Predictive Value of ^{18}F-FDG PET and Somatostatin Receptor Scintigraphy in Patients with Metastatic Endocrine Tumors

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The treatment of metastatic neuroendocrine tumors depends on the aggressiveness of the disease. We wanted to know whether ^{18}F-FDG PET and somatostatin receptor scintigraphy (SRS) can predict early disease progression and patient survival. **Methods:** We undertook a prospective study of patients with metastatic neuroendocrine tumor diagnosed between September 2003 and January 2006. After obtaining signed informed consent from the patients, we performed CT, SRS, and ^{18}F-FDG PET and reviewed histologic data. CT was repeated every 3 mo to assess the risk of early progressive disease (first 6 mo), progression-free survival, and overall survival. **Results:** Thirty-eight patients (mean age, 60 ± 15 y) were included. Histologically, 4 patients had a high-grade and 34 a low-grade tumor. The results of ^{18}F-FDG PET and SRS were positive in 15 and 27 patients. The 2-y overall survival and progression-free survival were 73% and 45%; 16 patients had early progressive disease. Most ^{18}F-FDG PET–positive patients had early progressive disease (14/15, vs. 2/23 ^{18}F-FDG PET–negative patients), and most SRS-negative patients had early progressive disease (9/11, vs. 7/27 SRS-positive patients); ^{18}F-FDG PET gave excellent negative and positive predictive values of 91% and 93%; ^{18}F-FDG PET results correlated with progression-free survival ($P < 0.001$) and overall survival ($P < 0.001$) even when only low-grade tumors were considered. SRS was associated with progression-free survival ($P < 0.001$) and overall survival ($P < 0.03$). At multivariate analysis, only ^{18}F-FDG PET was predictive of progression-free survival. **Conclusion:** ^{18}F-FDG PET exhibits excellent predictive values for early tumor progression. ^{18}F-FDG PET and SRS results correlate with progression-free survival and overall survival even for histologically low-grade tumors. These explorations could be included in the initial work-up for metastatic neuroendocrine tumor.

Key Words: ^{18}F-FDG PET; somatostatin receptor scintigraphy; metastatic endocrine tumor; prognosis

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Neuroendocrine tumors are uncommon (<2% of malignant tumors of the gastrointestinal tract) and generally arise from the upper airways, the small intestine, and the duodenopancreatic area. Usually asymptomatic in the early stage, these tumors are often discovered because of metastatic spread. For many patients with metastatic neuroendocrine tumors, palliative treatment is the only option. Most authors propose surveillance for patients with a well-differentiated tumor, until the tumor progresses. In this population, early recognition of a tumor's potential for progression could be helpful to avoid the wait-and-see period and thus enable early treatment for a better chance of efficacy and consequently a better prognosis. Several prognostic factors (*1,2*) have been studied. The prognostic value of several pathologic (*3,4*) (cytology, Ki67, p53) or biologic (chromogranin A (*5*), 5-hydroxyindoleacetic acid, and others) factors is known in nonmetastatic disease but is less studied in metastatic disease. An in vivo analysis of tumor behavior using nuclear medicine techniques might be of interest. Somatostatin receptor scintigraphy (SRS) has an excellent sensitivity and specificity for demonstrating tumor foci (*6*). The presence of cell surface receptors appears to depend on tumor differentiation, with well-differentiated tumors exhibiting a greater affinity for somatostatin (*7*). PET with ^{18}F-FDG could be used to differentiate more aggressive tumors exhibiting greater deoxyglucose uptake from slow-growing tumors (*8*) and to appreciate tumor control under treatment (*9,10*). ^{18}F-FDG PET has not been studied extensively in endocrine tumors (*11,12*). The overall sensitivity is low (*13*) for well-differentiated tumors but better for poorly differentiated tumors (*14*). Prospective data on the prognostic value of ^{18}F-FDG PET are lacking, and the retrospective reports have provided discordant results (*15,16*). We wanted to assess prospectively the predictive value of SRS and ^{18}F-FDG PET for rapid tumor progression in a significant number of patients with metastatic neuroendocrine tumor and without anticancer treatment at inclusion.

MATERIALS AND METHODS

Study Population

This prospective study was conducted between September 2003 and January 2006 among patients more than 18 y old and having a histologically proven well-differentiated metastatic neuroendocrine tumor (on initial data from the first biopsy, usually obtained at other centers) of the digestive tract or upper airways for whom our initially proposed management option was surveillance until tumor progression. Exclusion criteria were a high-grade poorly differentiated tumor requiring immediate treatment, pregnancy, and prior anticancer treatment other than surgery.

The therapeutic protocol, the information document, and the patient consent form were approved by the ethics committee of the Rennes University Hospital. All patients gave their written informed consent for inclusion in this study.

Examinations Performed and Follow-up

All patients underwent abdominothoracic CT, SRS, and ^{18}F-FDG PET at inclusion. Histology slides were reread at inclusion to confirm the diagnosis of well-differentiated metastatic neuroendocrine tumor. All slides were also reexamined at the end of the study to obtain Ki67 immunostaining results needed for the grading system, which was published after the end of patient inclusion. A physical examination was performed at inclusion and 6 wk later. The standard follow-up was a physical examination and CT at 3 and 6 mo and then every 6 mo. Supplementary CT was performed if the clinical situation worsened. Anticancer treatment was initiated if tumor progression was identified on the CT scan (using the Response Evaluation Criteria in Solid Tumors). The investigator physician was free to use long-acting somatostatin for antisecretory purposes irrespective of the SRS results.

The SRS was performed 4 h and then 20 h after injection of 185 MBq of ^{111}In-pentetreotide (OctreoScan; Mallinckrodt). Planar and tomoscintigraphic images were acquired with a double-head γ-camera (Hawkeye; GE Healthcare). Ordered-subsets expectation maximization (2 iterations, 8 subsets) was used for reconstructions. Two investigators who were unaware of the ^{18}F-FDG PET results interpreted the SRS findings as positive (tumor uptake > liver uptake, for liver lesions; tumor uptake > surrounding tissue, for lesions in other locations) or negative (the opposite) on the basis of visual inspection. After the patients had fasted for 4 h, imaging was performed on a dedicated ^{18}F-FDG PET camera (Advance; GE Healthcare) for 19 patients and on the same camera integrated with a CT scanner (Discovery LS; GE Healthcare) for the other 19 patients. Images were acquired 45–73 min after an intravenous injection of 105–494 MBq (mean, 310 MBq) of ^{18}F-FDG (Cisbio International). Ordered-subsets expectation maximization (32 iterations, 1 subset) was used for reconstruction without, and then with, attenuation correction. The ^{18}F-FDG PET results were interpreted independently by 2 physicians unaware of the SRS results. A consensus was reached in cases of disagreement. According to the visual interpretation, the ^{18}F-FDG PET results were considered to be negative (no ^{18}F-FDG uptake or discrete uptake) or positive (overt ^{18}F-FDG uptake). Uptake was standardized for injected activity and body weight to obtain the standardized uptake value (SUV) within a region of interest measuring 1 cm in diameter in a slice passing through the zone of greatest tumor uptake. The tumor-to-nontumor SUV ratio was determined from tumor uptake within a region of interest measuring 1 cm in diameter in a slice passing through the zone of greatest liver metastasis uptake and the average of 3 regions of interest measuring 1 cm within a slice of healthy liver tissue. The physician in charge of the patients did not know the SRS or ^{18}F-FDG PET results.

The histology slides were reread by 1 operator to confirm the diagnosis of endocrine tumor and to stage it using the World Health Organization (WHO) criteria (*4*). Tissue blocks were fixed and embedded in paraffin for standard staining and immunostaining procedures (streptavidin biotin peroxidase revelation with diaminobenzidine) using the following antibodies: chromogranin A (1/400 F/MS382-P; MMFrance), synaptophysin (1/50 A0010; DAKO), Ki67 (1/100 M7240; DAKO), and p53 (1/25 M7247; DAKO). The tumors were classified as high-grade poorly differentiated or low-grade well-differentiated endocrine carcinoma on the basis of morphologic characteristics. For p53 and Ki67, the results were expressed as percentage of positive cells. The low-grade tumors were then staged using a new grading system (*17*) taking into account the percentage of Ki67-positive cells: grade 1, ≤2%; grade 2, 3%−20%; and grade 3, >20%.

Statistical Analysis

Our main objective was to determine whether one of the nuclear medicine techniques could be used to identify patients whose tumor would progress early. For this purpose, we defined 2 groups of patients according to the pattern of tumor growth: early progressive disease (within 6 mo) or stable disease. We chose the 6-mo cutoff as the most clinically pertinent time point for early progression: 3 mo might have been clinically useful but would probably have corresponded more to poor initial staging than to actual rapid progression and 12 mo would have been somewhat long for early progression. In a retrospective analysis (unpublished) of 45 new cases diagnosed between 1998 and 2002 that were proposed to initially undergo surveillance, we found that 18 (40%) were cases of early progressive disease. We decided to consider as useful an examination that would correctly predict early progressive disease in at least 90% of the cases, with an α-risk of 5% and a β-risk of 20%. To achieve this statistical power, the prospective study would have to include 34 patients. Taking into account a possible dropout rate of 10%, we decided to include 38 patients. Secondary objectives were overall survival and progression-free survival as determined using the Kaplan–Meier method and compared with the log-rank test. Survival rates ± SD are given, and nondiscrete values are expressed as mean ± SD. Receiver-operating-characteristic analysis was used to determine a positive threshold for SUV and tumor-to-nontumor SUV ratio. Comparisons between SUV or tumor-to-nontumor SUV ratio and early progressive disease or stable disease used the Mann–Whitney test; correlation between ^{18}F-FDG PET results (positive or negative), WHO classification, Ki67 results (<15% vs. ≥15%), and P53 results (<15% vs. ≥15%) used the Fisher exact test.

Univariate analysis with the χ^2 test (or Fisher exact test if necessary) was applied to search for factors predictive of rapid progression. Univariate analysis to search for predictive factors of overall survival and progression-free survival used the Kaplan–Meier method, the curves being compared by a log-rank test. The variables tested included visual interpretation of the ^{18}F-FDG PET results, SUV (<4.5 vs. ≥4.5; threshold determined by receiver-operating-characteristic analysis), tumor-to-nontumor SUV ratio (<2.5 vs. ≥2.5; threshold determined by receiver-operating-characteristic analysis), SRS results (positive vs. negative), WHO stage (high grade vs. low grade), Ki67 results (<15% vs.

≥15%), and p53 results (<15% vs. ≥15%). Multivariate analysis using linear regression and a Cox model (forward Wald method) was performed with the following variables: visual interpretation of the ^{18}F-FDG PET results, SRS results, WHO stage, and Ki67 and p53 results (variables with $P < 0.05$ at univariate analysis); for ^{18}F-FDG PET evaluations, only visual interpretation was analyzed because the three ^{18}F-FDG PET parameters were autocorrelated.

SPSS was used for statistical analysis, and $P < 0.05$ was considered significant.

RESULTS

Study Population

From September 2003 through January 2006, 38 consecutive patients (24 men and 14 women; mean age, 60 ± 15 y; range, 23–68 y) were included prospectively. At inclusion, 31 patients had incident cases of metastatic neuroendocrine tumor and 7 were undergoing surveillance for an untreated metastatic neuroendocrine tumor; in 5 of these 7 patients, the diagnosis was established less than 6 mo before inclusion, and in the other two, the diagnosis was established less than 1 y before inclusion. Twenty-nine patients were in excellent general health (performance status, 0), and 9 had minor symptoms related to their disease (performance status, 1). The site of the primary tumor was unknown in 12 patients; localized foci were in the pancreas ($n = 9$), small intestine ($n = 11$), colon ($n = 3$), lung ($n = 2$), and gallbladder ($n = 1$). All patients had multiple metastases. Metastases were noted in the liver ($n = 34$ patients), lymph nodes ($n = 15$), peritoneum ($n = 8$), bones ($n = 3$), lungs ($n = 1$), and other locations (3). Among the 34 patients who had liver metastases, 18 had more than 10 metastases and 16 had fewer than 10; 1 patient had only 3 liver metastases but had metastases in several other locations. After multidisciplinary assessment, it was decided that the liver involvement in these patients was too advanced to allow curative surgery.

At the 6-mo follow-up, 16 patients (42%) had early progressive disease and 22 (58%) had stable disease. During the surveillance period (follow-up endpoint, September 2006; median follow-up of surviving patients, 20 mo), 19 patients (50%) received anticancer treatments and 11 (29%) died. The survival rates at 1 and 2 y were 86% ± 5.8% and 73% ± 7.9%, respectively, for overall survival and 55% ± 8.1% and 45% ± 8.5%, respectively, for progression-free survival.

Pathology Findings

The diagnosis of metastatic neuroendocrine tumor was confirmed in all patients. Ki67 and p53 immunostaining tests could not be performed for 4 patients (lack of sufficient material). The WHO stage (not taking into account grading based on Ki67 immunostaining) was high-grade in 4 patients and low-grade in 34. In these patients, the diagnosis of high-grade tumor was made some months after inclusion in the study, and the disease of all these patients had already progressed.

The percentage of Ki67-positive cells in the tumor samples was less than 2% in 14 patients, 3%−20% in 13, and more than 20% in 7. The percentage of p53-positive cells in the tumor samples was 0% in 15 patients, less than 10% in 5, 15%−20% in 4, and massive (>50%) in 4. Among the 34 low-grade tumors, 14 were grade 1, 13 were grade 2, and 4 were grade 3. This grading system could not be applied for 3 of the low-grade tumors.

Nuclear Medicine Studies

The SRS results were negative (Fig. 1) in 11 patients (29%) and positive (Fig. 2) in 27 (71%).

At visual inspection, the ^{18}F-FDG PET results were considered positive (Fig. 1) in 15 patients (39%) and negative (Fig. 2) in 23 (61%). SUV ranged from 35 to 1.4 (median, 3.7). The tumor-to-nontumor SUV ratio ranged from 0.7 to 15.2 (median, 1.9). The ^{18}F-FDG PET results correlated strongly with the WHO stage ($P < 0.001$) and with the Ki67 ($P < 0.001$) and p53 ($P < 0.05$) immunostaining results.

Factors Associated with Early Progression

Table 1 correlates the early follow-up with the results of pathology, PET, and SRS. WHO staging predicted tumor progression (early progressive disease vs. stable disease) ($P < 0.001$): tumor size increased within 6 mo in the 4 high-grade cases and in 12 of the 34 low-grade cases. The efficacy of the grading system was less clear: all 4 grade 3 tumors progressed within 6 mo, but 3 of 14 grade 1 tumors and 3 of 13 grade 2 tumors also did so.

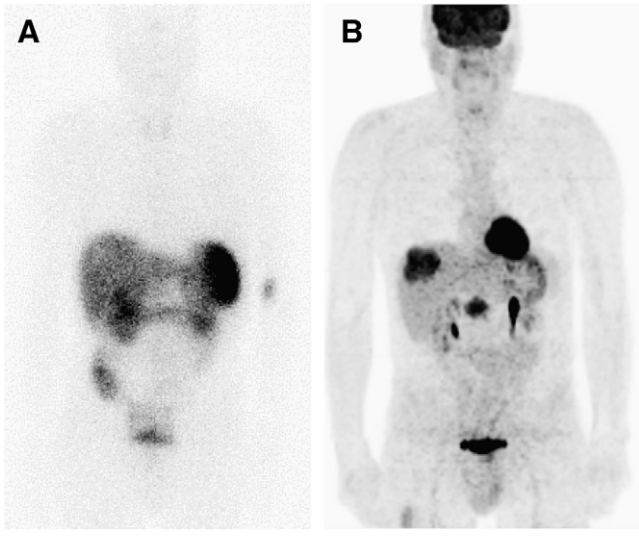

FIGURE 1. A 63-y-old patient who has liver metastases of pancreatic low-grade endocrine tumor. (A) SRS shows no uptake. (B) PET shows intense uptake in pancreatic tumor (SUV, 14.6; tumor-to-nontumor ratio, 6.3) and in liver metastases (SUV, 9.9; tumor-to-nontumor ratio, 4.3). Ki67 immunostaining was less than 2%; p53 immunostaining was 18%. Disease progressed at 3 mo.

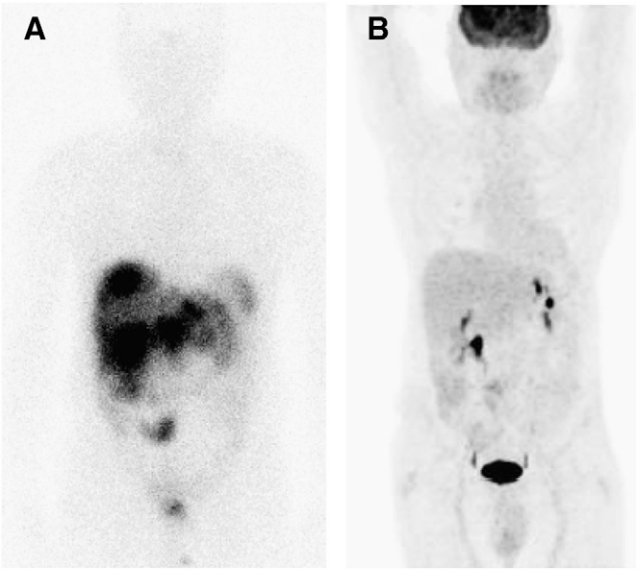

FIGURE 2. A 74-y-old patient who has low-grade ileal endocrine tumor with multifocal liver metastases. (A) SRS shows intense uptake in ileal tumor and in liver metastases. (B) PET shows no liver uptake and faint ileal uptake. Ki67 immunostaining was less than 2%; p53 immunostaining was 0%. Tumor was stable after 2.5 y of follow-up.

Fourteen of 15 ^{18}F-FDG PET–positive patients had early progressive disease, and 21 of 23 ^{18}F-FDG PET–negative patients had stable disease ($P < 0.001$). When one considers solely the 34 patients with low-grade tumors, ^{18}F-FDG PET distinguished those with early progression: 10 of 11 patients who were ^{18}F-FDG PET–positive and only 2 of 23 who were ^{18}F-FDG PET–negative were in the early progressive disease group ($P < 0.001$). When the analysis is limited to tumors that were low-grade or WHO grade 1 or 2 (excluding high-grade and grade 3 tumors), the same observations are made: 6 of the 7 patients who were ^{18}F-FDG PET–positive but only 2 of the 23 who were ^{18}F-FDG PET–negative were in the early progressive disease group ($P < 0.001$), and 3 of the 23 patients who were SRS-positive and 5 of the 7 who were SRS-negative had early progressive disease ($P < 0.001$). SUV was higher in patients with early progressive disease than in patients with stable disease (9.6 ± 7.9 vs. 2.8 ± 1.2, $P < 0.001$). The same was true for tumor-to-nontumor SUV ratio (5.4 ± 3.6 vs. 1.4 ± 0.6, $P < 0.001$). At receiver-operating-characteristic analysis, early progressive disease was predicted most accurately for the following thresholds: 4.5 for SUV and 2.5 for tumor-to-nontumor SUV ratio.

Negative findings on SRS were also significantly associated with early progression ($P < 0.03$): 20 of the 27 SRS-positive patients had stable disease, and 9 of 11 SRS-negative patients had early progressive disease.

Table 2 summarizes the diagnostic performance (sensitivity, specificity, negative and positive predictive values, and accuracy) of ^{18}F-FDG PET, SRS, WHO classification, and p53 and Ki67 immunostaining for the detection of rapid progressive disease. The best imaging test was ^{18}F-FDG PET; in cases of ^{18}F-FDG PET–positive findings, the relative risk of early progressive disease was 10.7 (95% confidence interval, 2.8–40.6).

Survival Analysis

Survival was better among patients with a low-grade tumor than among patients with a high-grade tumor ($P < 0.006$ for overall survival and $P < 0.003$ for progression-free survival), and survival was better among ^{18}F-FDG PET–negative patients than among ^{18}F-FDG PET–positive patients ($P < 0.001$ for both overall survival and progression-free survival) (Fig. 3). Overall survival (±SD) was 95% ± 5% and 95% ± 5% at 1 and 2 y, respectively, for ^{18}F-FDG PET–negative patients, versus 72% ± 12% and 42% ± 13% at 1 and 2 y, respectively, for ^{18}F-FDG PET–positive patients. Progression-free survival was 87% ± 7% and 75% ± 10% at 1 and 2 y, respectively, for PET–negative patients, versus 7% ± 6% and 0% at 1 and 2 y, respectively, for ^{18}F-FDG PET–positive patients. Similar results were observed for SRS: compared with negative SRS results, positive SRS results were associated with better overall survival (1- and 2-y survivals of 92% ± 5% and 70% ± 13%, respectively, for SRS-positive patients, vs. 60% ± 15% and 48% ± 17%, respectively, for SRS-negative patients; $P < 0.03$) and better progression-free survival (1- and 2-y survivals of 70% ± 9% and 61% ± 10%, respectively, for SRS-positive patients, vs. 18% ± 12% and 0%, respectively, for SRS-negative patients; $P < 0.001$) (Fig. 4).

Among the 34 patients with a low-grade tumor, progression-free survival was significantly better ($P < 0.001$) for the 23 who were ^{18}F-FDG PET–negative than the 11 who were ^{18}F-FDG PET–positive and for those who were SRS-positive than those who were SRS-negative ($P < 0.001$).

TABLE 1. Correlation Between Early Follow-up and Results of Pathology, PET, and SRS

	Pathologic result								
			WHO grade			PET result		SRS result	
Early follow-up result	High grade	Low grade	1	2	3	Positive	Negative	Positive	Negative
Early progressive disease	4	12	3	3	4	14	2	7	9
Stable disease	0	22	11	10	0	1	21	20	2
Total	4	34	14	13	4	15	23	27	11

TABLE 2. Diagnostic Performance of Various Tests for Detecting Rapidly Progressive Disease

Test	Sensitivity	Specificity	Negative predictive value	Positive predictive value	Accuracy
Visual PET	87.5	95.5	91	93	92
SRS	56.5	90.9	74.1	81.8	76.3
WHO classification	56.5	100	75.8	100	81.5
Ki67*	53.8	100	77.7	100	82.3
P53*	54.5	88.3	75	75	75

*<15% vs. ≥15%.
Data are percentages.

Overall survival was similar: better overall survival ($P < 0.007$) was found for ^{18}F-FDG PET–negative than ^{18}F-FDG PET–positive patients and for the 25 SRS-positive than the 9 SRS-negative patients ($P < 0.01$). Among the 15 patients who were ^{18}F-FDG–positive, those with positive SRS results had better progression-free survival ($P < 0.05$), but not better overall survival, than those with negative SRS results. When we excluded from the analysis the 4 patients who had a tumor initially considered to be low-grade but later graded as grade 3, the results remained unchanged except for progression-free survival, which was no longer significantly associated with SRS results ($P = 0.09$).

At univariate analysis, factors associated with progression-free survival and overall survival ($P < 0.05$) were ^{18}F-FDG PET result, SUV, tumor-to-nontumor SUV ratio, SRS result, WHO stage, and Ki67 and p53 results. At multivariate analysis, only the ^{18}F-FDG PET result ($P = 0.001$) was associated with progression-free survival. No independent factor predictive of overall survival could be identified.

DISCUSSION

Predicting the course of a metastatic neuroendocrine tumor is difficult. Treatment should be proposed for all

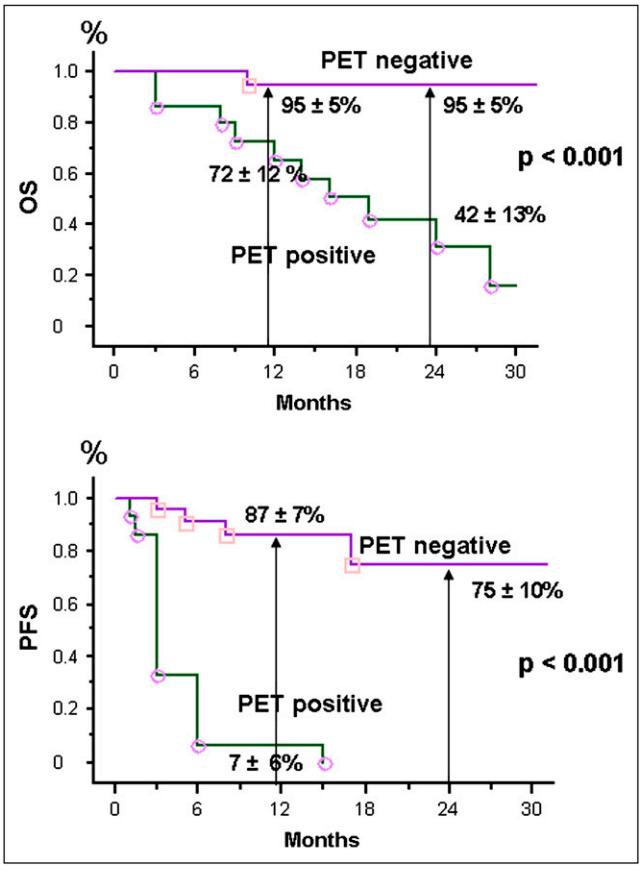

FIGURE 3. Progression-free survival (PFS) and overall survival (OS) are significantly ($P < 0.001$) better in PET-negative patients than in PET-positive patients; $n = 38$.

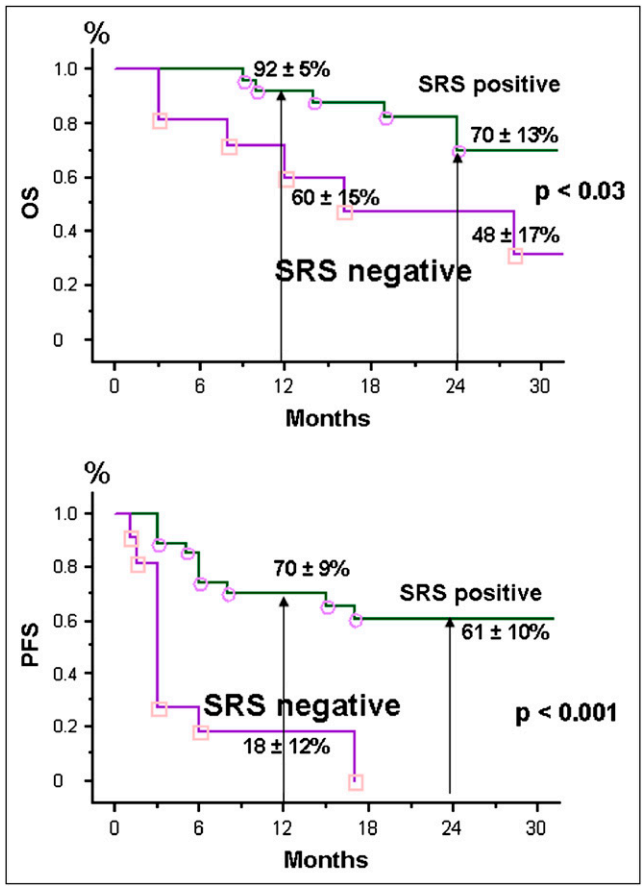

FIGURE 4. Progression-free survival (PFS) and overall survival (OS) are significantly ($P < 0.001$) better in SRS-positive patients than in SRS-negative patients; $n = 38$.

patients with high-grade tumors because of the aggressive nature of these tumors. The problem is different for low-grade tumors, because some can progress rapidly whereas others can remain stable for a long time. Because the available treatments have significant long-term toxicity and only moderate efficacy, it is important to distinguish between rapidly progressive tumors and relatively stable tumors. In our series, the WHO histologic classification appeared to be insufficient: although about half of low-grade tumors remained stable for 2 y, tumor size progressed within 6 mo in 12 of these 34 low-grade tumors. Several other systems have been proposed. We applied the new histopathologic system based on Ki67 immunostaining after the end of our study because this important grading system was not described until 2006; surprisingly, 4 of our patients had tumors that were classified as low-grade on the basis of morphologic characteristics but were grade 3. In this series, all high-grade and grade 3 tumors progressed within 6 mo. We also noted that the risk of progression was equivalent for grade 2 and grade 1 tumors, but the number of patients was really too small to draw any conclusion.

Our results show that nuclear medicine techniques have prognostic power. Regarding early progression (within 6 mo), ^{18}F-FDG PET appears to provide excellent information. Only 3 of our 38 cases were misclassified. The tumor did not progress in 1 patient who was ^{18}F-FDG PET–positive. Because this patient had the lowest SUV among the ^{18}F-FDG PET–positive patients and one of the lowest tumor-to-nontumor SUV ratios, the problem here might have been one of visual interpretation in an inflammatory and necrotic tumor. There were also 2 patients who had negative ^{18}F-FDG PET results but whose tumor progressed. These results appeared to be false-negative. SRS was also found useful for predicting early progressive disease but to a lesser extent than ^{18}F-FDG PET. ^{18}F-FDG PET offers excellent sensitivity, specificity, negative and positive predictive values, and accuracy.

This study had some limitations, the first concerning the study population. The sample was small, and the primary tumors were in a heterogeneous series of sites (pancreas, gut, and so forth). Four patients were found to have, in fact, a high-grade tumor after the histologic slides had been reread, yet these patients were included, as were 4 other patients with a grade 3 tumor. Another drawback is the high rate of negative SRS results. Considering our overall population, the SRS results were negative in 29%. This is a particularly high proportion, but in a recent review (*18*) on the diagnostic utility of SRS (19 series from 1994 to 2005), the detection rates ranged between 100% and 67%, with a median of 89%. This high rate of negative SRS results is not due to tumor size, because lesions were larger than 2 cm in all SRS-negative patients. Such a dissociation—SRS-negative results and ^{18}F-FDG PET–positive results—was previously noticed in a small series of patients (*15*). In this study, 6 of 6 patients with aggressive gastroenteropancreatic neuroendocrine tumors had positive ^{18}F-FDG PET findings and negative SRS findings, and 4 of 4 patients with nonaggressive gastroenteropancreatic neuroendocrine tumors had negative ^{18}F-FDG PET results and positive SRS results. The inclusion of some patients with high-grade and grade 3 tumors cannot be incriminatory because the SRS results were also negative in 23% (7/30) of the population with low-grade and grade 1 or 2 tumors.

As expected, overall survival correlated well with WHO stage (low-grade vs. high-grade). In addition, the results of nuclear medicine examinations correlated well with overall survival, with poorer survival being noted for ^{18}F-FDG PET–positive and SRS-negative patients; at multivariate analysis, only ^{18}F-FDG PET was independently predictive of progression-free survival. In this study, high-grade tumors were excluded, as they require immediate treatment; unfortunately, when the histologic slides were reread, 4 patients were found to have a high-grade tumor.

These findings are well in line with our initial hypothesis that less rapidly growing tumors would consume less energy and thus exhibit lower ^{18}F-FDG uptake on PET and that more aggressive tumors would have fewer somatostatin receptors detectable on SRS.

Data on the prognostic value of nuclear medicine examinations are scarce in the literature, especially data on ^{18}F-FDG PET in patients with metastatic neuroendocrine tumor. The only publication available (to our knowledge) reported findings similar to ours (*19*). A broader comparison with studies on other diseases shows that strong ^{18}F-FDG uptake in tumors is associated with a poor outcome in resected lung cancer (*20*), metastatic colorectal cancer (*21*), and resectable soft-tissue sarcoma (*22*). Other factors proposed for differentiating progressive metastatic neuroendocrine tumor from more stable tumors have included alkaline phosphatase (*23*), serum chromogranin A, and angiogenic cytokines (*24*).

CONCLUSION

This prospective analysis of prognostic factors in a small series of patients with metastatic neuroendocrine tumor showed that ^{18}F-FDG PET can be used to recognize patients who have a rapidly progressive tumor. At multivariate analysis, ^{18}F-FDG PET results were independently predictive of progression-free survival. ^{18}F-FDG PET could therefore be proposed as an extension of the work-up after diagnosis of a metastatic neuroendocrine tumor, particularly in the case of a histologically low-grade tumor, in order to propose a treatment or an intensified surveillance scheme for patients with a low-grade tumor but positive ^{18}F-FDG PET results. Beforehand, however, our results need to be confirmed through a larger prospective multicenter trial that includes patients with low-grade (grade 1 or 2) metastatic neuroendocrine tumor, stratified between pancreatic or carcinoid tumors, comparing the ability of nuclear medicine examination and pathologic parameters to predict early progression.

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