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EUS-FNA predicts 5-year survival in pancreatic endocrine tumors

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Background: Pancreatic endocrine tumors (PETs) differ in clinical behavior and prognosis. Determination of malignant potential through specimens obtained by EUS-FNA can help in the management of these patients.

Objective: To determine the value of EUS-FNA for diagnosing PETs and for classifying their underlying malignant potential based on the World Health Organization (WHO) classification.

Design: Single-center, retrospective, cohort study.

Setting: Tertiary referral hospital.

Patients: This study involved 86 consecutive patients (44 men, mean age 58 ± 14 years) who had been diagnosed with PETs and submitted to EUS-FNA from January 1999 to August 2008.

Intervention: EUS-FNA of a pancreatic mass and/or a metastasis site. Immunohistochemistry on microbiopsies or on monolayer cytology was routinely used. The lesions were classified as recommended by the WHO.

Main Outcome Measurements: EUS-FNA sensitivity and 5-year survival rate.

Results: Overall, in 90% (77 of 86) of patients in this study, PET was diagnosed with EUS-FNA. The sensitivity did not vary with tumor size, type, location, or the presence of hormonal secretion. Of 86 patients, 30 (35%) were submitted to surgical resection. The kappa correlation index between the WHO classification obtained by EUS-FNA and by surgery was 0.38 (P = .003). Major discrepancies were found in the group of patients diagnosed with endocrine tumor of uncertain behavior by EUS-FNA, because 72% turned out to have well-differentiated endocrine carcinoma. Sixteen patients (27%) died during a mean follow-up period of 34 ± 27 months. The 5-year survival rates were 100% for endocrine tumors, 68% for well-differentiated endocrine carcinomas, and 30% for poorly differentiated endocrine carcinomas (P = .008, log-rank test).

Limitations: Retrospective design, selection bias, and small sample size.

Conclusions: This largest single-center experience to date demonstrated the accuracy of EUS-FNA in diagnosing and determining the malignant behavior of PETs. EUS-FNA findings predict 5-year survival in patients with PETs. (Gastrointest Endosc 2009;70:907-14.)

Pancreatic endocrine tumors (PETs) make up 1% to 2% of pancreatic neoplasms.^{1,2} Nonfunctioning PETs (NF-PETs) are more common than functioning PETs (F-PETs)

Abbreviations: BBWDET, well-differentiated endocrine tumor of probable benign behavior; PET, pancreatic endocrine tumor; F-PET, functioning PET; NF-PET, nonfunctioning PET; PDEC, poorly differentiated endocrine carcinoma; UBWDET, well-differentiated endocrine tumor of uncertain behavior; WDEC, well-differentiated endocrine carcinoma; WHO, World Health Organization.

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and typically present because of a mass effect or metastatic spread.³ F-PETs may cause a variety of symptoms depending on the hormone produced.^{2,4} PETs have a much better prognosis than nonendocrine tumors of the pancreas. Several publications, however, support the concept that different endocrine tumor types differ in clinical behavior and prognosis.⁵⁻⁷

A recent World Health Organization (WHO) classification has been proposed.^{8,9} GI endocrine tumors are assigned as well-differentiated endocrine tumor of probable benign behavior (BBWDET), well-differentiated endocrine tumor of uncertain behavior (UBWDET), welldifferentiated endocrine carcinoma (WDEC), and poorly differentiated endocrine carcinoma (PDEC). This classification is based on tumor size, histology, and proliferative indices. Some recent publications have focused on the application of this classification in surgical specimens.^{5-7,10}

EUS and EUS-FNA have become the preferred modalities for localizing and diagnosing PETs. They are useful for distinguishing PET from adenocarcinoma and for localizing tumors not imaged by conventional studies.¹¹ Anderson et al¹² correctly localized tumors with EUS in 93% of cases. Several authors have shown sensitivity and accuracy rates greater than 80% for EUS-FNA.^{10,13,14} These studies, however, did not apply the recently proposed WHO classification to specimens obtained by EUS-FNA.

Recognition of the underlying malignant behavior of GI endocrine tumors has led to a much greater aggressiveness in their treatment, with both medical and surgical modalities. The outcomes emerging from this more aggressive approach to treatment are improved quality of life and 5year survival (from 40% to 82% for metastatic PETs).^{15,16} Despite the small number of cases, Sellner et al¹⁷ demonstrated the clinical importance of distinguishing between well-differentiated and poorly differentiated endocrine carcinomas. Tumor extension, metastases, secretor profile, and degree of differentiation should be determined as far as possible before treatment is planned.¹⁸ Determination of tumor malignant potential at an early stage of investigation, through specimens obtained by EUS-FNA, would be of great importance in the stratification, treatment, and follow-up of patients with PET.

The aim of this study was to determine the value of EUS-FNA for the diagnosis of PETs and for classifying the underlying malignant potential of these tumors based on the proposed WHO classification.^{8,9}

METHODS

This was a retrospective study. A detailed review of the medical records from January 1999 to August 2008 was performed to identify consecutive patients who had been diagnosed with PET and submitted to EUS-FNA, at the Institute Paoli-Calmettes, Marseille, France. The study protocol was conducted in accordance with the ethical principles and guidance of the Helsinki Declaration. The study was approved by the local ethics committee.

The diagnosis of PET was established by evaluation of microbiopsies or monolayer cytology obtained by EUS-FNA and/or histopathological evaluation obtained by surgical resection of a pancreatic mass and/or a metastasis site. All diagnoses were confirmed by immunohistochemistry. Demographic data, clinical and EUS findings, and cytology and histopathological results were reviewed.

EUS procedures were performed by experienced endosonographers who used linear-array echoendoscopes (FG36X or EG38UT, Pentax Europe Ltd., Hamburg, Germany) with an ultrasound platform (Hitachi 6500

Capsule Summary

What is already known on this topic

• Recognition of the underlying and variable malignant potential of GI endocrine tumors has led to increased aggressiveness in their treatment.

What this study adds to our knowledge

- In 77 of 86 (90%) patients EUS-FNA was successful in diagnosing pancreatic endocrine tumors.
- It is possible to apply the WHO classification and to determine the potential malignant behavior of PETs in specimens obtained by EUS-FNA.

or 8500, Hitachi Medical Systems GmbH, Wiesbaden, Germany). EUS-FNA was performed by using a 22-gauge FNA needle (Echotip, Cook Endoscopy, Winston-Salem, NC). Antibiotics were not administered prophylactically.

An immediate screening at the time of EUS-FNA was not performed. Direct smears were prepared by the endoscopist and were stained with May-Grunwald-Giemsa stain on air dried slides. ThinPrep preparation (monolayer cytology, Cytyc Corp., Boston, Mass) was used in all cases. Cell block material, fixed in 10% neutral buffered formalin, was collected at the reception of the aspirated material. Hematoxylin-eosin staining was performed on cell block preparations and on monolayer cytology slides. Endocrine differentiation was confirmed immunohistochemically on cell block preparations or in the absence of material on cell blocks on monolayer cytology specimens. Immunohistochemical analysis was performed according to the streptavidin-biotin technique. The antibodies used were synaptophysin (polyclonal, prediluted, Dako, France) and chromogranin A (clone LK2H10, 1/200, Beckman Coulter, France). In addition to the histological differentiation grade, p53 (clone DO-7, 1/10, Dako, France) and Ki-67 (clone Mib-1, prediluted, Dako, France) labeling indices were amended when sufficient tumor tissue was available.

Blocks of surgical specimens were generally fixed in formalin. Routine diagnostic sections were stained with hematoxylin-eosin. Endocrine differentiation was confirmed immunohistochemically by using antibodies against synaptophysin and chromogranin A. Antibodies p53 and Ki-67 were used. Where there had been evidence of ectopic hormone secretion, immunostaining was performed for the appropriate hormones.

The final diagnosis and differentiation of PET was established by a single experienced pathologist. The lesions were classified according to the WHO recommendation as shown in Table $1.^{8,9}$ The WHO classification obtained by EUS-FNA was compared with that obtained by surgical resection when both were available.

The statistical analysis was done with SPSS 11.0 (SPSS Inc, Chicago, IL) software. The categorical variables were

Group I		Group II	Group III	
BBWDET	UBWDET	WDEC	PDEC	
onfined to pancreas	Confined to pancreas	Well-to-moderately differentiated	Small-cell carcinoma	
2 cm	>2 cm		Poorly differentiated	
2 mitoses/10 HPF	>2 mitoses/10 HPF	Gross local invasion and/or metastasis	Necrosis common	
i-67 index <2%	Ki-67 index >2%		>10 mitoses/10 HPF	
lo vascular invasion	Vascular invasion	Mitotic rate often higher (2-10/10 HPF)	High mitotic/Ki-67 index Hyperexpression of p53	
		Ki-67 index >5%	Metastasis prominent vascular and/or perineural invasion	

WHO, World Health Organization; PET, Pancreatic endocrine tumor; BBWDET, Well-differentiated endocrine tumor of probable benign behavior; UBWDET, welldifferentiated endocrine tumor of uncertain behavior; WDEC, well-differentiated endocrine carcinoma (low-grade malignant); PDEC, poorly differentiated endocrine carcinoma (high-grade malignant).

Tumor characteristic	Sensitivity: no. of total (%)	
Overall	77 of 86 (90)	N/A
F-PET vs NF-PET	10 of 12 (83) vs 67 of 74 (91)	.63
PET \leq 10 mm vs $>$ 10 mm	12 of 14 (86) vs 65 of 72 (90)	.64
PET solid vs cystic	70 of 78 (90) vs 7 of 8 (88)	.99
PET location: head vs body vs tail	40 of 45 (89) vs 23 of 26 (88) vs 14 of 15 (93)	.82

expressed by their absolute (n) and relative frequency (%) and compared by using the χ^2 test or Fisher exact test. The continuous variables were expressed by mean and standard deviation and compared by using a *t*-test or Mann-Whitney test. Sensitivity and specificity of EUS-FNA for diagnosing and classifying PET was obtained. Overall survival analysis was performed by using the Kaplan-Meier method and log-rank test. Single-factor Cox regression analysis was conducted for tumor grading. A *P* value < .05 was considered statistically significant; all tests were 2-sided.

RESULTS

Eighty-six patients (44 men, mean age 58 ± 14 years) with a diagnosis of PET were identified. Of these patients, 12 (14%) were diagnosed with F-PET. The mean size of the lesions was 29 ± 20 mm (range 5-100 mm). Fourteen (16%) lesions were ≤ 10 mm. Forty-five (52%) tumors were located in the head/uncinate, 26 (30%) in the body, and 15 (18%) in the tail of the pancreas. Eight (9%) lesions had a cystic component. There were no procedure-related complications.

Seventy-eight patients (91%) underwent EUS-FNA of the pancreatic mass, and 15 (17%) underwent EUS-FNA of a metastasis site. Of these, 67 (78%) were diagnosed with PET at the first EUS-FNA. Eight (9%) patients had the diagnosis made at a second EUS-FNA and 2 (2.3%) at a third EUS-FNA. Overall, 90% (77 of 86) of patients had the diagnosis of PET established by EUS-FNA. There were no significant differences in the sensitivity of EUS-FNA according to tumor size, location, cystic component, or excess hormone production (Table 2).

Based on the results of EUS-FNA, patients were classified as follows: 15 (17.4%) BBWDET, 15 (17.4%) UBWDET, 21 (24.4%) WDEC, and 26 (30.2%) PDEC (Figs. 1 and 2). Nine (10.5%) patients had inconclusive results by EUS-FNA.

Of 86 patients, 30 (35%) were submitted to surgical resection. Based on the results of histopathological evaluation of surgical specimens, patients were classified as follows: 8 (26.7%) BBWDET, 1 (3.3%) UBWDET, 18 (60%) WDEC, and 3 (10%) PDEC. The sensitivity and specificity of EUS-FNA in the cases surgically confirmed were 80% and 100%, respectively. The classification obtained by surgical resection was compared to that obtained by EUS-FNA in the 24 patients who had records of both



Figure 1. Well-differentiated endocrine tumor of uncertain behavior (Group I of the WHO classification). **A**, Microbiopsies: regular, round cells (H&E, orig. mag. $\times 200$). **B**, Cytoplasmic immunohistochemical positivity with synaptophysin antibody (orig. mag. $\times 200$). **C**, Scarce nuclear cells positive with Ki-67 immunodetection (orig. mag. $\times 200$).

procedures available (Table 3). The kappa correlation index between the 2 classifications was 0.38, P = .003. The only major discrepancy was found in the 6 patients classified as UBWDET by EUS-FNA. Five (71%) of them turned out to have WDEC. Of the 9 patients with inconclusive results obtained by EUS-FNA, 6 underwent surgery. One patient had BBWDET, and 5 had WDEC.

We had follow-up data for 60 patients. Sixteen patients (27%) died during a mean follow-up period of 34 ± 27 months (range 3-108 months). The survival analysis classified according to the WHO classification indicated a significantly poorer survival rate for patients who had PDEC (Table 4 and Fig. 3). The 5-year survival rates according to the WHO classification were 100% for BBWDET and UBWDET, 68% for WDEC, and 30% for PDEC (P = .008, log-rank test). When only PET-related deaths (15 patients) were considered as events for survival analysis, the 5-year survival rates were of 100%, 68%, and 40%, respectively (P = .01, log-rank test).

Cox regression analysis was performed but did not include BBWDET and UBWDET, because of an absence

of any events, which excluded these categories from calculation within this model. This analysis confirmed an increased risk of reduced survival for patients with PDEC. Although not statistically significant, the relative risk of death trends toward an increase to approximately three-fold for PDEC compared to WDEC (hazard ratio = 2.8, P = .09, 95% CI, 0.8-9.5).

DISCUSSION

Recognition of the underlying malignant behavior of PETs in the setting of a slow rate of growth has led to a much greater aggressiveness in their treatment and has improved the 5-year survival rate.^{15,16} Our study is the largest single-center experience to date and demonstrates the success of EUS-FNA in accurately diagnosing and determining the malignant potential of PET. Furthermore, EUS-FNA added prognostic information by predicting 5-year survival. This may be very important in directing the management of patients with PETs.



Figure 2. Poorly differentiated endocrine carcinoma (Group III of the WHO classification). **A**, Microbiopsies: cohesive sheets of round, uniform, small cells, high mitotic rate (H&E, orig. mag. $\times 200$). **B**, Cytoplasmic immunohistochemical positivity with chromogranin A antibody (orig. mag. $\times 200$). **C**, Nuclear positivity in a high number of tumor cells with Ki-67 immunodetection (orig. mag. $\times 200$).

The study population was composed of 86 patients with PET, seen during a 9-year period. Our sample was predominantly of patients with NF-PET greater than 10 mm and with fairly advanced disease. It should be noted that our institution is a cancer center considered reference for taking care of patients with PET in the south of France. Therefore, a selection bias could be present.

There are few data on the accuracy of EUS-FNA in diagnosing PET. Our overall sensitivity rate of EUS-FNA for diagnosing PET was high (90%). We would like to emphasize that such a high sensitivity could be reached only with the repetition of EUS-FNA in negative results. Although we cannot discard a type II error due to a small sample size in our study, we did not find any difference in sensitivity of EUS-FNA between F-PET versus NF-PET, solid versus cystic tumors, lesions \leq and > 10 mm, and in tumors in different locations.

Ardengh et al¹³ reported an overall EUS-FNA sensitivity of 83% for diagnosing PET in 30 patients, with a decrease to 75% in the 11 patients with negative abdominal imaging. Recently, Pais et al¹⁴ presented data, in an abstract form, reporting an overall sensitivity of EUS-FNA of 84% for diagnosing PET in 66 patients, being 78% for F-PET, 89% for NF-PET, and a lower rate in tumors smaller than 15 mm in diameter (62%). Our better results probably reflect the experience of a reference center where 4 experienced endosonographers did the EUS-FNAs and only a single, highly experienced and dedicated pathologist performed all analysis. Additional factors were the use of the ThinPrep technique (monolayer cytology), immuno-histochemistry on microbiopsies or on monolayer cytology routinely, and persistence (to repeat EUS-FNA in negative cases). Therefore, the results may be generalizable only to institutions in which this expertise is available.

Although EUS-FNA is often used for diagnosing PET, as far as we know, there are no data on its accuracy in determining the malignant potential of PETs and in applying the WHO classification. In this study, there was a fair correlation between the WHO classification obtained by EUS-FNA and that obtained by surgery in the 24 patients who had records on both procedures available. All 10 patients classified as having an endocrine carcinoma by EUS-FNA had the diagnosis confirmed by surgery. Among them, EUS-FNA was able to correctly classify 80% of the

TABLE 3. Comparison between World Health Organization classification obtained by EUS-FNA and surgery in the 24 patients who had records of both procedures available

	WHO classification by surgery						
	Group		Gro	up I	Group II	Group III	
WHO classification by EUS-FNA		Class	BBWDET	UBWDET	WDEC	PDEC	Total
	I	BBWDET	5	1	1		7
		UBWDET	2		5		7
	П	WDEC			4	1	5
	Ш	PDEC			3	2	5
		Total	7	1	13	3	24

WHO, World Health Organization; *BBWDET*, well-differentiated endocrine tumor of probable benign behavior; *UBWDET*, well-differentiated endocrine tumor of uncertain behavior; *WDEC*, well-differentiated endocrine carcinoma; *PDEC*, poorly differentiated endocrine carcinoma. Kappa correlation index 0.38, P = .003.

TABLE 4. Mean survival and 5-year survival rates for patients with PETs, according to the World Health Organization classification

WHO classification	No. of deaths (%)	Survival time in months, mean ± SD (range), 95% Cl	5-year survival rate (%)
Overall	16 of 60 (27)	69 \pm 7 (56-82)	60
BBWDET	0 of 11 (0)	Cannot be computed	100
UBWDET	0 of 8 (0)	Cannot be computed	100
WDEC	4 of 17 (24)	66 \pm 7 (53-79)	68
PDEC	9 of 16 (56)	42 \pm 9 (24-61)	30
Inconclusive FNA	3 of 8 (38)	52 \pm 10 (33-72)	52
P value	.006*	.008†	

PET, Pancreatic endocrine tumor; *WHO*, World Health Organization; *BBWDET*, well-differentiated endocrine tumor of probable benign behavior; *UBWDET*, well-differentiated endocrine tumor of uncertain behavior; *WDEC*, well-differentiated endocrine carcinoma; *PDEC*, poorly differentiated endocrine carcinoma; *CI*, confidence interval. * χ^2 test.

+Log-rank test.

WDEC and 60% of the PDEC cases. Of 7 patients with BBWDET by EUS-FNA, only 1 (14%) had a change of diagnosis to WDEC after surgery. The problematic group for EUS-FNA was the UBWDET group, as 5 of 7 (72%) patients turned out to have WDEC. Care should be exercised when this diagnosis is obtained by EUS-FNA.

According to Sellner et al,¹⁷ the better outcome of surgical treatment of nonfunctioning neuroendocrine pancreatic carcinoma, compared to that of ductal pancreatic cancer, was confined to well-differentiated lesions. The outcome of undifferentiated endocrine lesions was as poor as for ductal pancreatic cancer. Although well and poorly differentiated lesions did not differ in terms of the T categories, poorly differentiated lesions had more node involvement (66% vs 20%), more metastasis (40% vs 17%), and lower 5-year survival rates (0% vs 100%) than did well-differentiated lesions.¹⁷ This different pattern of the 2 subsets of nonfunctioning neuroendocrine pancreatic cancer supports the high diagnostic and predictive value of the WHO classification in surgical specimens.

The possibility of applying the WHO classification in EUS-FNA specimens demonstrated in this study is of special interest for those obtaining prognostic information before deciding on the type of management. We started incorporating the WHO classification in the management of patients in our unit. Patients with BBWDET lesions equal or less than 1 cm in size are monitored at 12-month intervals by EUS. Patients with BBWDET lesions from 1 to 2 cm in size either can be monitored at 6-month intervals



Figure 3. Cumulative survival rate for patients with pancreatic endocrine tumors according to the WHO classification.^{7,8} P = .008, log-rank test. *PDEC*, poorly differentiated endocrine carcinoma (high grade malignant); *WDEC*, well-differentiated endocrine carcinoma (low grade malignant); *UBWDET*, well-differentiated endocrine tumor of uncertain behavior; *BBWDET*, well-differentiated endocrine tumor of probable benign behavior.

by EUS or submitted to an organ-sparing strategy for the pancreas (enucleation). All of the other lesions are resected when possible. We complement treatment with somatostatin analogs or chemotherapy, depending on differentiation of endocrine carcinoma.

Another potential advantage of using the WHO classification in EUS-FNA specimens is the possibility of comparison among studies. It has been difficult to compare results from different studies in PET because of a lack of uniformity in the pathologic classification of these tumors or standardization of the minimum criteria for histological diagnosis.²

One of the most striking findings in our study is that 5-year survival can be predicted by EUS-FNA. Similar to the findings of Pape et al,¹⁹ the current results demonstrate the prognostic accuracy of the newly proposed WHO classification system for PET. Mortality is seen only in patients classified as WHO groups II and III (endocrine carcinoma). The new classification system provides a valid and powerful tool for prognostic stratification of PET in clinical practice and for research. This prognostic information may help to determine the most appropriate management for patients, because a more aggressive approach improves quality of life and 5-year survival rates for patients with PET.^{15,16}

Some limitations of our study, similar to those of all retrospective studies, is underreporting and missing data. Because ours is a reference center, we probably have a selection bias of more advanced disease. We also lost part of our sample because the records were returned to the referring hospitals. On the other hand, as far as we know, ours is the largest single-center study demonstrating that it is possible to determine the potential malignant behavior of PETs in specimens obtained by EUS-FNA.

In summary, EUS-FNA is a safe and highly accurate technique for diagnosing PET. Our report, which is the largest experience of EUS-FNA in the diagnosis of PET, also identified new trends. It is possible to determine the potential malignant behavior of a PET in specimens obtained by EUS-FNA by applying the WHO classification. EUS-FNA findings predict 5-year survival in patients with PET. This may help to better guide the therapeutic approach for these patients.

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