Is the 2-cm size cutoff relevant for small nonfunctioning pancreatic neuroendocrine tumors: A French multicenter study

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Background. *Nonfunctioning pancreatic neuroendocrine tumors (NF-PNETs) are often discovered at a small size. No clear consensus exists on the management of NF-PNETs ≤ 2 cm. The aim of our study was to determine the prognostic value of indicators of malignancy in sporadic NF-PNETs ≤ 2 cm.*
Methods. *Eighty patients were evaluated retrospectively in 7 French University Hospital Centers. Patients were managed by operative resection (operative group [OG]) or observational follow-up (non-OG [NOG]). Pathologic characteristics and outcomes were analyzed.*
Results. *Sixty-six patients (58% women) were in the OG (mean age, 59 years; 95% CI, 56.0–62.3; mean tumor size, 1.6 cm; 95% CI, 1.5–1.7); 14 (72% women,* n *= 10) were in the NOG (mean age, 63 years; 95% CI, 56–70; mean tumor size, 1.4 cm; 95% CI, 1.0–1.7). All PNETs were ranked using the European Neuroendocrine Tumor Society grading system. Fifteen patients (19%) had malignant tumors defined by node or liver metastasis (synchronous or metachronous). The median disease-free survival was different between malignant and nonmalignant PNETs, respectively: 16 (range, 4–72) versus 30 months (range, 1–156;* P *= .03). On a receiver operating characteristic (ROC) curve, tumor size had a significant impact on malignancy (area under the curve [AUC], 0.75;* P *= .03), but not Ki-67 (AUC, 0.59;* P *= .31). A tumor size cutoff was found on the ROC curve at 1.7 cm (odd ratio, 10.8; 95% CI; 2.2–53.2;* P *= .003) with a sensitivity of 92% and a specificity of 75% to predict malignancy.*
Conclusion. *Based on our retrospective study, the cutoff of 2 cm of malignancy used for small NF-PNETs could be decreased to 1.7 cm to select patients more accurately. (Surgery 2016;159:901-7.)*

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Pancreatic neuroendocrine tumors (PNETs) represent a small proportion of pancreatic tumors (5%), with an incidence of 1 per 100,000 people per year.[1] Nonfunctioning PNETs (NF-PNETs) are defined by an absence of symptoms related to secretion of neuroendocrine peptide. NF-PNETs represent 50% of all PNETs. They are found in the same proportion in men and women at the mean ages of 55 and 65 years, respectively.[2] With a 5-year survival rate of 48%, PNETs have a much better prognosis than pancreatic adenocarcinoma. In contrast, NF-PNETs have a worse prognosis than functioning PNETs, with a 5-year survival rate of only 31%.[3] PNETs are classified according to the European Neuroendocrine Tumor Society (ENETS) grading system G1, G2, or G3[4] based on the Ki-67 and the mitotic count.[5] To provide

Accepted for publication October 1, 2015.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2015.10.003

an indication of the tumor prognosis, PNETs are grouped into NETs—neuroendocrine tumors (G1 or G2 tumors)—or into NECs—neuroendocrine carcinomas (G3 carcinoma)—according to the World Health Organization classification.[4]

In recent years, NF-PNETs are being diagnosed increasingly at a small size owing to improved cross-sectional imaging. The heterogeneity of PNETs, however, makes therapeutic decisions difficult with no clear consensus, especially for tumors ≤2 cm.[6] Despite the development of a parenchyma-sparing pancreatectomy (ie, central pancreatectomy and enucleation), the pancreatic operative procedure remains a high-risk operation with a 28–30% morbidity and 1% mortality.[7,8] Based on these considerations for NF-PNETs ≤2 cm with a low grade of malignancy, it is conceivable that close monitoring of the patient may be a better option.[9]

Currently, malignancy is less likely in small NF-PNETs according to cutoff size. Some studies have concluded that small PNETs >0.5 cm have a malignant potential. Gratian et al[10] found a rate of lymph node metastases and distant metastases in PNETs of <2 cm of 29% and 10%, respectively. Haynes et al[11] reported that in 3 of 39 patients (8%) with NF-PNETs <2 cm developed late metastases or recurrence. Despite the risks associated with pancreatic surgery, Sharpe et al[12] concluded that operative resection improves the overall survival (OS) of patients with small PNETs. Recently, Boninsegna et al[13] found that Ki-67 status and lymph node ratio were better predictors of the recurrence than tumor size. They confirmed the clinically important impact of a Ki-67 cutoff at 5% on NF-PNETs, suggested by Scarpa et al,[14] but in their study, the mean tumor size was 4.5 cm. Recently, Partelli et al[15] demonstrated the impact of lymph node metastases on disease-free survival (DFS) in PNETS.

Currently, NF-PNETs ≤2 cm may be managed in 2 ways: operative resection with the related risks of morbidity and mortality, and close observational monitoring with the risk of development of metastases. Despite many publications, assessing the malignancy of NF-PNETs ≤2 cm remains unclear, and no high-level recommendation exits concerning the management of these neoplasms. The aim of this study was to compare the results of operative treatment and nonoperative observational management of patients with sporadic NF-PNETs ≤2 cm to determine the prognostic criteria of these tumors.

PATIENTS AND METHODS

Data were collected retrospectively from the medical records in 7 French University Hospitals between 1999 and 2012: Nantes, Strasbourg, Tours, Toulouse, Angers, Poitiers, and Limoges. The patients were divided into 2 groups according to their management: an operative group (OG) or a non-OG (NOG). The decision to operate or not was made by each center according to their local approach.

Inclusion criteria were the existence of a NF-PNET ≤2 cm on the pretherapeutic imaging with computed tomography (CT), MRI, and/or endoscopic ultrasonography (EUS). The diagnosis of NF-PNET was made through histologic analysis. When the histologic report was missing, the diagnosis of NF-PNET was confirmed by a number of indicators, such as an increase in serum tumor markers (chromogranin A [CgA]), typical features on imaging, or somatostatin receptor scintigraphy (SRS). None of the patients had any endocrine-related symptoms. Patients excluded were those with a genetic predisposition syndrome (multiple endocrine neoplasia type 1, Von Hippel–Lindau disease).

Age, sex, and type of diagnosis (incidental, metastasis, and symptoms) were analyzed according to the type of management (OG vs NOG). The results of PET-^{18}FDG and SRS CT (ie, octreoscan) CT or MRI (size, location, and existence of lymph node or liver metastases) were collected. Regarding NF-PNET histology, the pretherapeutic biopsy/cytology results and determination of the Ki-67 status were noted whenever available. The ENETS grades were reviewed. For NF-PNETs managed before the ENETS grading was determined, the grade was determined based on the Ki-67 status and mitotic count results mentioned in the histologic report.

Follow-up. Follow-up began when the PNET was first diagnosed on imaging, and ended at the last patient contact or imaging. For the OG, the type of pancreatic operation (ie, standard or parenchyma-sparing resection) and 90-day postoperative outcomes were noted: postoperative pancreatic fistula (POPF), massive bleeding, or intraabdominal abscess. We used the POPF definition proposed by the International Study Group of Pancreatic Fistula.[16] For the NOG, the type of therapy was noted: medical (somatostatin analog or chemotherapy) or monitoring only. OS and DFS were analyzed according to the malignancy. Progression of the disease was defined for both groups by occurrence