Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): Role for nonoperative management

Louis C. Lee, MD,[a] Clive S. Grant, MD,[a] Diva R. Salomao, MD,[b] Joel G. Fletcher, MD,[c] Naoki Takahashi, MD,[c] Jeff L. Fidler, MD,[c] Michael J. Levy, MD,[d] *and* **Marianne Huebner, PhD,[e]**
Rochester, MN

Background. *Controversy exists regarding the optimal management of incidentally discovered, small pancreatic neuroendocrine tumors (PNETs). Our aim was to review the outcomes of patients who underwent nonoperative and operative management.*
Methods. *We retrospectively reviewed patients with nonfunctioning PNETs at our institution from January 1, 2000 to June 30, 2011. Patients were included if the tumor was sporadic and <4 cm without radiographic evidence of local invasion or metastases.*
Results. *Nonoperative patients (*n *= 77, median age, 67 years; range, 31–94) had a median tumor size of 1.0 cm (range, 0.3–3.2). Mean follow-up (F/U) was 45 months (max. 153 months). Median tumor size did not change throughout F/U; there was no disease progression or disease specific mortality. In the operative group (*n *= 56, median age, 60 years; range, 27–82), median neoplasm size was 1.8 cm (range, 0.5–3.6). Mean F/U was 52 months (max. 138 months). A total of 46% of the operative patients had some type of complication, more than half due to a clinically significant pancreatic leak. No recurrence or disease specific mortality was seen in the operative group, including 5 patients with positive lymph nodes.*
Conclusion. *Small nonfunctioning PNETs usually exhibit minimal or no growth over many years. Nonoperative management may be advocated when serial imaging demonstrates minimal or no growth without suspicious features. (Surgery 2012;152:965-74.)*

From the Departments of Surgery, Division of Gastroenterologic and General Surgery,[a] Pathology,[b] Radiology,[c] Gastroenterology,[d] and Biomedical Statistics and Informatics,[e] Mayo Clinic, Rochester, MN

Pancreatic neuroendocrine tumors (PNETs) are uncommon neoplasms estimated to account for 2% of all pancreatic neoplasms; they have a reported incidence around 3 per million.[1] The diagnosis is determined on the basis of morphologic features in addition to demonstration of neuroendocrine differentiation principally by immunohistochemical positivity for chromogranin A and/or synaptophysin. PNETs comprise a heterogeneous group of neoplasms that may produce a distinct clinical hormonal syndrome (functioning) or no clinical syndrome (nonfunctioning). They can be sporadic or genetically transmitted such as in Multiple Endocrine Neoplasia type I or Von Hippel-Lindau syndrome. Most are well-differentiated, but some carcinomas can be poorly differentiated with highly aggressive potential.[2] Neoplasms of 5 mm or smaller have been termed microadenomas; they are nonfunctioning, rarely grow and occur in up to 10% of autopsy studies.[3]

Two major staging systems have been proposed. In 2006, the European Neuroendocrine Tumor Society (ENETS) Tumor-Nodes-Metastasis (TNM) classification was developed.[4] This system uses neoplasm size, nodal disease, and metastases, along with a 3-tiered grading based on mitotic count or Ki-67 index (mitotic count <2, 2–20, >20 per 10 high-power field [HPF] or Ki-67 ≤2%, 3–20%, >20%). In 2010, for the first time, the American Joint Commission on Cancer (AJCC) introduced its version of an endocrine pancreas staging system in the manual's 7th edition.[5] The AJCC criteria were adapted from the staging of exocrine

Supported by the Department of Surgery, Mayo Clinic, Rochester, MN.

Accepted for publication August 20, 2012.

Reprint requests: Dr Clive S. Grant, MD, 200 First Street, SW, Rochester, MN, 55905. E-mail: cgrant@mayo.edu.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2012.08.038

pancreatic adenocarcinoma, which has prompted some criticism.[6]

Arising from this controversy, validation studies of the ENETS TNM system were performed on operatively resected patients. In these studies, prognostic stratification was successful but this was most evident only in either lesser- or greater-stage tumors.[6] Scarpa et al[6] refined the ENETS TNM criteria on the basis of 274 patients with surgically resected PNETs. Survival analysis highlighted that in the absence of nodal or distant metastasis, local infiltration and neoplasm size >4 cm had prognostic significance. Perhaps most importantly, the neoplasm parameters of duodenal, bile duct, pancreatic duct, or vascular invasion were reclassified as T4 irrespective of neoplasm size (Table I). Moreover, radiologic criteria of invasion were incorporated to facilitate accurate *nonoperative* staging. In stage I and II neoplasms, the 5-year survival was 100% and 93%, respectively, whereas the AJCC TNM reported 5-year adjusted survival was 76% and 64%, respectively.[7] Scarpa's approach would be particularly useful in patients with incidentally discovered, small, nonfunctioning PNETs.

Increasingly, small nonfunctioning PNETs are diagnosed on imaging studies, with one study showing a greater than 2-fold increase from 1986 to 2002.[8] This has been accompanied by an increase in the number of surgical resections. This is evident in the surgical experience at Massachusetts General Hospital, where during the 1980s to 1990s, only 1 to 7 PNET operations were performed per year. A steady increase occurred subsequently to a recent average of more than 15 operations per year.[9] There has been a void in information about the natural history of PNETs, especially when they are small. According to the Armed Forces Institute of Pathology and a review of PNETs by Klöppel,[3,10] all neoplasms greater than 0.5 cm have malignant potential. Although quite uncommon, small neoplasms have been associated with metastasis or neoplasm recurrence, prompting Haynes et al[9] to conclude, "Patients with incidentally discovered, nonfunctioning PETs should undergo neoplasm resection and careful postoperative surveillance, even if surgical pathologic findings suggest benign disease. No size cutoff exists beyond which malignancy can be safely excluded." In stark contrast, the current ENETS guideline states that "no data exist with respect to a positive effect of surgery on overall survival in small (<2 cm), possibly benign or intermediate-risk pancreatic endocrine tumors."[11] In these cases, the morbidity of pancreatic surgery must be carefully considered in light of the potentially benign and indolent course of selected neoplasms.

Therefore, the aim of this study was to determine disease specific mortality in patients who underwent nonoperative management of nonfunctioning, asymptomatic PNETs. We retrospectively identified a cohort of patients during the same time period that underwent operative treatment. There was no *a priori* intention of statistically comparing the two groups as there is an inherent bias based on the surgeon's decision to operate on the latter group. Our secondary aim was to calculate disease specific mortality and perioperative morbidity in this similar group of surgically managed patients. We hypothesized that nonoperative management was an acceptable option in this patient population.

MATERIALS AND METHODS

Patients. We performed a retrospective review of patients with a diagnosis of a PNET from January 1 2000, through June 30, 2011. This study was approved by the Mayo Foundation institutional review board. Patients were identified by keyword search through radiology, pathology, surgery, and gastroenterology databases. Diagnosis was determined by computed tomography (CT), magnetic resonance imaging (MRI), or endoscopic ultrasound (EUS) with or without fine-needle aspiration (FNA). Charts were reviewed by a general surgeon for clinical features of symptoms and pancreatic hormone levels. Imaging (CT, MR, EUS) reports were evaluated retrospectively by the same surgeon. Patients were included if there was (1) a primary imaging diagnosis of PNET, and (2) absence of symptoms of pancreatic disease (ie, epigastric pain, jaundice, pancreatitis or symptoms consistent with hormone hypersecretion). Functioning neoplasms were determined on the basis of clinical syndromes, not simply increased serum hormone levels.

Exclusion criteria included the following: (1) radiographic signs of local invasion, including ductal obstruction, venous thrombus or narrowing, invasion of adjacent structures or peripancreatic fat, or hepatic or other distant metastases; (2) neoplasm size ≥4 cm; (3) familial syndromes associated with PNETs; and (4) known metastases from a non-PNET neoplasm. For inclusion and exclusion criteria, the imaging report that first recorded the presence of a pancreatic neoplasm was considered the index imaging examination, from which imaging findings of neoplasm characteristics were extracted. In summary, on the basis

Table I. Comparison of AJCC, ENETS, and revised ENETS TNM staging systems for pancreatic neuroendocrine tumors[4-6]

	AJCC TNM	*ENETS TNM*	*Revised ENETS TNM**
T: primary tumor	T1 limited to pancreas <2 cm	T1 limited to pancreas <2 cm	T1 limited to pancreas <2 cm
	T2 limited to pancreas >2 cm	T2 limited to pancreas 2–4 cm	T2 limited to pancreas 2–4 cm
	T3 tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery	T3 limited to pancreas and >4 cm or invading duodenum or bile duct	T3 limited to pancreas >4 cm
	T4 tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)	T4 tumor involves adjacent organs or the wall of large vessels	T4 beyond the pancreas
Stage			
I	T1 or T2	T1	T1 or T2
II	T3 or N1	T2 or T3	T3
III	T4	T4 or N1	T4 or N1
IV	M1	M1	M1

*As proposed per Scarpa et al,[6] T4 tumors involve any nonpancreatic anatomical structures, including duodenum, bile duct, and fat.
AJCC TNM, American Joint Commission on Cancer Tumor-Nodes-Metastasis; *ENETS*, European Neuroendocrine Tumor Society.

of available clinical information and imaging reports at the time of diagnosis, all PNETs were asymptomatic T1/2N0M0 neoplasms per the AJCC and ENETS TNM system.

Operative complications. Surgical data were collected for patients who underwent operative resection. The type of operation, intraoperative findings, and perioperative morbidity information was collected. Perioperative complications were divided into pancreatic leak and nonpancreatic leak etiologies. Nonpancreatic leak morbidities were defined per the Clavien-Dindo classification (Table II).[12] Postoperative pancreatic fistulas were categorized according to the International Study Group on Pancreatic Fistula classification (Table III).[13]

Histopathologic review. Pathologic review of all specimens was performed (author D.S.) and neoplasms were classified on the basis of the 2010 WHO system. Grade I neoplasms (low grade) were characterized by a population of cells with round to oval nuclei, uniform in shape and size, finely granular chromatin and inconspicuous nucleoli. These neoplasms showed no necrosis and rare mitotic figures (<2 per 10 HPF; Fig 1). Grade II neoplasms (intermediate grade) were characterized by nuclear enlargement, moderate pleomorphism, prominent nucleoli, coarse chromatin, and greater numbers of mitoses (2–20 per 10 HPF; Fig 2). Grade III, or poorly differentiated neuroendocrine carcinomas, commonly consist of sheets of cells with marked pleomorphism, extensive necrosis, and abundant mitoses (>20 per 10 HPF). Neuroendocrine carcinomas were not part of this study. Formalin-fixed, paraffin-embedded tissue samples were stained for MIB-1 antibody to assess Ki-67 antigen reactivity. The Ki-67 proliferation rate was scored in the areas of greatest positivity as a percentage of positive cells. On the basis of Scarpa's study, Ki-67 cut off values of <5% and >20% were most sensitive in showing a survival difference in low-grade neoplasms, as opposed to <2% and >20%. Greater cut-off values also offered greater discernment for neoplasms within the same stage, increasing the concordance index between predicted and observed survival.[6] Neoplasms were staged by AJCC TNM, ENETS TNM, and Scarpa's modified ENETS TNM system.

Imaging review. CT/MRI scans were reviewed by subspecialized gastrointestinal radiologists (authors J.G.F., N.T., J.L.F., each with >7 years of experience in interpreting pancreatic CT/MRI) to confirm PNET as a primary diagnosis or principal differential consideration. Radiologists evaluated the index imaging examination or dedicated pancreatic imaging examination, if performed within 30 days of index CT/MRI. For each phase of enhancement (noncontrast, arterial, pancreatic, or portal), CT number or MRI intensity measurements were made in Houndsfield Units by drawing circular regions of interest over the neoplasm and nearby normal-appearing pancreatic parenchyma. When multiple phase measurements were available, the results were expressed as either the greatest or lowest lesion to normal pancreas Houndsfield Units ratio. Enhancement results are presented only for solid neoplasms.

Table II. Clavien-Dindo classification of surgical complications[12]

Grade I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacologic treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention.
Grade IV	Life-threatening complication requiring ICU management.
Grade V	Death of a patient.

ICU, Intensive care unit.

Table III. International study group on pancreatic fistula definition of postoperative pancreatic fistula[13]

	Grade A	*Grade B*	*Grade C*
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment*	No	Yes/No	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)†	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

*Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.
†With or without a drain in situ.
CT, Computed tomography; *POPF*, postoperative pancreatic fistula; *US*, ultrasound.

Follow-up and statistical methods. Follow-up (F/U) for the nonoperative group began when the neoplasm was first diagnosed on index imaging. F/U for the operative group began at the time of surgical resection. Two different end times were calculated. Clinical F/U ended at the last patient contact and radiological F/U ended at the last patient imaging (CT, MRI, or EUS). A clinical F/U calculation was necessary because some clinicians elected to stop or slow the frequency of imaging after many years of no growth (nonoperative) or no recurrence (operative). Data were considered unavailable if there were less than 3 months of F/U. Patients with incomplete records were contacted by mail and/or phone and their most recent imaging was obtained whenever possible. F/U data was collected until 4/1/2012. Descriptive statistics are reported as either frequency (percentage) or median/mean (range) as appropriate.

RESULTS

There were a total of 133 patients (77 nonoperative, 56 operative) with incidentally identified, nonfunctioning T1 or T2 lesions who met study criteria. Demographic and F/U results are presented in Table IV.

Nonoperative group. Median neoplasm size was 1.0 cm (range, 0.3–3.2) with a mean clinical and radiological F/U of 45 and 35 months, respectively. With the exception of 2 that were 3.0 and 3.2 cm, all neoplasms were ≤2 cm. Maximum F/U was 153 months. Median neoplasm size did not change throughout F/U, and there was no new local invasion, metastatic disease or disease-specific mortality. Twenty-two of 77 patients were confirmed as a PNET with biopsy, whereas the remaining patients were diagnosed on imaging. Of the biopsy confirmed PNETs, average clinical and radiologic F/U was 40 and 30 months, respectively. One patient was a poor operative candidate and underwent EUS-guided alcohol ablation of a 1.4 cm biopsy confirmed pancreatic head lesion with good results.

Operative group. Median neoplasm size was 1.8 cm (range, 0.5–3.6) with a mean clinical and radiological F/U of 52 and 41 months, respectively. Maximum F/U was 138 months. There was no disease-specific mortality, no recurrence, and no perioperative mortality, but 46% of the operative group patients had some type of postoperative complication. Fifteen patients (27%) developed a class B/C pancreatic leak, 5 patients (9%)

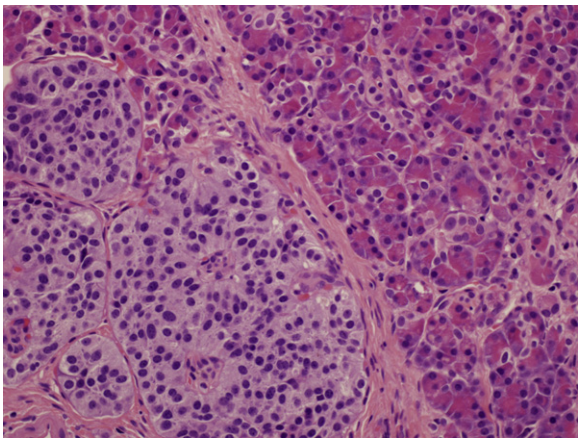

Fig 1. Grade I (low-grade) PNET. Nuclei are very similar in size and appearance to the acini and islet of Langerhans cells with round, stippled chromatin, and inconspicuous nucleoli. Normal acinar cells appear on the right side. Hematoxylin and eosin stain, ×400.

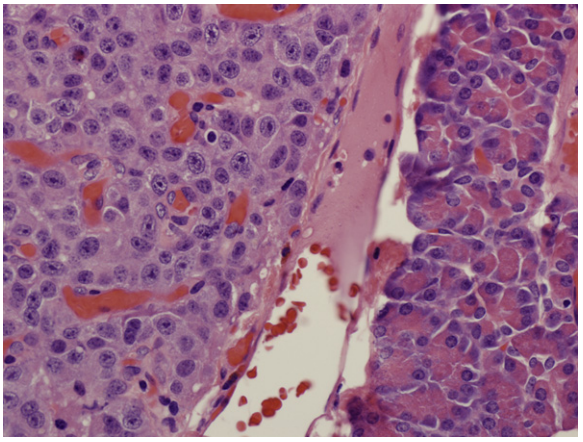

Fig 2. Grade II (intermediate-grade) PNET. Nuclei are larger with evidence of anisonucleosis (variations in nuclear size), prominent nucleoli and rare mitosis. Normal acinar cells appear on the right side. Hematoxylin and eosin stain, ×600.

developed a Grade IV (life-threatening) surgical complication and 5 patients (9%) required one or more reoperations to manage complications (Table V). One patient required a total pancreatectomy during re-operation.

All patients were AJCC TNM stage I, ENETS TNM stages I and II, and revised ENETS TNM stage I, except for 5 (9%) with unanticipated lymph node positivity which raised their staging in all three systems after the operation (Table V). All patients underwent R0 resections and 2 had suspicious lymphadenopathy recognized during the operation. Five patients with positive lymph nodes had a mean F/U of 47 clinical and 44 radiological months (maximum 89 months) with a median neoplasm size of 2.4 cm (range, 0.7–3.9) based on pathology specimen measurements. Upon re-review by a radiologist, only one of these patients had preoperative imaging evidence of peripancreatic lymph node enlargement >5 mm. Four patients did not have a PNET on final pathology (median r size, 1.9 cm; range, 0.9–3.3); 2 nodules were intrapancreatic ectopic splenic tissue, one was a benign fibroma, and the other, a serous adenoma.

Two patients initially were observed for a period of time before undergoing operative resection. The first patient had a 1.2-cm lesion seen on chest CT. EUS with biopsy demonstrated a cystic lesion with a benign aspirate. Repeat EUS with biopsy 1.5 years later confirmed a 1.3-cm PNET. Laparoscopic enucleation was performed with 3 negative lymph nodes. No recurrence was seen after 9 months of F/U. The second patient had a 1.2-cm lesion seen on renal magnetic resonance angiogram. In retrospect, the lesion was present 6 years earlier and was 0.8 cm. There was minimal growth on subsequent imaging, until 5 years later, when a CT scan showed new pancreatic duct dilatation. Distal pancreatectomy was performed with 17 negative lymph nodes. No recurrence was seen after 55 months of F/U.

Radiographic review. Re-review of the patient's index imaging (CT/MRI) confirmed neoplasm size <4 cm without evidence of ductal or extrapancreatic invasion (Table VI). Their location was spread throughout the pancreas, but nearly one-half were located in the tail. A majority of the neoplasms were solid and hyperenhancing, although hypo/isoenhancing, cystic, and mixed solid-cystic tumors were also seen. Of the 4 patients who did not have a PNET on final pathology, 3 were solid hyperenhancing lesions in the tail and one was a mixed solid-cystic tumor in the head (serous adenoma). Even in retrospect, these lesions were not easily distinguishable from their non-PNET final diagnoses.

Histopathologic review. Neoplasms in both the nonoperative and operative group were mostly low grade, although there were some of intermediate grade. Ki-67 values were all <5% in patients with available results (Table VII). Patients with positive lymph nodes also had low-/intermediate-grade neoplasms with Ki-67 values <5%.

DISCUSSION

Our study showed that of 77 patients with asymptomatic nonfunctioning PNETs managed nonoperatively, with a size range up to 3 cm, and a mean clinical follow-up of 45 months, there was

Table IV. Demographic and follow-up results for patients diagnosed with an incidental PNET

	Nonoperative group (n = *77*)	*Operative group* (n = *56*)
Median age, y (range)	67 (31–94)	60 (27–82)
Sex, *n* (%)		
Male	42 (55)	34 (61)
Female	35 (45)	22 (39)
Biopsy confirmation, *n* (%)	22 (29)*	32 (57)*
Median neoplasm start size (range), cm	1.0 (0.3–3.2)	1.8 (0.5–3.6)
Median neoplasm end size (range), cm	1.0 (0.4–4.0)‡	—
Clinical follow-up, mean (range), months	45 (3–153)†	52 (3–138)§
Radiological follow-up, mean (range), months	35 (3–153)‡	41 (4–138)‖
Clinical follow-up status		
Recurrence or died from disease	0	0
Alive, no evidence of disease	66 (86%)	50 (89%)
Dead, unrelated	6 (8%)†	3 (5%)
Data unavailable	5 (6%)	1 (5%)

*The non-biopsy confirmed patients were observed or resected on the basis of imaging diagnosis.
†Follow-up unavailable for 5 patients.
‡Follow-up unavailable for 12 patients.
§Follow-up unavailable for 1 patient and does not include 4 non-PNET patients.
||Follow-up unavailable for 7 patients and does not include 4 non-PNET patients.
PNET, Pancreatic neuroendocrine tumors.

no disease-related mortality. Most of the neoplasms biopsied by FNA to confirm diagnosis were low grade and had Ki-67 values <5%. Two patients, who were initially managed nonoperatively for 1.5 and 5 years, ultimately underwent resection with no disease recurrence. Moreover, on retrospective review, 21 of the nonoperative patients had evidence of a PNET on imaging available before the index imaging report. If one considers the retrospective finding date as the initial start time, then these patients had an average of 62 radiological months with minimal or no neoplasm growth (median size of 0.8 cm, max 2 cm).

These results not only illustrate the indolent potential of selected, small nonfunctioning PNETS but also reaffirm the substantial risk of complications, some of which were life-threatening, that can occur from operative intervention. The current recommendation for nonmetastatic PNETs by the National Comprehensive Cancer Network is surgical resection. However, "the risks and benefits of surgical resection should be carefully weighed in patients with small lesions."[5] The risks associated with pancreatic surgery are well recognized and the data specifically related to the surgery of PNETs are accumulating. One review of the Nationwide Inpatient Sample from 1998–2006 identified a 1.7% in-hospital mortality rate and 29.6% overall complication rate after pancreatectomy for PNETs.[14] Clinically significant leaks (Grade B/C) are variably reported, but two large studies report leak rates of 27% after pancreaticoduodenectomy and 12% after distal pancreatectomy.[15,16] Commensurate with previous reports, our Grade B/C leak rate was 27%. Enucleation, thought to significantly minimize pancreatic leak, also harbors risk. Of six patients in our study who underwent enucleation, 2 developed a Grade B/C leak. In one review of patients who underwent enucleation for small nonfunctioning PNETs, 3 of 26 (12%) patients developed a Grade B/C leak with one requiring reoperation.[17] Contributing to the technical challenge in this special set of patients is a normal-sized pancreatic duct in the face of soft pancreatic parenchyma.

Nonpancreatic leak complications occurred less frequently but were still of serious concern. Five of 56 (9%) patients developed a complication that mandated return to the operating room. Reoperative indications included intra-abdominal hemorrhage, gastric or colonic perforation, and pancreaticojejunostomy stricture. Long-term complications arose from incisional hernias, prolonged rehabilitation, and pancreatic insufficiency. Endocrine and exocrine pancreatic insufficiency occurs in up to 58% of pancreaticoduodenectomies and 29% of distal pancreatectomies.[18] In our study, 2 patients developed new onset postoperative diabetes, one patient developed exocrine insufficiency and one patient developed both after returning to the operating room for a total pancreatectomy. Although there was no perioperative mortality, the risk of these complications should weigh

Table V. Surgical complications and staging results for patients who underwent operation for an incidental PNET

	Operative group, N = *56*
Type of operation	
Lap/open distal pancreatectomy ± splenectomy	36 (64)
Lap/open central pancreatectomy	3 (5)
Lap/open pancreaticoduodenectomy	8 (14)
Lap/open enucleation	7 (13)
Pancreaticoduodenectomy + distal pancreatectomy	1 (2)
Data unavailable	1 (2)
Clavien-Dindo postoperative complication	14 (25)
Grade I	0
Grade II	6 (11)
Grade III	3 (5)
Grade IV	5 (9)
Grade V (death)	0
ISGPF pancreatic leak complication	19 (34)
Grade A	4 (7)
Grade B	10 (18)
Grade C	5 (9)
AJCC TNM stage*	
Stage Ia	30
Stage Ib	15
Stage 2b	5‡
Data unavailable	2
ENETS TNM stage*	
Stage I	26
Stage IIa	16
Stage IIb	3
Stage IIIb	5‡
Data unavailable	2
Revised ENETS TNM stage*,†	
Stage I	45
Stage II	0
Stage III	5‡
Data unavailable	2

*Four neoplasms not diagnosed as PNET on final pathology were excluded from staging.
†As proposed by Scarpa et al[6].
‡Five patients had unanticipated lymph node positivity.
Numbers in parentheses are percentages.
AJCC TNM, American Joint Commission on Cancer Tumor-Nodes-Metastasis; *ENETS*, European Neuroendocrine Tumor Society; *ISGPF*, International Study Group on Pancreatic Fistula; *PNET*, pancreatic neuroendocrine tumors.

heavily in light of the outcomes of our nonoperative group.

For PNETs in general, including carcinomas, reports associate neoplasm size and nodal status with survival.[6,19-21] This provides basis for all TNM staging systems. On multivariable analysis, Scarpa et al found that neoplasm size >4 cm had independent prognostic significance in the absence of lymph node involvement and distant metastasis.[6] However, other reviews, including Bilimoria's analysis of 3,851 national cancer database patients, found no such association with size alone as an independent predictor of survival on the basis of multivariate analysis.[1,22,23] Given the inconsistent results of neoplasm size as a prognostic indicator of survival, an aggressive surgical approach has been understandable. However, in Bilimoria's review of treatment trends in 9,821 patients, neoplasm size *greater* than 4.0 cm was independently associated with a lower likelihood of undergoing surgical resection, after excluding for metastatic disease.[24]

In our study, more than half of the patients in the operative group had neoplasms <2 cm. The risk of lymph node positivity may also influence proponents of routine resection. In our review, 5 patients with positive lymph nodes had complete F/U after resection and are without evidence of disease recurrence after an average of 38 radiological months. Interestingly, some reviews have found no relationship between nodal status alone and survival.[1,9,22] Overall, in this population of patients with neoplasms <2 cm, it appears that indolent neoplasm biology prevails over size and nodal status.

Diagnosis remains an uncertainty without biopsy or resection specimen confirmation. Only 29% of the nonoperative group had biopsy confirmation of a PNET, which raises the question of accurate diagnosis in the remaining patients. Despite high-quality pancreatic imaging, radiologists cannot always distinguish between different pancreatic pathologies or accessory splenic tissue. Four of 24 (17%) nonbiopsy-confirmed operative patients had false-positive preoperative imaging and one might expect a similar percentage in the nonoperative group. Additional preoperative studies such as octreotide scan or sulfur colloid scan (to identify ectopic splenic tissue) might improve diagnostic accuracy. EUS increasingly is being used to identify PNETs at our institution. In one study, EUS was found to be superior to CT scan with a sensitivity of 90% in the detection of small nonfunctioning neoplasms.[25] In experienced hands, EUS can detect ductal involvement, regional lymphadenopathy, or metastatic disease whereas FNA can provide important information regarding diagnosis and neoplasm grade. A minimum pathology data set has been suggested for biopsied PNETs: (1) presence of unusual histological features; (2) mitotic rate; (3) Ki-67 index; (4) evidence of nonischemic tumor necrosis; and (5) the presence of

Table VI. CT/MRI review of patients diagnosed with an incidental PNET

	Nonoperative group, n = *72**	*Operative group,* n = *49**
Location in the pancreas		
Head and neck	24 (33)	13 (26)
Body	11 (15)	15 (31)
Tail	37 (51)	21 (43)
Growth type		
Intraparenchymal	52 (72)	24 (49)
Exophytic	20 (28)	25 (51)
Solid versus cystic		
Solid	63 (88)	29 (59)
Enhancement (lesion:pancreas ratio)		
Hypoenhancement (<0.8)	1	1
Isoenhancement (0.8–1.2)	6	6
Hyperenhancement (>1.2)	56	22
Cystic	3 (4)	4 (8)
Mixed solid-cystic	6 (8)	16 (33)
Heterogeneity		
Homogenous	50 (69)	16 (33)
Heterogeneous	22 (31)	33 (69)
Vascular invasion		
Present	0	0
Absent	72 (100)	49 (100)
Calcifications		
Present	6 (8)	5 (10)
Absent	66 (92)	44 (90)
Pancreatic duct cut-off		
Present	0	0
Absent	72 (100)	49 (100)
Evidence of chronic pancreatitis		
Present	2 (3)	0
Absent	70 (97)	49 (100)
Peripancreatic lymph node >5 mm		
Present	8 (11)	4† (8)
Absent	64 (89)	45 (92)

*For the nonoperative group, 5 patients were diagnosed on EGD and were not included in this review. For the operative group, 5 patients were diagnosed on EGD and 2 images were unavailable.
†Only one patient had positive lymph nodes on final pathology.
Numbers in parentheses are percentages.
CT, Computed tomography; *MRI,* magnetic resonance imaging; *PNET,* pancreatic neuroendocrine tumors.

other pathological components.[2] Concerning findings on biopsy would influence surgical decision making.

Most of the current studies regarding PNETs do not apply to the patient population considered in this report. Information regarding survival, prognostic predictors and outcomes is gathered from patients who have undergone surgical resection or other treatment for symptomatic, familial-associated or metastatic disease.[1,9,22,24] We have clearly selected a cohort of patients that have indolent neoplasm biology. With such slow growing neoplasms, one might identify disease progression over the course of 10 or 20 years. Despite identifying some patients without neoplasm growth for over 10 years, our average follow-up is 3–4 years. For these patients, F/U is ideally measured in decades. Although there is a general understanding that small neoplasms can be observed, there has been no previous F/U results for nonoperative patients at this end of the disease spectrum.

Before our study, the natural history of unresected, small, nonfunctioning PNETS has been entirely unknown. Our data reveal that small <2 cm, nonfunctioning PNETs usually exhibit minimal or no growth over many years. In light of the potential complications of pancreatic surgery, when the patient is asymptomatic, and serial imaging reveals minimal or no growth without

Table VII. Histopathologic review of specimens in patients diagnosed with an incidental PNET

	Nonoperative group, n = *22**	*Operative group,* n = *52**
WHO grade		
I (low)	18 (81)	38 (73)
II (intermediate)	2 (9)	11 (21)
III (high)	0	0
Data unavailable	2 (9)	3 (6)
Ki-67 proliferative index†		
≤5%	12 (55)	46 (88)
>5%	0	0
Data unavailable	10 (45)	6 (12)

*For the nonoperative group, results were available for 22 patients who underwent fine needle aspiration. For the operative group, 4 neoplasms not diagnosed as PNET on final pathology were excluded.
†Cut-off values based on Scarpa's revised ENETS TNM guidelines.
Numbers in parentheses are percentages.
PNET, Pancreatic neuroendocrine tumors; *WHO,* World Health Organization.

locally invasive or metastatic features, a nonoperative approach may be advocated.

REFERENCES

1. Franko J, Feng W, Yip L, Genovese E, Moser A. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. J Gastrointest Surg 2010;14:541-8.
2. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010;39:707-12.
3. Lewis RB, Lattin GE, Paal E. Pancreatic endocrine tumors: radiologic-clinicopathologic correlation1. Radiographics 2010;30:1445-64.
4. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder W, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Archiv 2006;449:395-401.
5. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th ed. New York: Springer Press; 2009.
6. Scarpa A, Mantovani W, Capelli P, Beghelli S, Boninsegna L, Bettini R, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol 2010;23:824-33.
7. Bilimoria KY, Bentrem DJ, Merkow RP, Tomlinson JS, Stewart AK, Ko CY, et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. J Am Coll Surg 2007;205:558-63.
8. Fitzgerald TL, Hickner ZJ, Schmitz M, Kort EJ. Changing incidence of pancreatic neoplasms: a 16-year review of statewide tumor registry. Pancreas 2008;37:134-8.
9. Haynes AB, Deshpande V, Ingkakul T, Vagefi PA, Szymonifka J, Thayer SP, et al. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. Arch Surg 2011;146:534-8.
10. Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocrine-Related Cancer 2011;18:S1-16.
11. Falconi M, Plöckinger U, Kwekkeboom DJ, Manfredi R, Körner M, Kvols L, et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006; 84:196-211.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
13. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: An international study group (ISGPF) definition. Surgery 2005;138:8-13.
14. Smith JK, Ng SC, Hill JS, Simons JP, Arous EJ, Shah SA, et al. Complications after pancreatectomy for neuroendocrine tumors: a national study. J Surg Res 2010;163:63-8.
15. Reid-Lombardo K, Farnell M, Crippa S, Barnett M, Maupin G, Bassi C, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: a report from the Pancreatic Anastomotic Leak Study Group. J Gastrointest Surg 2007;11:1451-9.
16. Nathan H, Cameron JL, Goodwin CR, Seth AK, Edil BH, Wolfgang CL, et al. Risk factors for pancreatic leak after distal pancreatectomy. Ann Surg 2009;250:277-81.
17. Falconi M, Zerbi A, Crippa S, Balzano G, Boninsegna L, Capitanio V, et al. Parenchyma-preserving resections for small nonfunctioning pancreatic endocrine tumors. Ann Surg Oncol 2010;17:1621-7.
18. Falconi M, Mantovani W, Crippa S, Mascetta G, Salvia R, Pederzoli P. Pancreatic insufficiency after different resections for benign tumours. Br J Surg 2008;95:85-91.
19. Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 2011;150: 75-82.
20. Gullo L, Migliori M, Falconi M, Pederzoli P, Bettini R, Casadei R, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol 2003;98: 2435-9.
21. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO histological classification of tumours of the endocrine pancreas. Lyon, France: IARC Press; 2010.
22. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg 2008;247:490-500.
23. Martin RC, Kooby DA, Weber SM, Merchant NB, Parikh AA, Cho CS, et al. Analysis of 6,747 pancreatic neuroendocrine tumors for a proposed staging system. J Gastrointest Surg 2011;15:175-83.
24. Bilimoria K, Tomlinson J, Merkow R, Stewart A, Ko C, Talamonti M, et al. Clinicopathologic Features and Treatment Trends of Pancreatic Neuroendocrine Tumors: Analysis of 9,821 Patients. J Gastrointest Surg 2007;11:1460-9.
25. Khashab MA, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, et al. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc 2011;73:691-6.

DISCUSSION

Dr Richard A. Prinz (Evanston, IL): Maybe you can clarify one thing for me first. I gathered, if I heard this correctly, that it was only about a quarter of the patients who were in the nonoperative group had a biopsy that

confirmed they had a neuroendocrine tumor. I think that's important, because, to use the analogy with papillary thyroid cancer, we are looking at markers that might indicate aggressiveness, such as BRAF, and using that to base surgical approach here.

So I think it's very important to be certain what we are dealing with and to biopsy all these if you are going to treat them nonoperatively and to gain information that might be valuable.

You didn't deal with tumor location. And I think, among surgeons dealing with this problem, we are all very happy to explore that one laparoscopically in the tail. But, like the example you showed, we are very hesitant about getting in a position in the operating room where we may have to do a Whipple resection.

So I would like your comments on both those issues.

Dr Louis C. Lee: As was mentioned earlier, diagnosis is key, and that has to happen first. You are correct that it was 30% of those patients. We did do a subset analysis of those patients and they had about the same size of neoplasm and good follow-up with no change in their follow-up as well.

We wish that we would have 100% FNA on all those patients for diagnosis. Unfortunately, we didn't.

In speaking with our gastroenterologist who performs a lot of these endoscopic ultrasounds, there were actually a few of them that he specifically elected not to biopsy, which put the patient at risk for pancreatitis or bleeding, because the patient had a previous CT scan and/or octreotide scan and/or high-quality imaging that was very highly suggestive of a neuroendocrine neoplasm.

Regarding the location of the neoplasms, in the article, fully detailed, is our radiologist's review of where they were located. They were found throughout the pancreas. And you are correct, the distal pancreas would be much more amenable than the head tumor.

The current NCCN guidelines state that for nonmetastatic pancreatic neuroendocrine neoplasms, resection is the treatment. However, for small neoplasms, and especially given comorbidities and maybe location of the tumor, nonoperative management may be performed.

Having said that, we just had a very young, thin habitus patient with a 7-mm tumor in the head of her pancreas that we enucleated.

Dr Gerard M. Doherty (Boston, MA): Just 3 things I would like you to clarify for us for the patients that we're all going to see next week.

What imaging do you require to put them into this group? Would you biopsy them now? And what interval do you follow them up at, given the data that you have so far?

Dr Louis C. Lee: For the imaging, our radiologists with the pancreatic protocol, fine-cut CT scans are pretty good. And in their retrospective review, they were able to fairly accurately diagnosis neuroendocrine tumors. Now, there were the four that weren't, so that would be a great opportunity if gastroenterologists felt comfortable performing fine needle aspirations.

That would provide 2 opportunities: One, to make the diagnosis; and second, to look at the cytopathology for mitotic indices or Ki-67.

So I think that answers the question for the second one: Should we biopsy? In all cases, if you can, yes. And the interval for follow-up on these patients, we don't know. I think, right now, at least 3-, 6-month, annually, for what we have seen. Up to five, ten years of follow-up, we haven't seen any active metastatic disease or growth. Beyond that 10 years, why other studies have found that in 15, 20, 30 years, these have recurred, I think it would be reasonable to go 5 to 10 and then, after that, maybe slowing down the frequency.

Dr Janice Pasieka (Calgary): Two questions.

Can you tell us how many of these were picked up incidentally? There's a European paper that was just published that showed that the incidental, small, nonfunctioning PNET had a very benign pattern, versus those that were picked up in a truly nonincidental way.

And my second question is, what would you recommend for the patient whose biochemical profile is now increasing, their chromogranin A is continuing to climb, but the neoplasm itself, on radiology examination, has not changed?

Dr Louis C. Lee: All of these patients were what we defined as incidentally identified. That is, they did not have clearly attributable symptoms to their neuroendocrine tumor. If this was a 5-mm tumor that was seen in the tail, yet they came in for vague abdominal pain or diarrhea or right lower quadrant pain and had a CT scan. That is what we defined as incidental.

Regarding chromogranin A and the definition of biochemical, that brings up a good point of the definition of symptomatic. And that, we based on clinical symptomatology. If they had just slightly increased gastrin or slightly elevated insulin levels, that wouldn't be considered a symptomatic patient. They would have to have, for example, in a patient with insulinoma, symptoms of hypoglycemia treated with sugars and so on.

For chromogranins, the few reports that I have seen as a surrogate marker for recurrence of these, there's a suggestion that it is useful. Following it long term and for a prognosticator, I don't know the data on that.