Sporadic nonfunctioning pancreatic neuroendocrine tumors: Prognostic significance of incidental diagnosis

David Jérémie Birnbaum, MD,[a] Sébastien Gaujoux, MD, PhD,[a,b,c] Rim Cherif, MD,[a] Safi Dokmak, MD,[a] David Fuks, MD, PhD,[a,b] Anne Couvelard, MD, PhD,[b,c,d] Marie-Pierre Vullierme, MD,[e] Maxime Ronot, MD,[b,d,e] Philippe Ruszniewski, MD,[b,c,f] Jacques Belghiti, MD,[a,b] *and* **Alain Sauvanet, MD,[a,b]** *Clichy and Paris, France*

Background. *Sporadic nonfunctioning pancreatic neuroendocrine tumors (NF-PNETs) are increasingly diagnosed as incidentalomas, and their resection is usually recommended. The prognostic significance of this diagnosis feature is poorly studied, and management of these tumors remains controversial. Clinical, pathologic characteristics and outcome of resected incidentally diagnosed NF-PNET (Inc) were compared with resected symptomatic NF-PNET (Symp) to better assess their biologic behavior and tailor their management.*

Methods. *From 1994 to 2010, 108 patients underwent resection for sporadic nonmetastatic NF-PNET. Diagnosis was considered as incidental in patients with no abdominal symptoms or symptoms unlikely to be related to tumor mass. Patients with Inc were compared with patients with Symp, regarding demographics, postoperative course, pathology, and disease-free survival (DFS).*

Results. *Of the 108 patients, 65 (61%) had incidentally diagnosed tumors. Pancreas-sparing pancreatectomies (enucleation/central pancreatectomy) were performed more frequently in Inc (62% vs 30%, P = .001). Inc tumors were more frequently <20 mm (65% vs 42%, P = .019), staged T1 (62% vs 33%, P = .0001), node negative (85% vs 60%; P = .005), and grade 1 (66% vs 33%, P = .0001). One postoperative death occurred in the Inc group, and postoperative morbidity was similar between the two groups (60% vs 65%, P = .59). DFS was substantially better in the Inc group (5-year DFS = 92% vs 82%, P = .0016).*

Conclusion. *Incidentally diagnosed NF-PNETs are associated with less aggressive features compared with symptomatic lesions but cannot always be considered to be benign. Operative resection remains recommended for most. Incidentally diagnosed NF-PNET may be good candidates for pancreas-sparing pancreatectomies. (Surgery 2014;155:13-21.)*

From the Department of Hepato-Pancreato-Biliary Surgery - Pôle des Maladies de l'Appareil Digestif (PMAD),[a] AP-HP, hôpital Beaujon, Clichy; Université Paris Diderot,[b] Paris; Centre de Recherche Biomédicale Bichat Beaujon (CRB3)/INSERM U773,[c] Institut National de la Santé et de la Recherche Médicale, Paris; Département of Pathology,[d] AP-HP, hôpital Beaujon, Clichy; Department of Radiology,[e] AP-HP, hôpital Beaujon, Clichy; and Department of Gastroenterology,[f] Pôle des Maladies de l'Appareil Digestif (PMAD), AP-HP, hôpital Beaujon, Clichy, France

Pancreatic neuroendocrine tumors (PNET) are rare, representing 1% to 2% of all pancreatic neoplasms.[1] They represent a heterogeneous group of tumors with an extremely variable clinical behavior mainly depending on histologic features and disease staging.[2] When possible, operation provides the best chance for a cure and provides 5-year overall survival exceeding 60%.[3-5]

In recent years, PNET, particularly sporadic nonfunctioning (NF) cases, have been increasingly diagnosed,[6] often as incidentalomas, because of the widespread use of cross-sectional imaging.[7,8] Our understanding of the natural history of incidentally discovered NF-PNET is limited, but despite the lack of high-level evidence, operative resection is usually recommended. This aggressive management recently has been challenged because of the substantial morbidity of pancreatic surgery[5,9-11] contrasting with the favorable long-term outcome of these lesions[12]—even if this remains controversial.[13]

Accepted for publication August 12, 2013.

Reprint requests: Dr Alain Sauvanet, MD, Department of Hepatobiliary and Pancreatic Surgery - Hospital Beaujon, 100, Bd du Général Leclerc - 92110 Clichy, France. E-mail: alain.sauvanet@bjn.aphp.fr.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2013.08.007

To expand our knowledge regarding this increasingly frequent situation, we retrospectively analyzed our experience of pancreatectomy for sporadic nonmetastatic NF-PNET by comparing patients with tumors incidentally discovered with the remaining population.

PATIENTS AND METHODS

Data collection. From 1994 to 2010, 108 patients underwent complete resection for sporadic, nonmetastatic, NF-PNET in the Department of Hepatobiliary and Pancreatic Surgery - Beaujon Hospital, Clichy, France. Demographic variables, clinical presentation, preoperative workup, and intraoperative data including type of resection, postoperative course, and pathology were obtained from a prospective database with additional retrospective medical record review. NF tumors were defined as lesions without symptoms related to hormonal excess. Patients with incidentally diagnosed lesions were defined as patients without any symptoms or abnormal liver tests, ie, cholestasis, and/or patients with clinical manifestations unlikely to be related to the mass.

Preoperative work-up, operative procedures, and pathologic analysis. Preoperative tumor staging was done by computed tomography and/or magnetic resonance, endoscopic ultrasound, or somatostatin receptor scintigraphy at the surgeon's discretion, as previously reported.[5] All operative indications were discussed in a multidisciplinary pancreatic tumor board, including surgeons, radiologists, pathologists, oncologists, and gastroenterologists. Diagnosis of PNET was based on conventional histology and immunohistochemistry (chromogranin A, synaptophysin, and Ki67). All cases were reviewed and classified according to the 2010 World Health Organization (WHO) classification and assigned an ENETS (European Neuroendocrine Tumor Society)/TNM-based stage and grading score.[14,15]

Operative procedures were preoperatively planed based on tumor localization and intraoperatively confirmed after operative exploration assisted by routine intraoperative ultrasonography for evaluation of the proximity of the tumor from the vascular structure and the main pancreatic duct. Enucleation was performed when the tumor was near to or at the surface of the head or body of the pancreas, far enough (at least 1 to 2 mm) from the main pancreatic duct. Regarding tumors of the neck and body of the pancreas, if enucleation was not possible, central pancreatectomy was performed if the remnant pancreas was at least 5–7 cm long. In this setting, the proximal remnant was overseen after elective ligation of the main pancreatic duct. Reconstruction of the distal pancreas was done by end-to-side pancreaticogastrostomy. Pancreaticoduodenectomy and distal pancreatectomy were performed as previously reported by our group.[5]

Intraoperatively, all standard resections included regional lymph node dissection. During central pancreatectomy and enucleation, all visible lymph nodes located up to 5 cm around the tumor were resected but frozen section analysis was not routinely done. At the end of the procedure, drainage was placed close to the enucleation cavity or the pancreatic anastomosis or section and removed progressively from postoperative day 5.

Postoperative course and follow-up. Postoperative mortality included all deaths occurring before hospital discharge or within 90 days. Morbidity included all complications after operation until discharge and/or readmission and was graded according to the Clavien-Dindo classification.[16] Postoperative pancreatic fistula, hemorrhage, and delayed gastric emptying were defined according to the International Study Group of Pancreatic Surgery.[17,18]

Follow-up was based on clinical, radiologic, and laboratory assessments and updated upon outpatient evaluation, routine postoperative visits, and correspondence. Visits were scheduled every 6 months for the first 5 years and annually thereafter. Detection of recurrence was based on thoracoabdominal computed tomography scan and chromogranin A serum level. In case of suspected recurrence, magnetic resonance imaging or octreoscan scintigraphy were performed according to the clinical situation.

Statistical analysis. Values are expressed as median (range), or percentage, as appropriate. The Fisher exact test was used to compare differences in discrete or categorical variables, and the Wilcoxon rank-sum test was used for continuous variables. Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up if no event had occurred. Disease-free survival (DFS) was calculated from the date of surgery to the date of the first evidence of recurrence or last follow-up if no event had occurred. Patients who died during the postoperative course were excluded from the survival analysis to assess tumor behavior only. OS and DFS were estimated by the method of Kaplan-Meier, and the log-rank test was used to compare survival curves.

All tests were two-sided. Data were analyzed with the STATA 12 statistical software (StataCorp. 2011.