better select patients with more aggressive disease. (b) In patients with unknown disease status, ^{18}F-FDG PET is able to provide relevant clinical information, suggesting the choice of a more aggressive therapeutic approach in patients with positive examination. (c) On the contrary, if the disease status (PD or SD) is already known, as confirmed by comparing cross-sectional radiological examinations performed during previous follow-up, ^{18}F-FDG PET might be avoided, because it would not give any additional information on tumor behavior. These findings may help physicians dealing with advanced EP NENs to better select patients for whom ^{18}F-FDG PET is really needed, in order to plan tailored therapeutic approaches in patients with high risk of predictable unfavorable clinical outcome.

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Author Contributions

Conception/design: Maria Rinzivillo, Massimo Falconi, Gianfranco Delle Fave, Francesco Panzuto
Provision of study material or patients: Daniela Prosperi, Patrizia Pizzichini, Elsa Iannicelli, Matteo Salgarello
Collection and/or assembly of data: Maria Rinzivillo, Stefano Partelli, Gabriele Capurso, Elettra Merola, Francesca Muffatti
Data analysis and interpretation: Maria Rinzivillo, Francesco Scopinaro, Orazio Schillaci, Massimo Falconi, Gianfranco Delle Fave, Francesco Panzuto
Manuscript writing: Maria Rinzivillo, Francesco Panzuto
Final approval of manuscript: Maria Rinzivillo, Stefano Partelli, Daniela Prosperi, Gabriele Capurso, Patrizia Pizzichini, Elsa Iannicelli, Elettra Merola, Francesca Muffatti, Francesco Scopinaro, Orazio Schillaci, Matteo Salgarello, Massimo Falconi, Gianfranco Delle Fave, Francesco Panzuto

Disclosures

The authors indicated no financial relationships.

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