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Lesion-by-lesion correlation between uptake at FDG PET and the Ki67 proliferation index in resected pancreatic neuroendocrine tumors

Louis de Mestier[a,b,c,*], Margot Armani[d], Jérôme Cros[b,c,e], Olivia Hentic[a], Vinciane Rebours[a,b,c], Guillaume Cadiot[f], Alain Sauvanet[b,c,g], Anne Couvelard[b,c,d], Rachida Lebtahi[b,c,d], Philippe Ruszniewski[a,b,c]

[a] Department of Gastroenterology and Pancreatology, ENETS Centre of Excellence, Beaujon Hospital, APHP, Clichy, France
[b] Université de Paris, Paris, France
[c] INSERM U1149, Beaujon Hospital, Clichy, France
[d] Department of Nuclear Medicine, ENETS Centre of Excellence, Beaujon Hospital, APHP, Clichy, France
[e] Department of Pathology, ENETS Centre of Excellence, Beaujon-Bichat Hospitals, APHP, Clichy/Paris, France
[f] Department of Gastroenterology and Digestive Oncology, Robert-Debré Hospital, Reims, France
[g] Department of Hepato-Bilio-Pancreatic Surgery, ENETS Centre of Excellence, Beaujon Hospital, APHP, Clichy, France

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ABSTRACT

Background: Ki67 proliferation index and tumor uptake on 18fluorodeoxyglucose positron-emitting tomography (FDG-PET) could be correlated in pancreatic neuroendocrine tumors (PanNET), but the evaluation of the former is subject to tumor heterogeneity.
Aims: Explore the correlation between Ki67 and FDG-PET uptake at the lesion scale in PanNET.
Methods: We identified target lesions ≥10 mm in patients operated on for a PanNET and/or associated metastases with preoperative FDG-PET and without neoadjuvant treatment. We assessed the lesion-by-lesion correlation between Ki67 and the tumor-to-liver SUVmax ratio (SUVmax T/L), and between pathological grade (G) and metabolic grade (mG) (mG1, SUVmax T/L ≤ 1, mG2, SUVmax T/L 1–2.3 and mG3, SUVmax T/L > 2.3).
Results: Twenty-one patients underwent pancreatic (n = 12), liver (n = 2) or combined surgery (n = 7). Overall, 36 target lesions (21 primary PanNET, 13 liver metastases and 2 lymph-node metastases) were identified, of median Ki67 4%. Ki67 correlated with SUVmax T/L (r = 0.55, p < 0.001). Median SUVmax T/L was 0.76, 1.41 and 2.67 for lesions G1, G2 and G3, respectively (p = 0.005). Median Ki67 was 1, 4 and 25 for lesions mG1, mG2 and mG3, respectively (p = 0.005).
Conclusions: Uptake on FDG-PET could predict the pathological grade of PanNET lesions. Hence, FDG-PET could supplement pathological evaluation of tumor biological aggressiveness and could guide the choice of the most relevant lesions to biopsy.

1. Introduction

Pancreatic neuroendocrine neoplasms are classified depending on the pathological assessment of differentiation and tumor pathological grade (G), which is determined by the Ki67 proliferation index [1]. The 2017 WHO classification distinguishes well-differentiated G1, G2 and G3 pancreatic neuroendocrine tumors (PanNET) from poorly-differentiated G3 pancreatic neuroendocrine carcinomas [1]. This classification is of paramount importance for prognostic evaluation and therapeutic management. Nevertheless, the evaluation of Ki67 is subject to heterogeneity due to sampling bias, inter- and intra-tumor heterogeneity [2–4].

Tumor uptake on 18fluorodeoxyglucose (FDG) positron-emitting tomography (PET) may be relevant for the prognostic evaluation of PanNET. Higher tumor uptake, evaluated by the tumor maximal standardized uptake value (SUVmax) or the tumor-to-liver SUVmax ratio (SUVmax T/L), seems correlated to increased Ki67 and worse prognosis [5–9]. Accordingly, the diagnostic sensitivity of FDG-PET is higher for PanNET with Ki67 ≥ 10% [6,10]. The intensity of FDG-PET uptake was reported to be a better prognostic tool than Ki67 [8,10]. Especially, Ezziddin et al. [8] reported

* Corresponding author.
E-mail address: louis.demestier@aphp.fr (L. de Mestier).

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that a metabolic grading system ([mG], mG1, SUVmax T/L < 1; mG2, SUVmax T/L 1–2.3; mG3, SUVmax T/L > 2.3) was more discriminant for prognosis than the pathological grade.

However, these studies compared SUVmax (tumor pixel of highest uptake) determined on whole-body FDG-PET, with the Ki67 of the most easily accessible lesion that was generally sampled a long time ago and was not necessarily the lesion with highest uptake, leading to potential discrepancies. To better assess this relationship, we performed a lesion-by-lesion correlation between the preoperative SUVmax T/L ratio (and mG) and the Ki67 index (and the pathological grade) analyzed on surgically resected specimens of PanNET.

2. Methods

2.1. Patients

A retrospective analysis of consecutive patients operated on (primary tumor and/or metastases) for a pathologically proven sporadic or hereditary well-differentiated PanNET, between October 2010 and February 2018, was conducted at a tertiary center with expertise in neuroendocrine tumors. Patients were included if they had performed an FDG-PET within the 6 months prior to surgery. Surgery was always decided in NET-dedicated multidisciplinary board. Patients were excluded if they had poorly-differentiated neuroendocrine carcinoma, or if they had received neoadjuvant antitumor treatment. Epidemiological, clinical and tumor data were extracted from patient records. Tumor stage was classified according to the 2017 UICC classification. Data collection was performed following patient agreement according to the declaration of Helsinki and Institutional Review Board approval (CEERB Paris Nord, IRB no 00006477-15-073).

2.2. Target lesions

One or more target lesions measuring at least 1 cm were carefully selected in each patient. These target lesions had to be individualized and recognizable on preoperative hybrid PET/CT, on the surgical report and on the pathological report.

The Ki67 proliferation index of each resected target lesion was measured by immunohistochemistry on the "hot-spot" areas, using a Ventana™ automate (Tucson, AZ, USA) and a MIB1 antibody (Dako™, 1/100). We determined the histological differentiation and the pathological grade according to the 2017 WHO classification (G1, Ki67 < 3%; G2, 3% ≤ Ki67 ≤ 20%; G3, Ki67 > 20%) [1].

Hybrid PET/CT scanner acquisition was performed without intravenous contrast medium, 60 min after injection of 2.5 MBq/kg of FDG. The attenuation-corrected PET data underwent standardized ordered-subset expectation maximization iterative reconstruction with 3 iterations and 21 subsets. The SUV was determined as a measure of FDG uptake using the region-of-interest technique. The maximum pixel (SUVmax) and a 1-mL sphere at the region of highest uptake (SUVpeak) were measured for each target lesion and normal liver parenchyma in each patient. To reduce potential partial-volume effects, the reference region of interest in the liver was kept consistently at 2 cm in diameter. We calculated the tumor-to-liver SUVmax ratio (SUVmax T/L), as well as the SUVpeak T/SUVmax L ratio (SUVpeak T/L).

Tumor uptake at preoperative somatostatin-receptor scintigraphy was centrally reviewed for each target lesion. Planar and single-photon emission computed tomography images were performed at 24 h after the injection of 200–220 MBq of ^{111}In-pentetreotide. Uptake was quantified following the Krenning scale (1, less than the liver uptake; 2, equal to the liver uptake; 3, more than the liver uptake but less than the spleen uptake; 4, more than the spleen/kidney uptake) [11]. Krenning 3–4 uptake was considered strong.

2.3. Statistical analyses

Qualitative variables were described as frequencies (percentages) and compared using the Chi-2 or Fisher exact test. Continuous variables were described as medians (range) and compared using the Kruskal–Wallis test.

Ki67 inter-tumor heterogeneity was measured in patients with multiple target lesions and was considered significant in case of change in pathological grade. The correlations between Ki67 and the FDG-PET variables were explored using Pearson's test. To evaluate the discriminating value of the metabolic grading system proposed by Ezziddin et al. [8] (mG1, SUVmax T/L < 1; mG2, SUVmax T/L 1–2.3; mG3, SUVmax T/L > 2.3), AUC curves were performed to determine the values of SUVmax T/L and SUVpeak T/L that were best associated with G1 (vs G2–G3) and G3 (vs. G1–G2). The correlation between the metabolic grading system (using SUVmax T/L or SUVpeak T/L) with the pathological grade was explored using the Chi-2 test. The correlation between the pathological grade or mG with Krenning scale was also explored in patients who had performed preoperative somatostatin-receptor isotopic examination.

All tests were bilateral. Any p-value <0,05 was considered significant. All the analyses were performed using the SPSS© (version 20, IBM™) and Prism (version 6, Graphpad™) softwares.

3. Results

3.1. Patients

Twenty-one patients (male gender 62%) with a median age of 49.9 years, were operated on for PanNET and/or associated metastases (Table 1). Four patients had a functioning syndrome (one VIPoma, one glucagonoma, one gastrinoma and one parathormone-related syndrome). One patient had genetic predisposition (von Hippel–Lindau syndrome). No patient had received antitumor treatment with neoadjuvant purpose. Two patients had received previous somatostatin analogs (the patient with VIPoma and the one with glucagonoma). Metastases were present in 43% of patients at the time of surgery. A pancreatic surgery was performed in 19 patients and a liver surgery in 9 patients, 7 patients having a combination of both. Surgery was performed with curative intent in all patients but three: two patients underwent the surgical resection of primary tumor in a metastatic setting, and one patient with VIPoma underwent pancreatic and liver debulking resection with antisecretory intent.

3.2. Target lesions

FDG-PET was performed within a delay of 2.4 months (0.03–6) before the surgical resection of the target lesions. No patient had uncontrolled diabetes mellitus at the time of FDG-PET. Thirty-six target lesions (median size, 20 mm) were identified in 21 patients, 12 of them having only one target lesion (Table 1). At pathological examination of the resected target lesions, 44%, 36% and 19% of them were classified as G1, G2 and G3 PanNET, respectively.

Among the patients with multiple target lesions, 4/9 (44%) had significant intra-tumor Ki67 heterogeneity with the coexistence of lesions with different pathological grade (two with G1 and G2, one with G2 and G3 and one with G1 and G3). Conversely, only 2/9 patients (22%) had significant heterogeneity at FDG-PET (one with mG1 and mG2 and one with mG2 and mG3). Somatostatin-receptor uptake was not correlated to pathological grade, as 58%, 18% and 100% of PanNET G1, G2 or G3 had Krenning 3–4 uptake.

Table 1
Characteristics of 21 patients operated on for a pancreatic neuroendocrine tumor and/or associated metastases, in which 36 target lesions were identified.

Patients	n = 21
Male gender, n (%)	13 (62)
Age (years), median (range)	49.9 (27.9–61.3)
Functioning PanNET, n (%)	4 (19)
Surgical procedure, n (%)	
Pancreatico-duodenectomy	8 (38)
Distal pancreatectomy	4 (19)
Enucleation	5 (24)
Central pancreatectomy	2 (10)
Liver metastases resection	7 (33)
Right hepatectomy	1 (5)
Liver transplantation	1 (5)
Stage of the disease, n (%)	
Stage I	5 (24)
Stage II	3 (14)
Stage III	4 (19)
Stage IV	9 (43)
Target lesions	n = 36
Pancreatic primary tumor	21 (58)
Liver metastasis	13 (36)
Lymph-node metastasis	2 (6)
Size of the target lesions (mm), median (range)	20 (10–85)
Ki67 (%), median (range)	4 (1–60)
Pathologic tumor grade, n (%)	
G1 PanNET	16 (44)
G2 PanNET	13 (36)
G3 PanNET	7 (19)
Somatostatin-receptor scintigraphy uptake, n (%)*	
Krenning scale 1	9 (25)
Krenning scale 2	5 (14)
Krenning scale 3	7 (19)
Krenning scale 4	8 (22)

IQR, interquartile range; PanNET, pancreatic neuroendocrine tumor; WHO; * available for 29 target-lesions in 19 patients.

Similarly, somatostatin-receptor uptake was not correlated to mG, as 58%, 36% and 80% of PanNET mG1, mG2 or mG3 had Krenning 3–4 uptake.

3.3. Correlation between Ki67 and SUV

At the lesion level, Ki67 was correlated with SUVmax T/L ($r = 0.55$, $p < 0.001$) and SUVpeak T/L ($r = 0.56$, $p < 0.001$). The best mG1/mG2 and mG2/mG3 thresholds of both SUVmax T/L and SUVpeak T/L were 1 and 2.3, respectively (Table 2).

Median SUVmax T/L increased with the pathological grade: 0.76 (range 0.42–2.20, interquartile range 0.62–1.48), 1.41 (range 0.78–2.87, interquartile range 1.08–2.33) and 2.67 (range 0.94–3.76, interquartile range 1.09–3.67) for lesions G1, G2 and G3, respectively ($p = 0.005$, Fig. 1A,B). Similarly, median Ki67 values increased with the metabolic grade: 1 (range 1–60, interquartile range 1–5), 4 (range 1–40, interquartile range 1–14) and 25 (range 4–60, interquartile range 12–30) for lesions mG1, mG2 and mG3, respectively ($p = 0.005$, Fig. 1C,D). Examples are presented in the Fig. 2.

Preoperative mG was associated with the pathological grade assessed on the resected specimen ($p = 0.015$, Fig. 1B,D). Only one lesion mG1 was finally G3 (Ki67 = 60%). Only one G3 lesion was mG1 and no G1 lesion was mG3 on preoperative FDG-PET. The results observed with SUVpeak T/L were very close and statistically significant as well (data not shown).

4. Discussion

Our study confirms the correlation between Ki67 and tumor uptake at FDG-PET [8]. Preoperative mG was significantly associated with the pathological grade assessed on the resected specimen. Especially, all lesions but one with low FDG uptake (mG1) were G1 or G2, and all lesions with strong FDG uptake (mG3) were G3 or G2 with Ki67 > 10% (excepted one G2 lesion).

Previous studies suggested gross correlation between FDG uptake and tumor grade [5–10]. However, in these studies SUVmax was compared to the Ki67 of the most easily accessible lesion, which was generally sampled a long time ago and was not necessarily the lesion of highest uptake, leading to potential discrepancies. The methodology proposed herein was likely more rigorous: (1) surgical specimens were used as gold standard for Ki67 analysis; (2) FDG uptake of each target lesion was compared to the Ki67 value of the same lesion, rather than that of a random lesion, aiming to reduce inter-tumor heterogeneity; (3) FDG-PET and sample/resection of the same lesion was performed within a close time range in order to reduce temporal heterogeneity; and (4) we did not include patients who had neoadjuvant therapy, which could have strongly influence both FDG uptake and pathological results.

The evaluation of the G in advanced PanNET relies on biopsies of the most accessible tumor localization at diagnosis, usually biopsy of a liver metastasis. This might be inappropriate in regard of the Ki67 heterogeneity highlighted in this study. Reasons are multiple: (1) sampling techniques (biopsy or surgery) may not provide equivalent specimen volume [4]; (2) inter-tumor heterogeneity, Ki67 being different between tumor localizations in about 30% of patients (generally higher in metastases) [4,12–14], and between metastases in 30% of cases [2,4]; (3) it is recommended to report the highest Ki67 which may only represent a small portion of the tumor in PanNET with important intratumor heterogeneity (35–50% of cases) [2,3]; (4) temporal heterogeneity, because tumor biology is likely influenced by natural and chemo-induced clonal selection, resulting in differences in Ki67 in about 35% of metachronous metastases [2,4]. In the present study, 44% of patients had significant Ki67 heterogeneity between multiple target lesions resected simultaneously.

FDG-PET is less influenced by tumor heterogeneity. Indeed, Ki-67 is determined microscopically on hot spots of a very small part of the tumor (usually <0.1 mm^2), which is very different from the macroscopic imaging evaluation that provides a whole-body assessment, although a small percentage of tumor cells of higher grade may not be taken into account by FDG-PET. Moreover, Ki67 is usually determined in one single lesion but can be different in other localizations, which could be adequately taken into account by FDG-PET. In our study, significant inter-tumor heterogeneity at FDG-PET existed in 22% of patients, but without consequences for practice as FDG-PET is a whole-body examination and does not suffer from sampling bias.

Table 2
Thresholds of SUVmax T/L and SUVpeak T/L used to define the metabolic grading system.

	Threshold for distinguishing	Sensitivity (%)	Specificity (%)	Area under the ROC curve
SUV max T/L = 1	G1 from G2/G3	80.1	56.2	0.80
SUV max T/L = 2.3	G3 from G1/G2	57.1	89.7	0.78
SUV peak T/L = 1	G1 from G2/G3	70	68.7	0.82
SUV peak T/L = 2.3	G3 from G1/G2	57.1	89.7	0.78

SUV, standardized uptake value; T/L, tumor/liver.

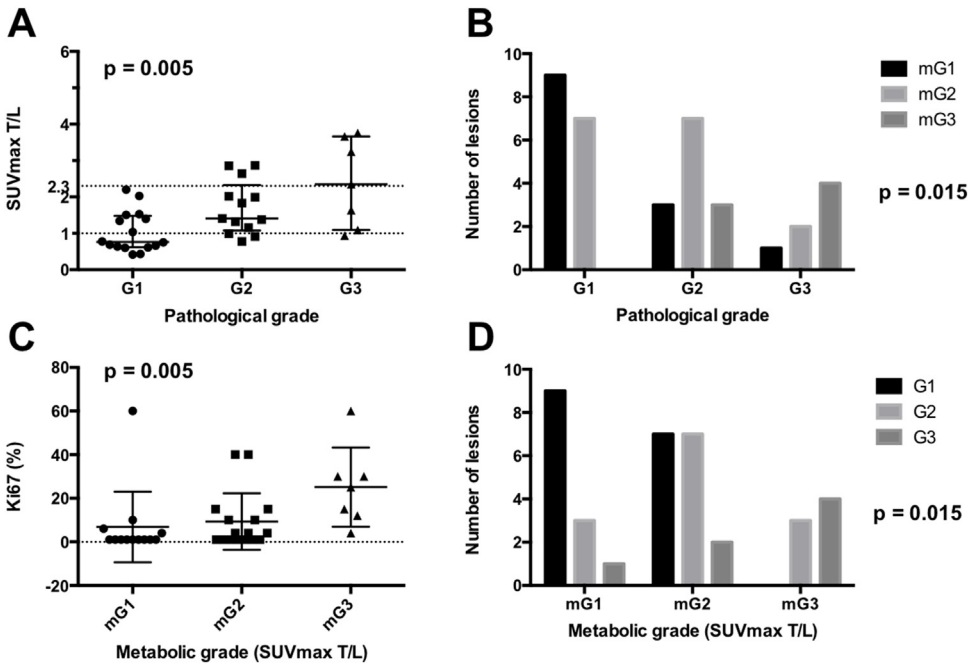

Fig. 1. Correlation between pathological grade (G1, Ki67 < 3%; G2, Ki67 between 3% and 20%; G3, Ki67 > 20%) and metabolic grade (mG1, SUVmax T/L ≤ 1; mG2, SUVmax T/L between 1 and 2.3; mG3, SUVmax T/L > 2.3), in 36 lesions from 21 patients with pancreatic neuroendocrine tumors.
Top, distribution of SUVmax T/L values (A) or metabolic grade (B) depending on pathologic grade. Bottom, distribution or Ki67 values (C) or pathologic grade (D) depending on metabolic grade.

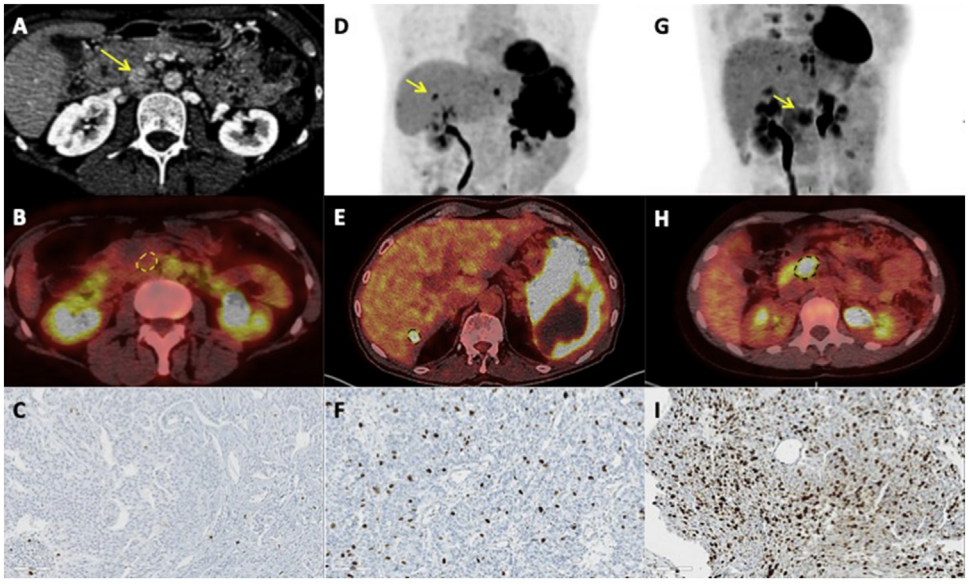

Fig. 2. Examples of correlation between Ki67 proliferation index assessed on the resected specimens of pancreatic neuroendocrine tumors, and the tumor-to-liver maximal standardized uptake value (SUVmax T/L) measured on the preoperative ^{18}fluorodeoxyglucose positron-emitting tomography (FDG PET).
Case 1 (A–C), PanNET of the pancreatic uncus (arrow) measuring 17 mm (A, transaxial contrast-enhanced CT) with low preoperative FDG uptake (SUVmax T/L 0.64; mG1) (B, transaxial PET/CT). At pathology, Ki67 was 1% (G1) (C, MIB1 immunostaining 20X).
Case 2 (D–F), PanNET-associated metachronous 11-mm liver metastasis (arrow) localized in the segment VI (D, FDG-PET) with intermediate preoperative FDG uptake (SUVmax T/L 1.85; mG2) (E, transaxial PET/CT). At pathology, Ki67 was 8% (G2) (F, MIB1 immunostaining 20×).
Case 3 (G–I), PanNET of the pancreatic head (arrow) measuring 30 mm and associated with synchronous metastases (G, FDG-PET) with high uptake on preoperative FDG uptake (SUVmax T/L 2.65; mG3) (H, transaxial PET/CT). At pathology, Ki67 was 30% (G3) (I, MIB1 immunostaining 20×).

We believe that the main contribution of FDG-PET could be to identify lesions with higher pathological grade than the lesion(s) biopsied for initial diagnosis (due to spatial and/or temporal intra-tumor heterogeneity). The lesion with the highest FDG uptake could be expected to be that with the highest Ki67 value and pathological grade, thus an important tumor localization to be taken into account for the management of the patient. Hence, FDG-PET could help guiding biopsies either during the initial work-up of PanNET or during evolution. Otherwise, our results suggest that FDG-PET may not be useful for the management of patients with small-localized PanNET, since the distinction between G1 (candidate for surveillance) and G2 (candidate for surgery) is not accurate (except for mG3 lesions, which were all G2 or G3 in our series). Importantly, FDG-PET aims at supplementing pathological data by reducing the

consequences of tumor heterogeneity on PanNET management. Nevertheless and obviously, it cannot replace pathological evaluation of the proliferation index since the correlation between SUVmax T/L (or SUV peak T/L) and Ki67 was good but imperfect. Additionally, one must keep in mind that high FDG uptake can be secondary to VHL pathway inactivation (sporadic or constitutive) in some low-grade NET [9]. This may explain why some of the G1 pNET can have high FDG uptake but indolent behavior.

The main limitations of our study are those inherent to the retrospective study, and its relatively limited population due to stringent inclusion criteria (PanNET operated on with close preoperative FDG-PET and isotopic/pathology data available). Somatostatin-receptor tumor uptake could not be quantified as it was mainly measured on scintigraphy. Nevertheless, its correlation with the Ki67 index was not the purpose of this study. Our study did not aim to report the postoperative outcomes, mainly because the patients' characteristics at baseline were too different. Indeed, our inclusion criteria mainly relied on the coexistence of PanNET, surgery and preoperative FDG-PET, in order to study the correlation between Ki67 and SUV, which does not rely on the indication for surgery (which could be very different between patients) or type of surgical procedure. Future studies should compare the prognostic impact of FDG-PET and Ki67 taking into account tumor heterogeneity, in a homogeneous cohort of patients.

In conclusion, this is the first study to demonstrate that Ki67 is correlated with SUVmax T/L (and SUVpeak T/L) on FDG-PET at the lesion scale. Tumor uptake on FDG-PET could predict the pathological grade of PanNET lesions and is less influenced by tumor heterogeneity. Hence, FDG-PET supplements the pathological evaluation of tumor biological aggressiveness and could be relevant at guiding biopsies.

Conflict of interest

None declared.

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