Performance of ^{18}Fluorodeoxyglucose-Positron Emission Tomography and Somatostatin Receptor Scintigraphy for High Ki67 (≥10%) Well-Differentiated Endocrine Carcinoma Staging

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Objective: The purpose of this prospective study was to compare the performance of ^{111}In-octreotide somatostatin receptor scintigraphy (SRS) and ^{18}fluorodesoxyglucose positron emission tomography (FDG-PET) in aggressive well-differentiated endocrine carcinoma (WDEC) defined by a high Ki67 (≥10%).

Methods: Eighteen consecutive patients explored in a single hospital between November 2003 and 2008 for high Ki67 (≥10%) WDEC were prospectively included. WDEC were sporadic in 17 cases and secreting in 16 cases. FDG-PET, SRS, and computed tomography (CT) were performed within a maximum of 3 months and reviewed by two independent readers. For each patient, an analysis per organ and lesion was performed. Both the results of conventional imaging and the highest number of metastatic organs and distinct lesions visualized by all imaging methods including SRS, FDG-PET, and thoraco-abdomino-pelvic CT were considered for the determination of the standard. Correlation between tumor slope and maximum standardized uptake value, Ki67 value, and grade of uptake at SRS was evaluated.

Results: FDG-PET, SRS, and CT showed at least one lesion in 18 (100%), 15 (83%), and 17 (94%) patients, respectively. A total of 254 lesions were diagnosed in 59 organs. FDG-PET, SRS, and CT detected 195 (77%), 109 (43%), and 195 (77%) lesions in 53 (90%), 30 (51%), and 39 (66%) organs, respectively. FDG-PET, compared to SRS, detected more, the same as, and less lesions in 14 (78%), one (6%), and three (17%) patients, respectively. A statistical trend was found between Ki67 value and tumor slope ($P = 0.07$). Median survival after diagnosis was 25 months (range, 6–71 months).

Conclusion: These results suggest that FDG-PET is more sensitive than the SRS for high Ki67 WDEC staging. (***J Clin Endocrinol Metab*** **96: 665–671, 2011)**

Scintigraphic imaging plays a major role in the characterization of neuroendocrine tumors, including staging and treatment decision for peptide receptor radionuclide therapy (1–4). The scintigraphic method used is dependent upon pathological differentiation. Indeed, somatostatin receptor scintigraphy (SRS) is recommended

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Abbreviations: CI, Confidence interval; CT, computed tomography; FDG, fluorodesoxyglucose; FDG-PET, PET with FDG; PET, positron emission tomography; RECIST, Response Evaluation Criteria In Solid Tumors; SRS, somatostatin receptor scintigraphy; SUVmax, maximum standardized uptake value; TAP, thoraco-abdomino-pelvic; WDEC, well-differentiated endocrine carcinoma.

for well-differentiated endocrine carcinoma (WDEC), whereas positron emission tomography with fluorodesoxyglucose (FDG-PET) is used in addition to conventional imaging in cases of poorly differentiated endocrine carcinoma (5–8). This is in accordance with the high uptake of FDG seen in aggressive cancer with an accelerated rate of glycolysis that mirrors the aggressiveness of cancer (9, 10). Pheochromocytoma is, however, an exception to this statement because, and despite being well differentiated in most cases, FDG-PET is recognized as the most sensitive molecular imaging (11). These recommendations are also supported by the various patterns of expressions of somatostatin receptor: highly expressed in WDEC in contrast to poorly differentiated endocrine carcinoma (1–4).

Within the last decade, three studies suggested a potential role of FDG-PET in the staging of gut aggressive WDEC (12–14). Indeed, these three studies demonstrated a higher performance of FDG-PET in comparison to SRS in subgroups of patients defined by high proliferative index or progressive disease. However, only three to eight patients were enrolled, so that firm conclusions could not be drawn. In addition, the low diagnostic performance of FDG-PET in most WDEC has been illustrated best in lung tumors (15, 16), which, together with cost-effectiveness, makes the routine use of FDG-PET in WDEC very unlikely. More recently, FDG-PET has been proposed as a prognostic tool in WDEC (17). The prognostic role of proliferative index in WDEC is being increasingly recognized in WDEC and forms the basis of the recently proposed grade classification (18–26). Due to the known relationship between proliferative index in cancer and FDG-PET uptake (10, 17, 27, 28), it appeared to us a logical step forward to investigate further the role of FDG-PET in staging of WDEC characterized by a high Ki67 level.

The primary goal of this prospective study was to compare the performance of SRS and FDG-PET for the staging of WDEC characterized by a Ki67 index above or equal to 10%. The second objective was to search for factors correlated with tumor slope.

Patients and Methods

Patients and pathology

Consecutive patients with confirmed WDEC and Ki67 above or equal to 10%, referred to the Institut Gustave Roussy from November 2003 to November 2008, were retrieved from a local institutional database and enrolled in this prospective study. Inclusion criteria for enrollment were: 1) diagnosis of WDEC based upon a pattern of well-differentiated endocrinoid pattern together with a positive immunohistochemistry for chromogranin A and synaptophysin and the absence of necrosis, as reviewed by a single experienced pathologist (P.D.); 2) Ki67 index above or equal to 10%; and 3) all imaging methods performed in our center.

Study design was approved by our institutional review board, and all patients gave written informed consent.

Histological parameter of proliferation: Ki67

Expression of Ki67 was determined by a single pathologist with the immunohistochemistry method. This value was evaluated on primary tumor after surgery (n = 7) or after a biopsy (n = 11). At the time of pathological evaluation, patients were treatment naive in all cases but two where patients previously benefited from chemotherapy (adriamycin-streptozocin and 5-fluorouracil-streptozocin). Ki67 labeling index was calculated as percentage by observing 2000 nuclei in areas of the section with the highest labeling rates assessed using MIB1 stains (clone MIB1; Dako A/S, Glostrup, Denmark) as recommended (19, 20).

Imaging techniques

FDG-PET, SRS, and thoraco-abdomino-pelvic (TAP)-computed tomography (CT) were performed using usual recommendations within 3 months for all patients but three in which the maximal interval between examinations was 2 months (1, 29).

Positron emission tomography

All imaging and data acquisitions were performed on an integrated PET/CT Biograph LSO system (Siemens Medical Solutions, Erlangen, Germany) using a single table serving for both the attenuation correction CT and PET elements. PET/CT scanning was performed after an iv injection of 5 MBq/kg FDG, followed by a 55- to 65-min uptake phase. All patients had fasted for 4–6 h, and capillary glycemia was normal in all patients. During the image acquisition, patients maintained their arms above their heads, and no specific breathing instructions were given. The PET elements of the system are based on a full-ring tomography (ECAT ACCEL; CPS Innovation, Knoxville, TN). Emission data were acquired for 4 min at each bed position from the top of the head to the midthigh. Three-dimensional mode was used for PET image acquisition. PET data were reconstructed on a 128 × 128 matrix, using an iterative algorithm (FORE and AWOSEM) with two iterations, eight subsets, and a 5-mm FWHM Gaussian post-filter. Reconstruction data were acquired with a single slice spiral CT (Somatom Emotion; Siemens Medical Solutions) without iv contrast agent. CT parameters were set to 80 mA and 110 kV, slice thickness of 5 mm, and pitch of 1.5. CT data were reconstructed using filtered back projection with a smooth filter on a 512 × 512 matrix.

Somatostatin receptor scintigraphy

SRS was performed after iv injection of 170–220 MBq indium-111-DTPA-Phe1-octreotide (OctreoScan; Mallinckrodt Medical, Petten, The Netherlands). Digestive artifacts were reduced with an adequate colonic preparation (64 g macrogol 4000 in the evening after the injection and again the next morning before 24-h imaging). Acquisition was performed using both ^{111}In photopeaks (171 and 245 kV) and using a large field of view doublehead γ-camera equipped with a medium-energy collimator (Axis; Philips Medical Systems, Best, The Netherlands). Four static anterior and posterior spot views covering the abdomen and pelvis were acquired at 4 h, and six static anterior and posterior spot views covering the whole body were acquired at 24 h and, when needed, at 48 h (256 × 256 word matrix, at least 10 min per view or 300,000 preset counts for the head and neck and 500,000 for the rest of the body). Thoracic or abdominal single-photon emission CT was performed at 24 h (64 projec-

tions, 128 × 128 word matrix, 1 min per projection, and iterative reconstruction). When necessary, additional lateral views of the head were performed.

TAP-CT scanning

TAP-CT examinations were performed with a Hispeed spiral scanner (GE Medical Systems, Milwaukee, WI). Spiral CT images were obtained before a monophasic injection of 100 ml of monoionic contrast material (Xenetix 300; Guerbet, Roissy, France), at early arterial phase and portal time (29). Scanning was performed at 120 kV and 270 mA. Contiguously reconstructed sections (pitch of 1:1) were obtained with 5-mm collimation.

Image analysis

All examinations were reviewed by two readers, blindly and independently.

An abnormal FDG-PET was defined by nonphysiological FDG uptake in at least one site. Maximum standardized uptake value (SUVmax) was determined in patients with abnormal FDG uptake.

An abnormal SRS was defined by nonphysiological ^{111}Indium-octreotide uptake. Maximal grade of uptake was recorded as grade 0, 1, 2, 3, and 4 in case of no uptake, an uptake lower than the liver, identical to the liver, above the liver, or higher than the liver or the spleen, respectively, according to Krenning scale (8).

An abnormal CT was defined by the detection of at least one tumor site. According to Response Evaluation Criteria In Solid Tumors (RECIST) criteria, a target was defined by any lesions of soft tissue equal or greater than 1 cm in size that can be accurately measured. All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions and were recorded and measured at baseline (30).

Lung, liver, nodes, and bones were considered as distinct organs. Bones and cervico-mediastinal and abdomino-pelvic lymph nodes were considered as a single organ. When more than 10 lesions were depicted in a given organ, 11 were considered for the analysis. The total number of lesions was determined by summing the highest number of distinct lesions visualized by at least one of all imaging exams performed. Indeed, for both ethical and practical reasons, every suspected involved lesion was not evaluated by histology. In addition, SRS and FDG-PET results were also compared per patient, per involved organs, and per number of detected lesions to the results of TAP-CT.

Tumor slope

Tumor slope was evaluated by conventional imaging. According to RECIST, all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions at baseline and monitored during follow-up. Results of tumor slope were normalized per 3 months to allow comparison between patients. A progressive disease was defined by a 20% increase of the sum of maximum diameters of targets (30). During this time frame, three patients received a systemic therapy including chemotherapy.

Statistics

Data were analyzed using SAS statistical software (SAS Institute Inc., Cary, NC).

Sensitivities of FDG-PET, SRS, and CT and their 95% confidence intervals (CIs) were calculated and compared using the McNemar test for matched proportion.

A statistical correlation was searched for the tumor slope (percentage of enlargement) and the following parameters: Ki67 value (categorized as ≤15% and >15%) with a Kruskall-Wallis test and, respectively, FDG-PET SUVmax (analyzed as a continuous parameter), uptake grade in SRS (categorized in three subgroups grade 0; grade 1–2; grade 3–4) with a Spearman test.

All reported *P* values are two-sided. Significance level was 0.05.

Survival

Median survival from diagnosis was evaluated.

Results

Patients

Among 130 consecutive patients, who were referred to our institution between November 2003 and November 2008 for WDEC and met inclusion criteria, 18 (14%) (10 males, eight females; median age, 59 yr; range, 46–71 yr) presented an elevated Ki67 above or equal to 10% (range, 10–50%; median value, 17.5). No exclusion criteria were found.

Primary WDEC sites were located in foregut in 15 cases (83%) (pancreas, n = 7; lung, n = 5; thymus, n = 2; stomach, n = 1), hindgut (ovary) in one case (6%), and unknown sites in two cases (11%). Tumors were sporadic in 17 cases (94%) and part of a multiple endocrine neoplasia type 1 in one case (6%). Six of 18 tumors (33%) were functioning (carcinoid syndrome in four cases, Cushing syndrome in one case, and hypoglycemia in one case due to an insulinoma in the last case). Increased hormonal secretions were found in 16 of the 18 cases and consisted of chromogranin A secretion in 14 cases, 5-hydroxy-indole-acetic acid secretion in five cases, and other hormonal secretion in 11 cases. All patients had distant metastases and were classified as stage IV.

Thirteen of 17 evaluable patients were classified as progressive, including 11 patients with progressive RECIST criteria and two early deaths. Tumor slope could not be determined in one patient whose follow-up was not performed in our center.

Imaging results

The median time between the realization of the FDG-PET and SRS was 33 d (range, 1–119 d). It was 59 d (range, 1–125 d) between FDG-PET and TAP-CT and 50 d (range, 1–122 d) between SRS and TAP-CT.

TABLE 1. Comparative results of SRS, FDG-PET, and TAP-CT (per-patient analysis)

	SRS	FDG-PET	CT
≥1 lesion	15/18 (83%)	18/18 (100%)	17/18 (94%)
95% CI	59–96	81–100	73–99

TABLE 2. Comparative results of SRS, FDG-PET, and TAP-CT (per-organ analysis)

Organs	SRS	FDG-PET	CT
Lung	3/7 (43%)	7/7 (100%)	6/7 (86%)
95% CI	10–82	59–100	42–99
CM LN	5/9 (56%)	8/9 (89%)	5/9 (56%)
95% CI	21–86	52–99	21–86
Liver	8/12 (67%)	9/12 (75%)	11/12 (92%)
95% CI	35–90	43–95	62–99
AP LN	3/12 (25%)	11/12 (92%)	6/12 (50%)
95% CI	5–57	62–99	21–79
Bone	8/8 (100%)	7/8 (88%)	6/8 (75%)
95% CI	63–100	47–99	35–97
Other	3/11 (27%)	11/11 (100%)	5/11 (45%)
95% CI	6–61	72–100	17–77

Sensitivity is defined taking into account the highest number of distinct metastatic organs visualized by at least one imaging method. CM LN, Cervico-mediastinal lymph nodes; AP LN, abdomino-pelvic lymph nodes.

Per-patient analysis

FDG-PET, SRS, and TAP-CT showed at least one lesion, respectively, in 18 (100%; 95% CI, 81–100), 15 (83%; 95% CI, 59–96), and 17 (94%; 95% CI, 73–99) patients (Table 1). All imaging methods were positive in 14 patients. In one case, SRS was the only abnormal examination. For three patients, FDG-PET and TAP-CT were positive, whereas SRS was negative.

Lesions were located in the following organs: in the lungs in seven (39%) cases, in cervico-mediastinal lymph nodes in nine (50%) cases, in the liver in 12 (67%) cases, in abdomino-pelvic lymph nodes in 12 (67%) cases, in bone in eight (44%) cases, and other sites in 11 (61%) cases.

The average tumoral SUVmax in FDG-PET was 6.0 ± 2.2 (range, 2.8–10.2). Grade uptake at SRS was 0, 1–2, and 3–4 in 3, 6, and 9 cases, respectively.

Per-organ analysis

The total number of metastatic organs was 59. FDG-PET detected lesions in 53 organs, SRS in 30 organs, and TAP-CT in 39 organs.

Taking as a standard the highest number of distinct organs visualized by at least one imaging method, sensitivities of FDG-PET, SRS, and TAP-CT for the diagnosis of metastatic organs were 90, 51, and 66%, respectively. The sensitivity of invaded organs for all imaging examinations are summarized in Table 2.

Taking TAP-CT as a standard, FDG-PET detected more metastatic organs, the same number of metastatic organs, or a lower number of metastatic organs than TAP-CT in nine (50%), six (33%), and three (17%) cases, respectively. SRS detected more lesions, the same number of lesions, or a lower number of lesions than TAP-CT in three (17%), eight (44%), and seven (39%) cases, respectively. FDG-PET detected more metastatic organs, the same number of metastatic organs, or a lower number of metastatic organs than SRS in 10 (55%), seven (39%), and one (6%) case, respectively.

The difference in sensitivity per organ between FDG-PET and SRS was statistically significant for abdomino-pelvic lymph nodes ($P = 0.013$). The difference in sensitivity per organ between PET and TAP-CT was statistically not significant.

TABLE 3. Comparative results of SRS, FDG-PET, and TAP-CT (per-lesion analysis)

Lesions	SRS	FDG-PET	CT
Lung	3/18 (17%)	17/18 (94%)	8/18 (44%)
95% CI	4–41	73–99	22–69
CM LN	8/19 (42%)	17/19 (89%)	9/19 (47%)
95% CI	20–67	67–99	24–71
Liver	35/95 (37%)	67/95 (71%)	83/95 (87%)
95% CI	27–47	60–79	79–93
AP LN	3/31 (10%)	19/31 (61%)	24/31 (77%)
95% CI	2–26	42–78	59–90
Bone	56/72 (78%)	58/72 (81%)	64/72 (89%)
95% CI	66–87	70–89	79–95
Other	4/19 (21%)	17/19 (89%)	7/19 (37%)
95% CI	1–46	67–99	16–62

Sensitivity is defined taking into account the highest number of distinct metastatic lesions visualized by at least one imaging method. CM LN, Cervico-mediastinal lymph nodes; AP LN, abdomino-pelvic lymph nodes.

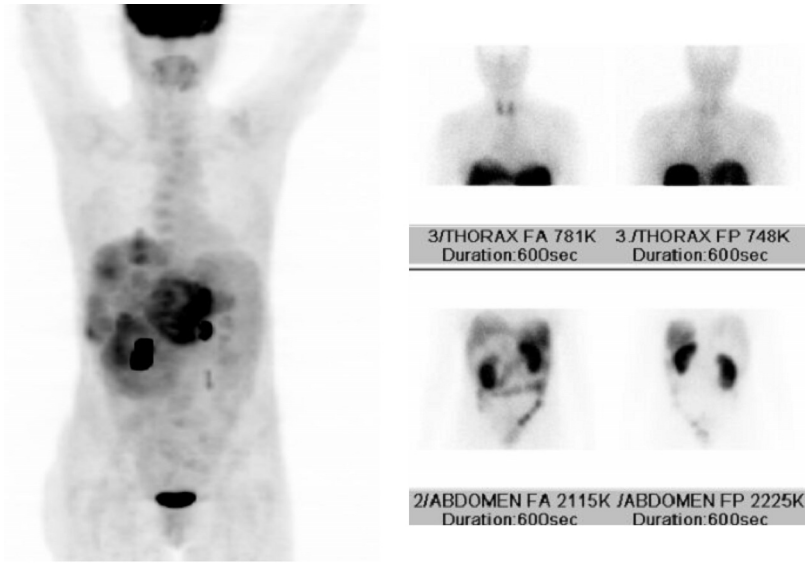

FIG. 1. Woman 54 yr old showing multiple hepatic metastases and abdominal lymph nodes of a lung WDEC primary (Ki67 = 10%) at FDG-PET (A) and with a negative SRS (B; anterior and posterior view of the thorax and abdomen).

The best combination was achieved by combining FDG-PET and TAP-CT, allowing the detection of 93% of metastatic organs.

Per-lesion analysis

The total number of lesions detected was 254 in the 18 patients. FDG-PET detected 195 lesions, SRS 109 lesions, and TAP-CT 195 lesions.

Taking as a standard the highest number of distinct lesions visualized by at least one imaging method, sensitivities of FDG-PET, SRS, and CT for the diagnosis of lesions were 77, 43, and 77%, respectively. The sensitivity of detected lesions for all imaging examinations is summarized in Table 3.

Taking TAP-CT as a standard, FDG-PET detected more lesions, the same number of lesions, or a lower number of lesions than TAP-CT in 11 (61%), one (6%), and six (33%) cases, respectively. SRS detected more lesions, the same number of lesions, or a lower number of lesions than TAP-CT in three (17%), three (17%), and 12 (66%) cases, respectively. FDG-PET detected more lesions (Fig. 1), the same number of lesions, or a lower number of lesions than SRS in 14 (78%), one (6%), and three (17%) cases, respectively.

FDG-PET was statistically significantly more sensitive than SRS for the diagnosis of abdomino-pelvic lymph nodes ($P = 0.008$), cervico-mediastinal lymph nodes ($P = 0.034$), and other lesions ($P = 0.006$) including pancreas, peritoneal carcinomatosis, kidney, spleen, and pleura. TAP-CT was statistically significantly more sensitive than SRS for the diagnosis of abdomino-pelvic lymph nodes ($P = 0.042$). No difference was found between FDG-PET and TAP-CT.

The best combination was achieved by combining FDG-PET and TAP-CT, allowing the detection of 87% the lesions.

Of the 16 patients with a known primary, FDG-PET detected 14 primaries (88%), SRS seven (50%), and TAP-CT 12 (75%). Pancreatic primary was detected by FDG-PET in 100% of cases (seven of seven), whereas SRS was found positive in only 29% cases (two of seven).

Parameters associated with tumor slope

Thirteen of 17 patients followed in our center were classified as progressive after two imaging tests.

A trend toward significant correlation was found between the Ki67 category and the tumor slope ($P = 0.07$). Indeed, five of nine patients with Ki67 levels below or equal to 15% experienced a progressive disease. In contrast, eight of eight patients with Ki67 levels above 15% experienced a progressive disease.

Survival

One patient was lost to follow-up during the study. Ten of the 17 other patients (65%) died within an average of 17 months after diagnosis. Median survival was 25 months (range, 6–71 months). Figure 2 shows the overall survival of the population under study.

Discussion

The process of characterization of neuroendocrine tumors is mainly dependent on pathological differentiation, as

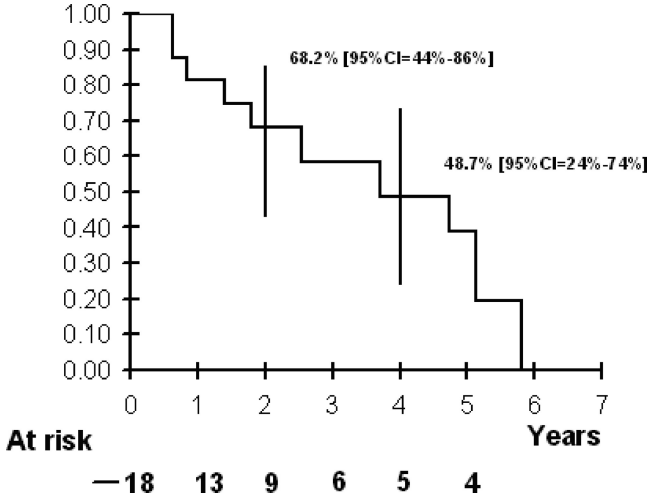

FIG. 2. Overall survival of the population.

defined by the World Health Organization classification, grade, TNM classifications, and primary location in case of WDEC (1–4, 18, 19, 21). Nowadays, the use of FDG-PET for staging is restricted to poorly differentiated endocrine carcinoma, but recent studies suggest a prognostic role for FDG-PET in WDEC, which renewed the interest for FDG-PET in WDEC for prognosis but also for staging purposes. Our study demonstrates that within a rare subgroup of WDEC characterized by a Ki67 above or equal to 10%, FDG-PET constitutes the most performant nuclear imaging for staging. This result suggests first that the choice of the tracer should be based upon proliferative index results in WDEC; and second, that a superior FDG-PET over SRS staging should not be considered pathognomonic of a poorly differentiated endocrine carcinoma.

The subgroup of patients investigated in this series is rare, representing 14% of the total number of WDEC seen during the time of investigation, and is characterized by its aggressiveness as illustrated by a stage IV TNM staging in all patients, a progressive tumor slope in most patients (76%), as well as a median survival of 25 months. The cutoff of Ki67 was chosen based on statistical consideration to obtain a significant number of patients to analyze. We are well aware that this cutoff overlaps the recent grade classification that categorized grade 2 or 3 neuroendocrine carcinoma based on a cutoff of 20%. However, only seven patients (5%) seen during the investigated period fit this criteria. Interestingly, the superiority of FDG-PET over SRS was obvious for all anatomical locations, suggesting that SRS in these patients could be omitted, at least for staging purposes. However, high-grade uptake at SRS was observed in 50% of cases, and the question of an active antitumoral role of peptide-radiolabeled receptor therapy in these cases remains open (31). Therefore, we suggest that in this rare subgroup of patients both scintigraphy methods should be performed until additional data on the effectiveness of peptide-radiolabeled receptor therapy in these patients are provided. One critical point of this study is the definition of WDEC despite a high Ki67. Indeed, the well-conserved pattern of endocrinoid architecture of these tumors together with absence of necrosis favored this diagnosis, as is also recognized by others (22, 25, 32). The observed median survival of 25 months together with a survival of more than 6 months in all cases provides other evidence that those patients should not be classified as poorly differentiated (3).

To the best of our knowledge, this series is the largest published to date in this rare subgroup of patients. Additionally, the consecutive nature of enrollment of the patients together with the systematic review of slides and Ki67 count, according to recent European Neuroendocrine Tumor Society recommendations, increase the robustness of our study (8). In keeping with this, imaging review of all exams by two investigators per type of imaging blinded from other imaging results should also be underlined.

Recently, Garin *et al.* (17) reported a prognostic role for FDG-PET, categorized as positive or negative, in 38 WDEC and found it superior to Ki67 proliferative index information. For obvious cost-effective reasons and low staging performance of FDG-PET in the majority of WDEC, it is unlikely that FDG-PET will become a standard for initial characterization of WDEC. An alternative to a systematic use of FDG-PET in metastatic WDEC patients would be to focus FDG-PET indication on well-characterized subgroups of metastatic WDEC in whom rapid prognostic classification is required. Our study demonstrates the impact of FDG-PET in case of WDEC with high Ki67 for staging purpose. No further information could be drawn from FDG-PET standardized uptake value results. In addition, metastatic WDEC patients with a significant liver involvement, in whom the prognosis has been shown to be poor but still heterogeneous, could constitute another subgroup of patients in whom the prognostic role of FDG-PET could be investigated in the future (26, 33–36).

In conclusion, the results of our study suggest that FDG-PET is the scintigraphic method of reference for staging of metastatic WDEC with Ki67 above or equal to 10%.

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