

High Prognostic Value of ^{18}F -FDG PET for Metastatic Gastroenteropancreatic Neuroendocrine Tumors: A Long-Term Evaluation

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This study aimed to evaluate the long-term prognostic usefulness of ^{18}F -FDG PET for patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEPNETs). **Methods:** Thirty-eight patients with metastatic GEPNETs were prospectively enrolled. Initial check-up comprised CT scan, ^{111}In -pentetate scintigraphy (SRS), and ^{18}F -FDG PET. Only ^{18}F -FDG PET-positive lesions with a maximum standardized uptake value (SUV_{max}) greater than 4.5 or an SUV ratio (SUV_{max} tumor to SUV_{max} nontumoral liver tissue, or T/NT ratio) of 2.5 or greater were considered positive for prognosis—that is, indicating a poor prognosis. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Factors associated with survival were assessed with univariate and multivariate analyses, using the Cox regression model. **Results:** Median PFS and OS were significantly higher for patients with a negative ^{18}F -FDG PET finding, with an OS of 119.5 mo (95% confidence interval [CI], 72– ∞), than for patients with a positive ^{18}F -FDG PET finding (only 15 mo [95% CI, 4–27]) ($P < 10^{-3}$). Median PFS and OS were significantly higher for the patient group that had a positive SRS than the group with a negative SRS ($P = 0.0002$). For patients with a positive SRS, PFS and OS were significantly shorter when the ^{18}F -FDG PET finding was positive: 19.5 mo (95% CI, 4–37) for PFS and 119.5 mo (95% CI, 81– ∞) for OS ($P < 10^{-3}$). In the patient group with a low-grade GEPNET and a positive SRS, PFS and OS were also significantly lower for patients with a positive ^{18}F -FDG PET. At 48-mo follow-up, 100% of patients who had a positive ^{18}F -FDG PET for disease progression (of which 47% were also SRS-positive) were deceased, and 87% of patients with a negative ^{18}F -FDG PET were alive ($P < 0.0001$). The T/NT ratio was the only parameter associated with OS on multivariate analysis. **Conclusion:** Overall, ^{18}F -FDG PET appears to be of major importance in the prognostic evaluation of metastatic GEPNET. A positive ^{18}F -FDG PET with an SUV ratio (T/NT) of 2.5 or greater was a poor prognostic factor, with a 4-y survival rate of 0%. A positive SRS does not eliminate the need for performing ^{18}F -FDG PET, which is of greater prognostic utility.

Key Words: prognosis; PET; FDG; neuroendocrine

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Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are rare and form a heterogeneous group of tumors, with different progression profiles (1).

Different histoprosthetic classifications (2–4) have been proposed, but determining the prognosis for neuroendocrine tumors (NETs) remains problematic even in the case of metastatic disease. These tumors are characterized by somatostatin receptor expression, which varies quantitatively and qualitatively from one tumor type to another (5).

It is now clearly known that functional imaging based on somatostatin receptor expression (^{111}In - or ^{68}Ga -radiolabeled analogs) has better diagnostic performance than ^{18}F -FDG PET. It is also known that somatostatin receptor expression correlates with well-differentiated NET (6–8) and is a favorable prognostic factor (9–11).

In contrast, a positive ^{18}F -FDG PET finding would correlate with a poorly differentiated NET and be a poor prognostic factor. But so far, only few studies have been performed on this subject (9,11,12). The main objective of our study, with preliminary findings already published (9), was to evaluate on a long-term basis the progression-free survival (PFS) and overall survival (OS) of metastatic GEPNET patients based on ^{18}F -FDG PET and ^{111}In -pentetate scintigraphy (SRS) results.

MATERIALS AND METHODS

In this prospective study, 38 patients with a histologically confirmed metastatic NET, mainly gastroenteropancreatic ($n = 36$), were enrolled from September 2003 to January 2006. The trial was approved by the ethics committee of our university hospital, and written informed consent was obtained from each patient. There were 24 men and 14 women (mean age \pm SD, 60 \pm 15 y).

The primary tumor site was known for 26 patients (pancreas, 9; midgut, 11; hindgut, 3; lung, 2; and gallbladder, 1). For the other 12 patients, the primary tumor site was unknown, but they had neuroendocrine hepatic metastases.

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All of the patients had metastatic disease. The site of metastases was as follows: liver ($n = 34$ patients), lymph nodes ($n = 15$), peritoneum ($n = 8$), bone ($n = 3$), lungs ($n = 1$), central ($n = 1$), and ovaries ($n = 1$). The Ki67 index was available for 34 patients, established at less than 2% in 13 patients and greater than 15% in 7. Four tumors were classed as high-grade according to the World Health Organization (WHO) classification. Of the 34 low-grade tumors (WHO), 4 were classed grade 3 according to the European Neuroendocrine Tumor Society classification.

The study protocol, histologic diagnosis, and study population were detailed in a previously published article (9).

SRS and ^{18}F -FDG PET were performed in a standard fashion (9). ^{18}F -FDG uptake was quantified with the maximum standardized uptake value (SUV_{max}) and using the tumor-to-nontumor ratio (T/NT), calculated as the ratio of SUV_{max} tumor to SUV_{max} nontumoral liver. Poor prognosis was defined as patients with rapidly progressive disease—that is, with progressive disease at 6 mo (9), given that 6 mo is the typical timeframe used to discriminate rapidly progressive disease (requiring aggressive therapy) from nonrapidly progressive disease (requiring no aggressive therapy).

For prognostic evaluation, ^{18}F -FDG PET was considered as positive (i.e., predictive of a poor prognosis) only for an SUV_{max} of 4.5 or greater or a T/NT ratio of 2.5 or greater.

Specific antitumor treatments, such as chemotherapy or chemoembolization, were initiated only when tumor progression was identified on a CT scan in accordance with Response Evaluation Criteria In Solid Tumors.

Statistical Analysis

Receiver-operating-characteristic (ROC) analysis was applied to determine the positive threshold for SUV (standardized uptake value) and T/NT ratio with respect to prognostic evaluation.

The factors associated with PFS and OS were analyzed on univariate and multivariate analyses using a forward Cox model (Wald method). The tested parameters consisted of T/NT ratio (<2.5 or ≥ 2.5), SUV (<4.5 or ≥ 4.5), SRS, histologic grade, and Ki67 index ($<15\%$ or $\geq 15\%$). For the multivariate analysis, neither SUV nor histologic grade was analyzed because T/NT ratio and SUV were linked variables, as were histologic grade and Ki67 index.

PFS and OS were estimated using the Kaplan–Meier method, and their comparison was based on log-rank test.

The statistical analyses were conducted using SPSS software (IBM). The significance level was set at 0.05.

RESULTS

The mean follow-up duration was 55.2 ± 37.9 mo, ranging from 1 to 119.2 mo. Only 1 patient was lost to follow-up, at 81 mo of follow-up. During the follow-up period, 27 patients (71%) exhibited disease progression, and 24 (63%) died.

TABLE 1
Results Using ^{111}In -Octreotide Scintigraphy and ^{18}F -FDG PET Scanning ($n = 38$ Patients)

Modality	PET+*	PET–	Total
^{111}In -octreotide scintigraphy (positive)	7 (2 [†])	20	27
^{111}In -octreotide scintigraphy (negative)	8 (2 [†])	3	11
Total	15	23	38

*T/NT ≥ 2.5 .

[†]High-grade tumor according to WHO/ENETS classification.

TABLE 2
Results of ^{18}F -FDG PET and SRS Depending on Ki67 ($n = 34$ Patients)

Modality	Ki67 < 2% ($n = 13$)	Ki67 2%–15% ($n = 14$)	Ki67 $\geq 15\%$ ($n = 7$)
PET+*	3	3	7
PET–	10	11	0
SRS+	8	13	3
SRS–	3	1	4

*T/NT ≥ 2.5 .

^{18}F -FDG PET and SRS positivity or negativity related to the histologic grade and Ki67 are presented, respectively, in Tables 1 and 2. ^{18}F -FDG PET correlated with the histoprognoic grade ($P = 0.01$) and Ki67 ($P < 10^{-3}$) whereas SRS results did not.

The identified thresholds of positivity for prognosis were 4.5 for SUV (area under the ROC curve, 0.897) and 2.5 for T/NT ratio (area under the ROC curve, 0.920), (Fig. 1).

Using univariate analysis, we found SUV, T/NT ratio, Ki67, and histologic grade to be significantly correlated to PFS and OS (Table 3). Yet at multivariate analysis, T/NT ratios were still found to highly significantly correlate with PFS and only T/NT ratio was still found to significantly ($P < 0.0001$; relative risk of death: 26.8) correlate with OS (Table 3).

Fifteen patients (39%) had a positive ^{18}F -FDG PET. PFS and OS were highly significantly better in the patient group with a negative ^{18}F -FDG PET than in the patient group that had a positive

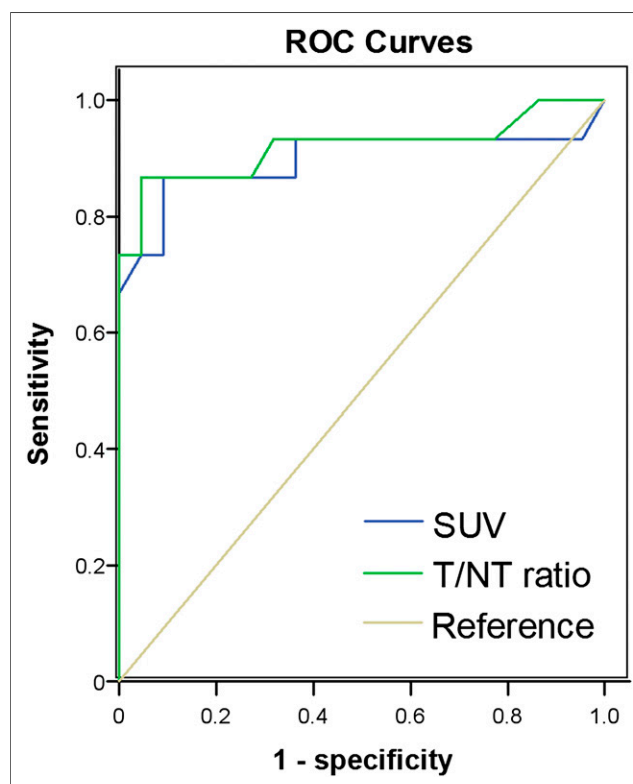


FIGURE 1. ROC curves for SUV and T/NT ratio for identification of poor prognosis (i.e., rapidly progressive disease).

TABLE 3
Univariate and Multivariate Analysis (Cox Regression Model) of Factors Associated with PFS and OS

Prognostic parameter	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	<i>P</i>	Relative risk	<i>P</i>	Relative risk	<i>P</i>	Relative risk	<i>P</i>	Relative risk
T/NT ratio (< or ≥ 2.5)	<0.0001	17.7 (2.4–14.7)	0.0012	18.6 (3.2–109)	<0.0001	23 (6.1–86.4)	<0.0001	26.8 (5.2–139.7)
SUV (< or ≥ 4.5)	<0.0001	6.0 (2.4–14.7)	Not available		<0.0001	6.3 (2.5–15.7)	Not available	
SRS	0.0012	0.23 (0.09–0.56)	0.0372	0.31 (0.01–0.93)	0.0007	0.2 (0.08–0.51)	0.11 (not significant)	0.41 (0.13–1.27)
Histologic grade	0.0007	6.9 (2.3–21.2)	Not available		<0.0001	0.1 (0.1–0.2)	Not available	
Ki67 (< or ≥ 15%)	0.0008	5.6 (2.1–15.5)	0.2996 (not significant)	1.88 (0.56–6.25)	<0.0001	9.5 (4.7–80)	0.08 (not significant)	3.5 (0.8–15.2)

Data in parentheses are 95% CI.

^{18}F -FDG PET: respectively, 71 mo (IC 95%, 50 mo– ∞) versus 3 mo (IC 95%, 3–6 mo), $P < 0.0001$, for PFS, and 119.5 (IC 95%, 72 mo– ∞) versus 15 mo (IC 95%, 4–27 mo) for OS, $P < 0.0001$ (Fig. 2).

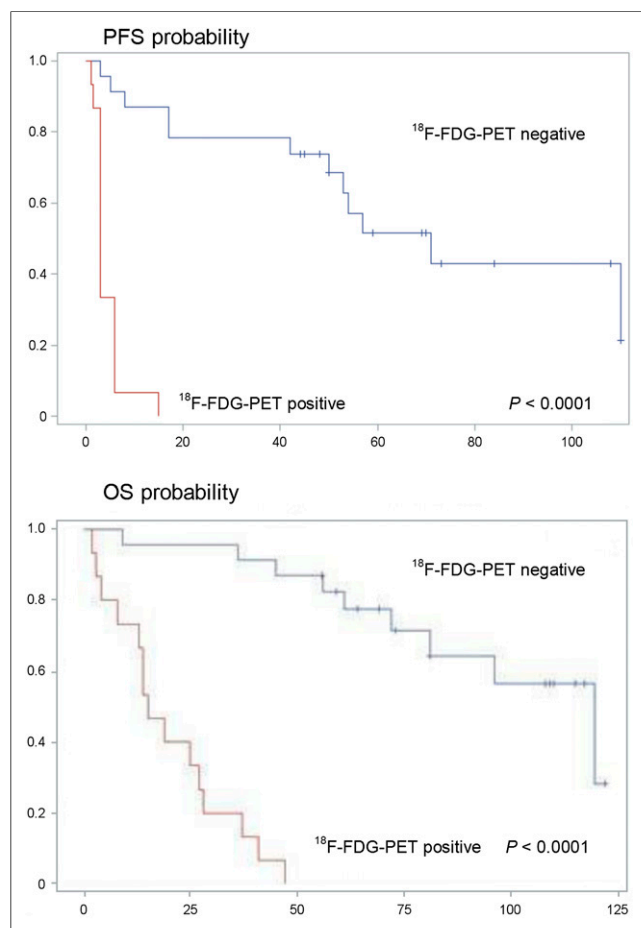


FIGURE 2. PFS and OS probabilities (time in mo) according to ^{18}F -FDG PET.

We observed that 23 patients (61%) had a positive SRS. PFS and OS were significantly better in the patient group with a positive SRS than in the patient group that had a negative one: respectively, 54 mo (IC 95%, 8–110 mo) versus 3 mo (IC 95%, 1.5–6 mo) for PFS, $P = 0.0002$, and 96 mo (IC 95%, 47 mo– ∞) versus 27 mo (IC 95%, 3–41 mo) for OS, $P = 0.0002$ (Fig. 3).

Twenty-nine percent of the patients with a positive SRS also had a positive ^{18}F -FDG PET (i.e., 11 patients). For those patients, PFS and OS were highly significantly better in the patient group with a negative ^{18}F -FDG PET than in the patient group that had a positive ^{18}F -FDG PET: respectively, 71 mo (IC 95%, 50 mo– ∞) versus 6 mo (IC 95%, 3–15 mo) for PFS, $P < 0.0001$, and 119.5 mo (IC 95%, 81 mo– ∞) versus 19 mo (IC 95%, 4–37 mo) for OS, $P < 0.0001$ (Fig. 4).

In the patient group with the best assumed prognostic profile—that is, patients with low-grade GEPNET (WHO/ENETS) and positive SRS—PFS and OS were highly significantly better in patients who had a negative ^{18}F -FDG PET (of the patients of this group) than in patients who had a positive ^{18}F -FDG PET (of the patients of this group): respectively, 71 mo (IC 95%, 50 mo– ∞) versus 6 mo (IC 95%, 3–15 mo) for PFS, $P < 0.0001$, and 119.5 mo (IC 95%, 81 mo– ∞) versus 37 mo (IC 95%, 14–47 mo) for OS, $P < 0.0001$ (Fig. 5).

Survival rates regarding ^{18}F -FDG-negative and -positive patients were, respectively, 73% versus 95% ($P < 0.0001$) at 1 y, 40% versus 95% ($P < 0.0001$) at 2 y, 20% versus 91% ($P < 0.0001$) at 3 y, and 0% versus 87% ($P < 0.0001$) at 4 y.

Survival rates regarding SRS-negative and -positive patients were, respectively, 92% versus 72% ($P = 0.0002$) at 1 y, 81% versus 54% ($P = 0.0002$) at 2 y, 77% versus 27% ($P = 0.0002$) at 3 y, 70% versus 9% ($P = 0.0002$) at 4 y, and 57% versus 0% ($P = 0.0002$) at 6 y.

DISCUSSION

In this study, median PFS and OS were highly significantly better ($P < 10^{-3}$) in the patient group with a negative ^{18}F -FDG PET than in the group with a positive ^{18}F -FDG PET (respectively,

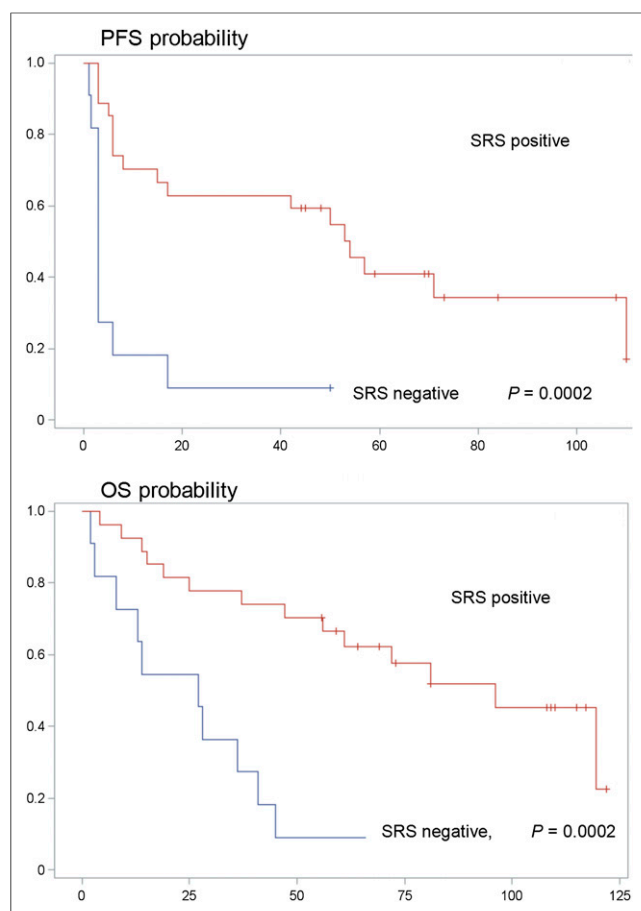


FIGURE 3. PFS and OS probabilities (time in mo) related to SRS.

119.5 and only 15 mo), whatever the results of other prognostic tools, including SRS and even Ki67 or histologic classification. To our knowledge, no other prospective study has performed a long-term prognostic evaluation in metastatic GEPNET patients, based on both ^{18}F -FDG PET and SRS.

Indeed, Binderup et al. (12) evaluated survival in NET patients over only a short period (average follow-up, 11.5 mo). Median OS was not reached but the authors also found that a positive ^{18}F -FDG PET with an SUV_{max} cutoff of 9 strongly correlated with a greater risk of mortality (hazard ratio, 0.8; 95% CI, 2.7–28.7; $P < 0.001$). In this study, a comparison with the SRS prognostic value was not performed.

A positive SRS has been reported to be factor of good prognosis (9,11,12). In our study, median PFS and OS were significantly better in the patient group that had a positive SRS than in the one exhibiting a negative SRS ($P < 10^{-3}$), confirming the prognostic value of SRS. However, the prognostic value of SRS has been shown to be lower than that of ^{18}F -FDG PET. We have, in fact, found that SRS was no longer correlated to OS when using multivariate analysis, as opposed to ^{18}F -FDG PET.

For patients with both a positive SRS and a positive ^{18}F -FDG PET, prognosis can be difficult to anticipate (because of the contradictory prognosis information provided by SRS and ^{18}F -FDG PET). In this situation representing 18.2% of the global population and 25% of the positive SRS patients, our study clearly demonstrates for the first time that prognosis is related to the positivity of the ^{18}F -FDG PET (poor prognosis), because median OS is only

17 mo when ^{18}F -FDG PET is positive versus 119.5 mo when it is negative ($P < 10^{-3}$).

Because SRS sensitivity for tumor detection is far better than ^{18}F -FDG PET (6–8), most recommendations reserve ^{18}F -FDG PET for cases in which SRS is negative, for high-grade tumors with a high proliferation index (Ki67), or for tumors shown to be rapidly progressing based on morphologic examinations (13–15).

However, in our results 25% of the patients with a positive SRS and 21% of the patients who had a tumor with a low proliferation index (Ki67 $< 2\%$) also had a ^{18}F -FDG PET-positive result and a poor prognosis. Binderup et al. (12) reported similar findings, namely 40% of patients who had a NET with a low proliferation index (Ki67 $< 2\%$) had a positive ^{18}F -FDG PET. These results are of great interest, suggesting that ^{18}F -FDG PET is indicated in metastatic NETs, even in cases of low Ki67 index (i.e., $< 2\%$).

Elsewhere, the usefulness of SRS in known metastatic NETs remains a matter of debate. Given its lower prognostic impact than ^{18}F -FDG PET, it should be performed solely if surgery or radiolabeled somatostatin analog therapy is proposed, and this is still the case for patients with a high Ki67 index, because 42% of our patients with a Ki67 index of 15% or greater also exhibited a positive SRS.

In the patient group having both a low-grade NET (WHO/ENETS) and a positive SRS ($n = 23$), 3 patients also had an ^{18}F -FDG PET-positive finding. Here again, median PFS and OS were highly significantly lower when ^{18}F -FDG PET was positive versus when it was negative ($P < 10^{-3}$).

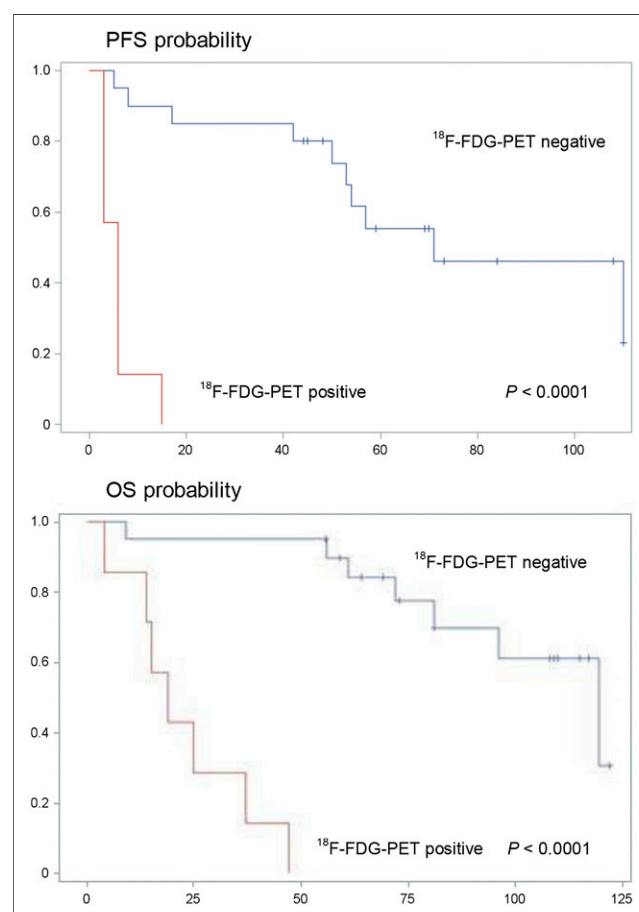


FIGURE 4. PFS and OS probabilities (time in mo) for SRS-positive patients related to ^{18}F -FDG PET.

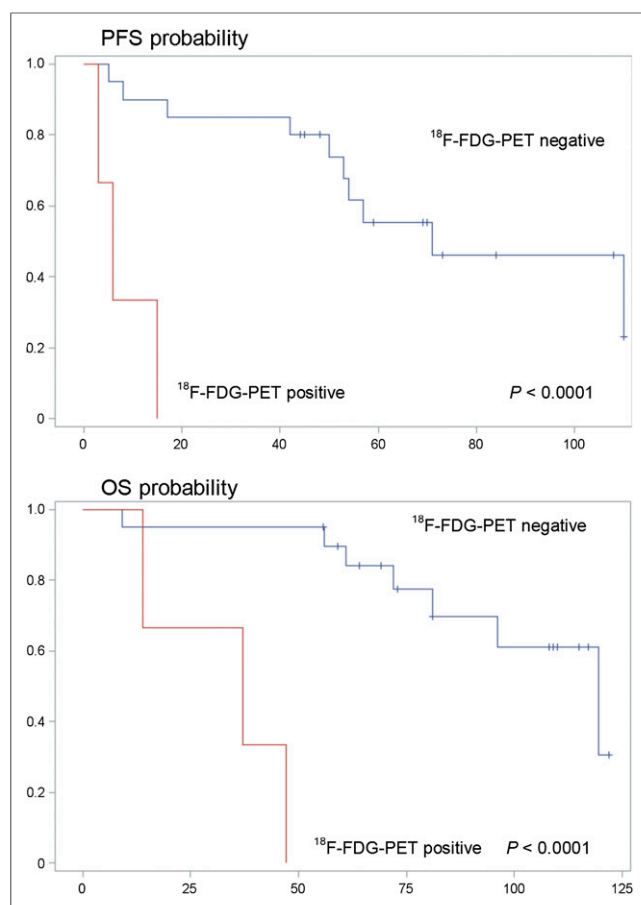


FIGURE 5. PFS and OS probabilities (time in mo) for the group of patients with both SRS positivity and low grade.

The coexistence in the same patient, or even in the same tumor, of well-differentiated and poorly or undifferentiated tumor clones (5) may explain why some NETs exhibit uptake of both ¹¹¹In-pentetreotide and ¹⁸F-FDG. This coexistence would also explain the variability of tumor behavior and the sometimes fatal progression of certain patients with a NET who had wrongly been classed as of low risk.

Thus, in the case of metastatic NETs, ¹⁸F-FDG PET should be more widely used for prognostic evaluation.

The prognostic impact of ¹⁸F-FDG PET is confirmed by the long-term evaluation with an overall 4-y survival rate of 0% in the patient group that had a positive ¹⁸F-FDG PET, compared with 87% in the group that had a negative ¹⁸F-FDG PET. On the basis of this finding, ¹⁸F-FDG PET appears to be of dramatic prognostic value. This point is of major interest because aggressive therapeutic approaches including chemotherapy, radiolabeled somatostatin analog internal radiation therapy (for SRS-positive patients), liver radioembolization (especially for PET-positive and SRS-negative patients), or targeted therapy can be proposed to patients with poor prognosis.

The main drawback of this study is a relatively small number of patients and heterogeneity of the population (NETs of different origin), but these drawbacks are almost always the case in others' published data on PET and NETs. The interesting result observed in this prospective study—the highly significant dramatic prognostic impact of ¹⁸F-FDG PET in metastatic patients—should be

validated in a larger multicentric trial. The prognostic value of ¹⁸F-FDG PET has also to be evaluated in nonmetastatic patients.

CONCLUSION

Our study results clearly demonstrate the usefulness of ¹⁸F-FDG PET for metastatic GEPNET. A positive SRS does not eliminate the need for an ¹⁸F-FDG PET, because ¹⁸F-FDG PET is of greater prognostic value even when SRS is positive or in some cases of low-grade lesions.

Early prognostic assessment of these tumors could be used for the selection of patients requiring aggressive treatment. The prognostic value of ¹⁸F-FDG PET in nonmetastatic patients has also to be evaluated because it was not evaluated in this study.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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