Dual-Tracer (^{68}Ga -DOTATOC and ^{18}F -FDG)-PET/CT Scan and G1-G2 Nonfunctioning Pancreatic Neuroendocrine Tumors: A Single-Center Retrospective Evaluation of 124 Nonmetastatic Resected Cases

Salvatore Paiella^a Luca Landoni^a Sarah Tebaldi^a Michele Zuffante^b
Matteo Salgarello^c Sara Cingarlini^d Mirko D'Onofrio^e Alice Parisi^f
Giacomo Deiro^a Erminia Manfrin^f Beatrice Bianchi^a Greta Montagnini^a
Stefano Francesco Crinò^g Claudio Bassi^a Roberto Salvia^a

^aPancreas Institute, General and Pancreatic Surgery Unit, University of Verona Hospital Trust, Verona, Italy;

^bNuclear Medicine Unit, Integrated University Hospital of Verona, Verona, Italy; ^cDepartment of Nuclear Medicine, Ospedale Sacro Cuore Don Calabria, Negrar, Verona, Italy; ^dPancreas Institute, Oncology Unit, University of Verona Hospital Trust, Verona, Italy; ^ePancreas Institute, Radiology Unit, University of Verona Hospital Trust, Verona, Italy;

^fPancreas Institute, Department of Diagnostics and Public Health, Section of Pathology, University of Verona Hospital Trust, Verona, Italy; ^gPancreas Institute, Gastroenterology and Digestive Endoscopy Unit, University of Verona Hospital Trust, Verona, Italy

Keywords

^{18}F -FDG PET/CT · ^{68}Ga -DOTATOC · Dual-tracer PET/CT Scan · Neuroendocrine tumors · Ki67

Abstract

Introduction: The combined use of ^{68}Ga gallium (^{68}Ga)-DOTA-peptides and ^{18}F fluorine-fluoro-2-deoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) scans in the workup of pancreatic neuroendocrine tumors (PanNETs) is controversial. This study aimed at assessing both tracers' capability to identify tumors and to assess its association with pathological predictors of recurrence. **Methods:** Prospectively collected, preoperative, dual-tracer PET/CT scan data of G1-G2, nonmetastatic, PanNETs

that underwent surgery between January 2013 and October 2019 were retrospectively analyzed. **Results:** The final cohort consisted of 124 cases. There was an approximately equal distribution of males and females (50.8%/49.2%) and G1 and G2 tumors (49.2%/50.8%). The disease was detected in 122 (98.4%) and 64 (51.6%) cases by ^{68}Ga -DOTATOC and by ^{18}F -FDG PET/CT scans, respectively, with a combined sensitivity of 99.2%. ^{18}F -FDG-positive examinations found G2 tumors more often than G1 (59.4 vs. 40.6%; $p = 0.036$), and ^{18}F -FDG-positive PanNETs were larger than negative ones (median tumor size 32 mm, interquartile range [IQR] 21 vs. 26 mm, IQR 20; $p = 0.019$). The median Ki67 for ^{18}F -FDG-positive and -negative examinations was 3 (IQR 4) and 2 (IQR 4), respectively ($p = 0.029$). At least 1 pathological predictor of recurrence was present in 74.6% of ^{18}F -FDG-positive cases (vs.

56.7%; $p = 0.039$), whereas this was not found when dichotomizing the PanNETs by their dimensions ($\leq/\geq 20$ mm). None of the 2 tracers predicted nodal metastasis. The receiver operating characteristic curve analysis showed that ^{18}F -FDG uptake higher than 4.2 had a sensitivity of 49.2% and specificity of 73.3% for differentiating G1 from G2 ($\text{AUC} = 0.624$, $p = 0.009$). **Conclusion:** The complementary adoption of ^{68}Ga -DOTATOC and ^{18}F -FDG tracers may be valuable in the diagnostic workup of PanNETs despite not being a game-changer for the management of PanNETs ≤ 20 mm.

© 2021 S. Karger AG, Basel

Introduction

Pancreatic neuroendocrine tumors (PanNETs) are rare pancreatic tumors with an incidence of 1–5 cases/100,000 inhabitants/year in Italy [1]. These tumors, especially some NF-PanNETs, especially compared with the exocrine ones, are generally considered clinically indolent due to their biology, despite some displaying aggressive behavior, with a tendency toward systemic dissemination [2]. Due to the rarity and the heterogeneous natural history, therapeutic pathways are based on consensus decisions rather than on robust clinical evidence [3, 4]. Preoperative staging is of utmost importance in adopting the most appropriate therapeutic choice and avoiding over- and undertreatment even when considering the complexity of pancreatic surgery. It includes anatomic imaging (such as computed tomography [CT], magnetic resonance imaging [MRI], and/or endoultrasoundography [EUS]) and receptor-based imaging, basically a positron emission tomography (PET)/CT with gallium-68 (^{68}Ga). Indeed, PanNETs show overexpression of somatostatin receptors on their cell membranes [5], which allow for the use of somatostatin receptor-targeted PET radiotracers [6], such as gallium-based tracers (^{68}Ga -DOTATOC and ^{68}Ga -DOTATATE).

Some prognostic factors for PanNETs may be identified. In an analysis of the historical cohort of 487 cases, the authors found that 12.3% of recurrence was predicted by tumor size, grading, nodal metastasis, and microvascular invasion at final pathology [7]. Some of these findings have already been reported by other groups [8, 9].

Preoperatively, the possibility to obtain a surrogate of tumor biology, such as Ki67 value and grading through a tumor biopsy [10, 11] or functional/metabolic activity through PET/CT, is intriguing, yet this possibility still requires further investigations. Current guidelines and expert panels include somatostatin analogs radiotracers-

PET at the time of diagnosis to stage the disease, define the extent of metastatic lesions if any, and determine whether somatostatin analogs may be used as a treatment option [12–14].

In a few centers, ^{18}F fluorine-fluoro-2-deoxyglucose (^{18}F -FDG)-PET/CT has been performed in conjunction with ^{68}Ga -DOTA-PET/CT since it may provide more reliable information about tumor aggressiveness [15, 16]. ^{18}F -FDG-PET/CT appears to be more useful for the localization of high-grade PanNETs. [13] Up to now, few studies have evaluated the performances of the 2 techniques using a head-to-head design. Recently, 2 systematic reviews of studies analyzing the dual-tracer PET scan reported conflicting results as to what is the optimal placement of such an examination in the diagnostic workup of PanNETs, suggesting it should be adopted for advanced cases for staging purposes only [17, 18]. In particular, it aimed at assessing both tracers' capability to identify tumors and to assess its association with pathological predictors of recurrence.

Materials and Methods

Study Design

The Institutional Review Board approved the present study, which follows the guidelines developed by "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE), as shown in (Fig. 1) [19]. Patients who underwent pancreatic resection from January 2013 to October 2019 with a final diagnosis of PanNET and with a preoperative PET scan examination for staging purposes were selected from the prospectively maintained electronic database at the General and Pancreatic Surgery Unit, Pancreas Institute, University of Verona Hospital Trust. Data were retrospectively analyzed (Fig. 1, Box#1). Paper medical records were reviewed if necessary. For the study, patients who had undergone a single-tracer PET only were excluded (Fig. 1, Box#2). To homogenize the cohort, the following cases were excluded as follows: patients receiving any systemic treatment before surgery, metastatic (either at the structural or the molecular imaging), multifocal, and genetic (Fig. 1, Box#4). Patients were treated according to the institutional routine procedures for PanNETs [20], following the ENETS recommendation [13]. Each patient underwent at least 1 cross-sectional imaging technique (CT or MR) before surgery, and in selected cases, EUS was performed, possibly with biopsy [21]. The use of a dual-tracer ^{18}F -FDG- and ^{68}Ga -DOTA-TOC-PET scan was adopted on a quasi-routine basis for each case since 2013 and was discussed at a multidisciplinary meeting afterward. The pathologist was not blinded to the results of the ^{18}F -FDG-PET and ^{68}Ga -DOTATOC-PET/CT scans.

Data Collection

Demographic, clinical, radiological, nuclear imaging, surgical, and pathological data were collected. For pathological assessments and reporting, PanNETs were classified according to the World Health Organization's criteria [22]. For the study and considering

Fig. 1. STROBE [19] flowchart of the study population. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; PET, positron emission tomography; CT, computed tomography.

the institutional analysis of predictors of recurrence [7], indicators of aggressiveness were considered: grading >1, nodal metastases, and microvascular invasion on the final pathology. For the cutoff of 20 mm, the radiological preoperative diameter was used as a surrogate of the pathological one [23].

⁶⁸Ga-DOTATOC-PET/CT and ¹⁸F-FDG-PET/CT Data and Protocols

Data were retrieved from stored medical records. The PET/CT scan was performed using the Gemini TF Big Bore system (Philips Inc, High Point, NC, USA) at the Nuclear Medicine Department of the Integrated University Hospital of Verona, Verona, or the Siemens Biograph mCT-S (64) system (Siemens, Knoxville, TN, USA) at the Nuclear Medicine Department of the IRCCS Sacro Cuore Don Calabria Hospital of Negrar, Verona.

Patients underwent 2 whole-body PET/CT scans, one from the level of the skull base to the mid-thigh starting 60 ± 10 min after the injection of ¹⁸F-FDG, and a whole-body PET/CT scan from the level of the vertex to the mid-thigh starting 60 ± 10 min after the injection of ⁶⁸Ga-DOTATOC. The patients fasted for 6 h before the study. Blood glucose levels were checked before an ¹⁸F-FDG-PET/CT was done.

CT scan images were reconstructed using a filtered back projection with 2-mm thickness and 512×512 matrix. PET images were reconstructed as slices using iterative algorithms. CT images were used to correct the PET emission data for photon attenuation.

A positive lesion at ¹⁸F-FDG-PET/CT was defined as the presence of higher tracer uptake with respect to the surrounding pancreatic parenchyma and for standardized uptake values (SUV_{max}) of >3. As for ⁶⁸Ga-DOTATOC, a lesion was deemed visually positive if it showed a definite increase in tracer accumulation compared with the background. Analyses of PET/CT images were interpreted by experienced nuclear medicine physicians who had the clinical information for each case.

Statistical Analysis

Normally distributed variables were expressed as means and standard deviations, variables not following a normal distribution were reported as medians and interquartile ranges (IQRs), and categorical variables were expressed as frequencies and proportions. The Shapiro-Wilk test was used to determine the normality of data distribution. Association between ¹⁸F-FDG uptake and Ki67 was assessed using linear regression analysis. The Mann-Whitney or Student's *t* tests were used to discover the differences between the groups in continuous variables, and Fisher's exact test was used for binary variables. The receiver operating characteristic (ROC) analysis was used to identify a SUV_{max} threshold (cutoff value) for discrimination between G1 and G2 tumors. A *p* value of <0.05 was considered statistically significant, and only two-tailed tests were used. The data analysis was performed using SPSS version 21 (IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software, Ostend, Belgium).

Table 1. Patient characteristics ($n = 124$)

Age, median (IQR)	58 (17)
Sex, M/F (%)	63/61 (50.8/49.2)
Symptoms (yes), n (%)	48 (37.8)
Site, n (%)	
Head-neck	53 (42.6)
Body	28 (22.6)
Tail	43 (34.7)
Tumor diameter, mm, mean (SD)	32.1 (19.1)
$\leq$ / $>$ 20 mm, n (%)	37/87 (29.8/70.2)
Cromogranin A, ng/mL, mean (SD) ($n = 47$)	164 (264)
Surgery, n (%)	
Type	
Distal pancreatectomy with/without splenectomy	69 (56)
Pancreaticoduodenectomy	38 (31)
Total pancreatectomy with/without splenectomy	8 (6)
Atypical resections*	9 (7)
Approach, minimally invasive	44 (35.5)

* Middle pancreatectomy, enucleation. IQR, interquartile range; SD, standard deviation.

Results

Study Population

A total of 124 patients formed the final population. Table 1 shows the demographic, clinical, and surgical features of the whole cohort. A slight prevalence of males (50.8%, 63/124) was noted, and the overall median age was 58 years (IQR 17). Tumors were usually discovered occasionally (62.2%, 76/124), they were located in the body-tail (57.2%, 71/124), and distal pancreatectomy was the most commonly performed surgery (47.6%, 59/124).

Pathological features are summarized in Table 2. G1 and G2 tumors had almost the same prevalence. The overall rate of N+ was 34.7% (43/124), which was higher for G2 PanNETs (46%, 29/63). The overall median Ki67 was 3 (IQR 4).

Dual-Tracer PET/CT Scan General Characteristics

The median time between the 2 examinations was 1 day (IQR 4.5). The median time from the last PET scan to surgery was 51 days (IQR 55). The examinations were both positive in 63 PanNETs (50.8%; 25 G1 [41% of G1]; 38 G2 [60.3% of G2]). Overall, 1 examination was negative for both tracers (0.8%), in 59 cases (47.6%), and in 1 case (0.8%), only 1 tracer was positive (^{68}Ga -DOTATOC-PET/CT and ^{18}F -FDG-PET/CT, respectively). In 99.2% of cases (123/124), the examination was positive at a single tracer at least. Figure 2 shows 2 cases of PanNETs that were positive with only 1 tracer.

The SUV_{max} was retrievable from medical records for 98 (79%) ^{68}Ga -DOTATOC-PET/CT scans only. Among the 26 missing values, 2 examinations were negative, and

Table 2. Pathologic findings ($n = 124$)

Grading, n (%)	
G1	61 (49.2)
G2	63 (50.8)
Macroscopic appearance, n (%)	
Solid	104 (83.9)
Cystic	13 (10.5)
Mixed	7 (5.6)
Ki67, overall, median (IQR)	3 (4)
N+, n (%)	43 (34.7)
Of G1	14 (23)
Of G2	29 (46)
American Joint Committee on Cancer staging [40]	
Ia	31 (25)
Ib	42 (33.9)
IIa	8 (6.5)
IIb	36 (29)
III	7 (5.6)
European Neuroendocrine Tumor Society staging [41]	
I	31 (25)
IIa	42 (33.9)
IIb	8 (6.5)
IIIb	43 (34.7)
R1, n (%)	4 (3.2)
Microvascular invasion (V+), n (%)	32 (25.8)

IQR, interquartile range.

the remaining 24 were positive. A total of 122 exams (98.4%, 122/124) were ^{68}Ga -DOTATOC-PET/CT positive, with a median SUV_{max} value of 43 (IQR 50). Sixty-four ^{18}F -FDG-PET/CT scans (51.6%) were positive, with a median SUV_{max} value of 8 (IQR 6).

Table 3. ¹⁸F-FDG-PET/CT scan positivity/negativity and pathological findings (overall cohort)

Variable	¹⁸ F-FDG-PET positive (n = 64, 51.6%)	¹⁸ F-FDG-PET negative (n = 60, 48.4%)	p value
Age, years, median (IQR)	55 (37.2)	58 (18.8)	0.498
Symptoms (yes), n (%)	24 (37.5)	24 (40)	0.357
Tumor size, mm, median (IQR)	32 (21)	26 (20)	0.019
Grading, n (%)			
G1	26 (40.6)	35 (58.3)	0.036
G2	38 (59.4)	25 (41.7)	
N+* (yes), n (%)	23 (35.9)	20 (33.3)	0.851
Ki67, median (IQR)	3 (4)	2 (4)	0.029
V+ [†] yes, n (%)	17 (26.6)	15 (25)	1
Predictors of recurrence, [‡] yes, n (%)	47 (74.6)	34 (56.7)	0.039

Italics indicate statistical significance. F-FDG, fluorine-fluoro-2-deoxyglucose; PET, positron emission tomography; CT, computed tomography; IQR, interquartile range. * Microvascular invasion. [†] Nodal metastasis. [‡] G2, V+, or N+.

Fig. 2. Dual-tracer PET/CT scans. Upper 2 examinations: G1 PanNET ⁶⁸Ga-DOTA-TOC highly avid (left) and ¹⁸F-FDG negative (right); lower 2 scans: G2 PanNET showing modest and heterogeneous ⁶⁸Ga-DOTA-TOC uptake (left) but intense glucose metabolism (right). PanNET, pancreatic neuroendocrine tumor; PET, positron emission tomography; CT, computed tomography; ¹⁸F-FDG, fluorine-fluoro-2-deoxyglucose; Ga, gallium.

Dual-Tracer PET/CT Scan Characteristics and Pathologic Findings (Overall Cohort)

The only 2 negative ⁶⁸Ga-DOTA-TOC PET/CT scans came from 2 G1 tumors (Table 3). The uptake of ⁶⁸Ga-

DOTA-TOC in G1 tumors was not statistically significantly different than the one of G2 tumors (median SUV_{max} 42, IQR 50 vs. 43.4, IQR 51, *p* = 1). The very small number of negative ⁶⁸Ga-DOTA-TOC-PET/CT scans did

Fig. 3. a Comparison of median SUV_{max} of ¹⁸F-FDG tracer and grading (G1 vs. G2; $p < 0.009$). **b** Ki67 $\leq$ / $>$ 5% (24) ($p = 0.038$). The orange box and the horizontal line indicate the median, and the error bars mark the 75th and 25th percentiles. IQR, interquartile range; SUV_{max}, standardized uptake value; ¹⁸F-FDG, fluorine-fluoro-2-deoxyglucose.

Fig. 4. ROC curve analysis for the differential diagnosis of G1 and G2 PanNET according to SUV_{max} of ⁶⁸Ga-DOTATOC (left) and ¹⁸F-FDG-PET/CT (right). ROC, receiver operating characteristic; PanNET, pancreatic neuroendocrine tumor; SUV_{max}, standardized uptake value; ¹⁸F-FDG, fluorine-fluoro-2-deoxyglucose; Ga, gallium; PET, positron emission tomography; CT, computed tomography.

not allow an association analysis to be made with the pathological findings.

When considering ¹⁸F-FDG-PET/CT scan results, most G1 tumors were ¹⁸F-FDG negative (57.3%), whereas most G2 tumors (59.4%) were ¹⁸F-FDG positive ($p =$

0.036). The median ¹⁸F-FDG uptake in G1 tumors was lower than in G2 tumors (2.8, IQR 1.8 vs. 4, IQR 6, $p < 0.009$, Fig. 3a). When dichotomizing for the other Ki67 cutoff of 5% [24], the median SUV_{max} values remained statistically significant (2.8, IQR 3.2 for Ki67 $\leq$ 5%, and

4.1, IQR 6.2 for Ki67 >5%; $p = 0.038$; Fig. 3b). All PanNETs with a Ki67 ≥ 10 ($n = 16$) were positive on the ^{68}Ga -DOTATOC-PET/CT scan, and 9 (56%) were positive at ^{18}F -FDG-PET/CT scan.

Notably, some statistically significant associations were found between a ^{18}F -FDG-PET/CT scan positive and some parameters, such as grading >G1 ($p = 0.036$) and the presence of any predictor of recurrence (>G1, N+, or V+; $p = 0.039$). Table 3 shows the association between ^{68}Ga -DOTATOC- and ^{18}F -FDG-PET/CT scans values and pathological variables. Linear regression did not show any association between the SUV_{max} of ^{18}F -FDG and ^{68}Ga -DOTATOC and the tumor Ki67 ($r = 0.09$, $p = 0.301$ and $r = 0.03$, $p = 0.759$, respectively).

Figure 4 shows ROC curve analysis. A ^{18}F -FDG uptake higher than 4.2 had a sensitivity of 49.2% and specificity of 73.3% for differentiating G1 from G2 PanNETs (AUC = 0.624, $p = 0.009$). The same analysis for ^{68}Ga -DOTATOC was not statistically significant.

^{68}Ga -DOTATOC-PET/CT and ^{18}F -FDG-PET/CT Scans and PanNETs ≤ 20 or > 20 mm

^{68}Ga -DOTATOC-PET/CT scan was positive in 36 out of 37 (97.3%) PanNETs ≤ 20 mm, with a median SUV_{max} of 43.4 (IQR 50) and in 86 out of 87 (98.8%) PanNETs > 20 mm (median SUV_{max} 42.4, IQR 50). ^{18}F -FDG-PET/CT scan results were associated with demographic and pathological variables stratifying PanNETs according to the dimensions (> 20 or ≤ 20 mm, online suppl. Table 1; see www.karger.com/doi/10.1159/000514809 for all online suppl. material). The ^{18}F -FDG-PET/CT scan was positive in 49 out of 87 (56.3%) PanNETs > 20 mm and in 15 out of 37 (40.5%) PanNETs ≤ 20 mm (online suppl. Table 1).

Discussion

In this study, we aimed to investigate the metabolic profile of nonadvanced, unifocal, resected PanNETs that underwent dual-tracer PET/CT scan before surgery. Our results support the concept that ^{68}Ga -DOTATOC and ^{18}F -FDG tracers provide useful metabolic information of PanNETs that may be adopted to identify the tumors, tailor the treatment (for ^{68}Ga -DOTATOC-positive ones), and provide information on the putative aggressiveness. The results here presented, which come from the largest cohort so far, may not be completely comparable to the current literature. Indeed, referral studies are heterogeneous in terms of histological subtypes of neuroendo-

crine tumor (pancreatic vs. nonpancreatic), stage of the disease (advanced vs. nonadvanced), and treatment (resected vs. nonresected) [17, 18].

The overall ^{18}F -FDG-PET/CT scan sensitivity of 51.6% is in line with most previous reports [25–28], demonstrating that many PanNETs do not reveal their metabolic fingerprint. This happens mostly for G1 than for G2 tumors (nearly 40 and 60%, respectively). ^{18}F -FDG-PET/CT scan positivity was associated significantly with grading and with the presence of recurrence predictors. In contrast, it was not associated with the prediction of nodal metastasis. A positive direct association was found between tumor dimensions and ^{18}F -FDG-PET/CT scan positivity/negativity, whereby ^{18}F -FDG-positive tumors were larger than ^{18}F -FDG-negative ones ($p < 0.001$). Finally, Ki67 and ^{18}F -FDG-PET/CT scan results were significantly associated in terms of positivity/negativity of the examination (^{18}F -FDG-positive tumors showed a higher Ki67 than ^{18}F -FDG-negative ones). These results show direct associations between tumor dimensions, Ki67 values and ^{18}F -FDG-PET/CT, have already been reported by other authors. [27, 29–33] The SUV_{max} of both tracers did not significantly associate with tumor Ki67. After ROC curve analysis, an SUV_{max} cutoff value of 4.2 was found as the best compromise between sensitivity and specificity for differentiating G1 from G2 tumors ($p = 0.009$). If further confirmed, the SUV_{max} value may be a valuable element to include in the diagnostic workup.

Considering that almost all examinations were ^{68}Ga -DOTATOC-PET/CT positive, we did not perform any statistical analyses between this tracer and pathological features as the findings would have been clinically meaningless. We confirmed the very high sensitivity (98.4%) of ^{68}Ga -DOTATOC-PET/CT [27, 28, 33–35] for detecting PanNETs. Almost half of the cases (48.4%) were positive at this examination only. An excellent combined sensitivity of >99% replicates previous reports [35, 36] and gives strength to the combined use of the 2 tracers, especially for those small, doubtful cases.

This study's results contribute to the literature reporting on the role of dual-tracer PET/CT scans in the diagnostic workup of PanNETs. In our experience, the complementary adoption of the 2 methods helps identify the disease (combined sensitivity of 99%), to predict the presence of possible recurrence predictors, and, considering Ki67 as a surrogate of tumor biology, to assess the prognosis (this latter is speculation as no survival analysis was performed due to the median short follow-up time of 18.5 months). No clinically impacting results were found when stratifying the tumors according to their dimension

(>20 or ≤20 mm). The dual tracer seems to lack the capability of contributing to the decisional therapeutic process of nonfunctioning PanNETs ≤20 mm; therefore, for ¹⁸F-FDG-PET/CT, it should not be adopted on a routine basis in such cases, where EUS fine-needle aspiration may provide reliable information on the biology of the tumor [11].

Peculiar scenarios, where the complementary adoption of both tracers may be even more useful, are the diagnostic workup of small doubtful cases (the smallest PanNET ⁶⁸Ga-DOTATOC-PET/CT scan positive was 6 mm), or when a imaging and metabolic confirmation of the grading obtained at biopsy are needed (whereby G1 tumors are more prone to be ¹⁸F-FDG-PET/CT-negative and vice versa for G2 ones). Some limitations mitigate the considerations made. First, the retrospective nature did not allow us to investigate precisely if and how the results of dual-tracer PET/CT scan impacted the decision to perform surgery, especially for small PanNETs where ¹⁸F-FDG avidity may have played a role. Second, patients were managed and operated on at a single institution. However, the dual-tracer PET/CT scan may have been performed at one of the 2 institutions, using different PET/CT scan equipment and operators; no PET-imaging revision was made. Third, the examination may have occurred either before or after the fine-needle aspiration of PanNETs, so the evaluation may have been influenced accordingly. No survival analyses were done by purpose due to the short follow-up period. To conclude, the adoption of dual-tracer PET/CT scan may provide very useful metabolic information that can be used for multiple purposes.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the institutional review board (approval number for the retrospective collection of data, PAD-R 1101CESC).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was funded by Fondazione Italiana Malattie Pancreas–Ministero Salute (FIMPCUP_J38D19000690001), Associazione Italiana Ricerca Cancro (AIRC 5×1000 no. 12182), and Fondazione Cariverona: Oncology Biobank Project “Antonio

Schiavi” (prot. 203885/2017). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Salvatore Paiella: substantial contributions to the conception or design of the work and to the acquisition, analysis, and interpretation of data; drafting the work; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Luca Landoni: substantial contributions to the conception or design of the work and to the interpretation of data; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Sarah Tebaldi: substantial contributions to the acquisition of data; drafting the work; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Michele Zuffante: substantial contributions to the conception or design of the work and to the analysis of data; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Matteo Salgarallo: substantial contributions to the conception or design of the work and to the analysis of data; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Sara Cingarlini: substantial contributions to the conception or design of the work and to the interpretation of data; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Mirko D’Onofrio: substantial contributions to the conception or design of the work and to the analysis of data; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Alice Parisi: substantial contributions to the conception or design of the work; drafting the work; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Giacomo Deiro: substantial contributions to the acquisition of data and to the interpretation of data; drafting the work; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Erminia Manfrin: substantial contributions to the conception or design of the work; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Beatrice Bianchi: substantial contributions to the acquisition

tion of data; drafting the work; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Greta Montagnini: substantial contributions to the acquisition of data; drafting the work; final approval of the version. Stefano Francesco Crinò: substantial contributions to the conception or design of the work and to the analysis of data; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Claudio Bassi:

substantial contributions to the conception or design of the work and to the interpretation of data; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Roberto Salvia: substantial contributions to the conception or design of the work and to the interpretation of data; critical revision for important intellectual content; final approval of the version; accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- 1 Associazione Italiana di Oncologia Medica (AIOM). Linee guida neoplasie neuroendocrine gastroenteropancretiche. 2019.
- 2 Oberg K, Eriksson B. Endocrine tumours of the pancreas. *Best Pract Res Clin Gastroenterol*. 2005 Oct;19(5):753–81.
- 3 Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2016;103(2):153–71.
- 4 Partelli S, Cirocchi R, Crippa S, Cardinali L, Fendrich V, Bartsch DK, et al. Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. *Br J Surg*. 2017 Jan;104(1):34–41.
- 5 Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia*. 2017 Dec;19(12):991–1002.
- 6 Brabander T, Teunissen JJ, Van Eijck CH, Franssen GJ, Feelders RA, de Herder WW, et al. Peptide receptor radionuclide therapy of neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab*. 2016 Jan;30(1):103–14.
- 7 Marchegiani G, Landoni L, Andrianello S, Masini G, Cingarlini S, D'Onofrio M, et al. Patterns of recurrence after resection for pancreatic neuroendocrine tumors: who, when, and where? *Neuroendocrinology*. 2019; 108(3):161–71.
- 8 Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. *Ann Surg*. 2008 Mar; 247(3):490–500.
- 9 Genc CG, Falconi M, Partelli S, Muffatti F, van Eeden S, Doglioni C, et al. Recurrence of pancreatic neuroendocrine tumors and survival predicted by Ki67. *Ann Surg Oncol*. 2018 Aug;25(8):2467–74.
- 10 Li H, Li W, Zhou QY, Fan B. Fine needle biopsy is superior to fine needle aspiration in endoscopic ultrasound guided sampling of pancreatic masses: a meta-analysis of randomized controlled trials. *Medicine*. 2018 Mar;97(13):e0207.
- 11 Paiella S, Landoni L, Rota R, Valenti M, Elio G, Crino SF, et al. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis and grading of pancreatic neuroendocrine tumors: a retrospective analysis of 110 cases. *Endoscopy*. 2020 Jun 4;52(11):988–94.
- 12 Partelli S, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology*. 2017;105(3): 255–65.
- 13 Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. *Neuroendocrinology*. 2017;105(3):212–44.
- 14 Hope TA, Bergsland EK, Bozkurt MF, Graham M, Heaney AP, Herrmann K, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. *J Nucl Med*. 2018 Jan;59(1):66–74.
- 15 Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res*. 2010 Feb 1;16(3):978–85.
- 16 Bahri H, Laurence L, Edeline J, Leghzali H, Devillers A, Raoul JL, et al. High prognostic value of 18F-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. *J Nucl Med*. 2014 Nov; 55(11):1786–90.
- 17 Carideo L, Prosperi D, Panzuto F, Magi L, Pratesi MS, Rinzivillo M, et al. Role of Combined ([68]Ga) Ga-DOTA-SST Analogues and (18F) FDG PET/CT in the Management of GEP-NENs: a systematic review. *J Clin Med*. 2019 Jul 13;8(7):1032.
- 18 Muffatti F, Partelli S, Cirocchi R, Andreasi V, Mapelli P, Picchio M, et al. Combined 68Ga-DOTA-peptides and 18F-FDG PET in the diagnostic work-up of neuroendocrine neoplasms (NEN). *Clin Transl Imaging*. 2019 2019 Jun 1;7(3):181–8.
- 19 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007 Oct 20;370(9596):1453–7.
- 20 Landoni L, Marchegiani G, Pollini T, Cingarlini S, D'Onofrio M, Capelli P, et al. The evolution of surgical strategies for pancreatic neuroendocrine tumors (Pan-NENs): time-trend and outcome analysis from 587 consecutive resections at a high-volume institution. *Ann Surg*. 2019 Apr;269(4):725–32.
- 21 Paiella S, Landoni L, Rota R, Valenti M, Elio G, Crinò SF, et al. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis and grading of pancreatic neuroendocrine tumors: a retrospective analysis of 110 cases. *Endoscopy*. 2020;52(11):988–94.
- 22 Lloyd R, Osamura RY, Kloppel G, Rosai J. *WHO classification of tumours of endocrine organs*. 4th ed. IARC Lyon; 2017.
- 23 Paiella S, Impellizzeri H, Zanolini E, Marchegiani G, Miotto M, Malpaga A, et al. Comparison of imaging-based and pathological dimensions in pancreatic neuroendocrine tumors. *World J Gastroenterol*. 2017 May 7; 23(17):3092–8.
- 24 Scarpa A, Mantovani W, Capelli P, Beghelli S, Boninsegna L, Bettini R, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol*. 2010 Jun;23(6):824–33.
- 25 Naswa N, Sharma P, Gupta SK, Karunanithi S, Reddy RM, Patnecha M, et al. Dual tracer functional imaging of gastroenteropancreatic neuroendocrine tumors using 68Ga-DOTA-NOC PET-CT and 18F-FDG PET-CT: competitive or complimentary? *Clin Nucl Med*. 2014 Jan;39(1):e27–34.
- 26 Nilica B, Waitz D, Stevanovic V, Uprimny C, Kendler D, Buxbaum S, et al. Direct comparison of (68) Ga-DOTA-TOC and (18) F-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle. *Eur J Nucl Med Mol Imaging*. 2016 Aug; 43(9):1585–92.

- 27 Cingarlini S, Ortolani S, Salgarello M, Butturini G, Malpaga A, Malfatti V, et al. Role of combined 68Ga-DOTATOC and 18F-FDG positron emission tomography/computed tomography in the diagnostic workup of pancreas neuroendocrine tumors: implications for managing surgical decisions. *Pancreas*. 2017 Jan;46(1):42–7.
- 28 Sampathirao N, Basu S. MIB-1 index-stratified assessment of dual-tracer PET/CT with (68) Ga-DOTATATE and (18) F-FDG and multimodality anatomic imaging in metastatic neuroendocrine tumors of unknown primary in a prrt workup setting. *J Nucl Med Technol*. 2017 Mar;45(1):34–41.
- 29 Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. *Cancer*. 2008 Jun;112(11):2447–55.
- 30 Luo G, Liu Z, Guo M, Jin K, Xiao Z, Liu L, et al. 18F-FDG PET/CT can be used to detect non-functioning pancreatic neuroendocrine tumors. *Int J Oncol*. 2014 Oct;45(4):1531–6.
- 31 Panagiotidis E, Alshammari A, Michopoulou S, Skoura E, Naik K, Maragkoudakis E, et al. Comparison of the Impact of 68Ga-DOTATATE and 18F-FDG PET/CT on clinical management in patients with neuroendocrine tumors. *J Nucl Med*. 2017 Jan;58(1):91–6.
- 32 de Mestier L, Armani M, Cros J, Hentic O, Rebours V, Cadiot G, et al. Lesion-by-lesion correlation between uptake at FDG PET and the Ki67 proliferation index in resected pancreatic neuroendocrine tumors. *Dig Liver Dis*. 2019 Dec;51(12):1720–4.
- 33 Majala S, Seppänen H, Kemppainen J, Sundström J, Schalin-Jäntti C, Gullichsen R, et al. Prediction of the aggressiveness of non-functional pancreatic neuroendocrine tumors based on the dual-tracer PET/CT. *EJNMMI Res*. 2019 Dec 23;9(1):116.
- 34 Has Simsek D, Kuyumcu S, Turkmen C, Sanli Y, Aykan F, Unal S, et al. Can complementary 68Ga-DOTATATE and 18F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? *J Nucl Med*. 2014 Nov;55(11):1811–7.
- 35 Partelli S, Rinzivillo M, Maurizi A, Panzuto F, Salgarello M, Polenta V, et al. The role of combined Ga-DOTANOC and 18FDG PET/CT in the management of patients with pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2014;100(4):293–9.
- 36 Zhang P, Yu J, Li J, Shen L, Li N, Zhu H, et al. Clinical and prognostic value of PET/CT imaging with combination of 68Ga-DOTATATE and 18F-FDG in gastroenteropancreatic neuroendocrine neoplasms. *Contrast Media Mol Imaging*. 2018;2018:2340389.