Implications of Incidentally Discovered, Nonfunctioning Pancreatic Endocrine Tumors: Short-term and Long-term Patient Outcomes

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Abstract

Objectives—To describe the characteristics and outcomes after resection of incidentally discovered, nonfunctioning pancreatic endocrine tumors (PETs).

Design—Case series.

Setting—Academic hospital.

Patients—Consecutive patients with an incidentally identified, nonfunctioning PET resected from May 1, 1977, through July 31, 2009.

Main Outcome Measures—Operative morbidity and survival after resection.

Results—A total of 139 patients with median age of 56 years (range, 21–85 years) underwent resection; tumor size ranged from 0.4 to 17.0 cm, with median size of 3.0 cm. No perioperative deaths were reported. Sixty-one patients (43.9%) experienced a perioperative complication. Twenty-six tumors (18.7%) were classified as benign, 39 (28.1%) as malignant, and 72 (51.8%) as uncertain. We were unable to confidently classify 2 tumors due to lack of information regarding mitotic rate in the pathology report. Complete follow-up was available for 112 patients (80.6%) (median, 34.2 months). Five-year actuarial survival rates were 88.8% for patients with benign disease, 92.5% for patients with tumors of uncertain biology, and 49.8% for those with malignant tumors (P=.01). Late metastasis, tumor recurrence, or disease progression were seen in 1 patient (3.8%) with tumors initially classified as benign, 8 patients (11.1%) with uncertain tumors, and 15
patients (38.5%) with tumors classified as malignant \((P<.001)\). Of the 39 patients with tumors 2 cm or smaller, 3 (7.7%) had late metastases or recurrence. When compared with patients with symptomatic, nonfunctioning PETs, no large difference was observed in tumor size, patient age, disease, or survival.

**Conclusions**—Incidentally detected, nonfunctioning PETs can display aggressive behavior, even when small. Although patients with malignant disease had diminished survival and increased rates of recurrence, benign histologic findings did not eliminate the possibility of progression. Patients with incidentally discovered, nonfunctioning PETs should undergo tumor resection and careful postoperative surveillance, even if surgical pathologic findings suggest benign disease.

Tumors of endocrine origin represent a small but increasing proportion of pancreatic neoplasms. These tumors may be hormone secreting, but currently most patients do not present with a syndrome of endocrine excess.\(^1\) In the past, nonfunctioning tumors were not detected until they produced symptoms from mass effect or invasion. However, with the widespread use of diagnostic axial imaging has come an increase in the detection of otherwise asymptomatic lesions of the pancreas, including cysts and nonfunctioning endocrine tumors.\(^1,2\) Our understanding of the natural history of incidentally discovered pancreatic endocrine tumors (PETs) is limited, but because nonfunctioning PETs were traditionally associated with aggressive tumor behavior, most institutions, including the Massachusetts General Hospital, have recommended surgical resection on discovery.\(^3,4\) We present a large cohort of patients with incidentally identified, nonfunctioning PETs. We describe their characteristics, surgical outcomes, and survival and compare them with patients with symptomatic, nonfunctioning PETs, with the aim of gaining insight into tumor behavior and potential strategies for clinical management.

**METHODS**

Patients who underwent pancreatic resection at Massachusetts General Hospital from May 1, 1977, to July 31, 2009, were identified from preexisting institutional registries. Tumors of endocrine origin were selected based on surgical pathologic reports. Two surgeon-reviewers (A.B.H. and T.I.) retrospectively examined patient medical records. Tumors were considered nonfunctional if the patient presented without symptoms of hormonal excess. We considered patients without clinically apparent jaundice, patients with no abdominal symptoms, and those whose symptoms were unlikely to be related to the mass to have an incidentally identified tumor. We also considered patients with known multiple endocrine neoplasia type 1 to have nonincidental tumors. Pathologic characteristics were obtained from surgical pathology reports. Data regarding survival and long-term outcomes were obtained from the medical record, a separate institutional registry, and the Social Security Index. Patients were considered to have complete follow-up information if they had been in contact with Massachusetts General Hospital or their primary care physician within the previous 12 months or if we had documentation of death. Survival was calculated from the date of surgery to the date of death. Data from patients who were alive at the date of last contact were censored at this date. Overall survival graphs and point estimates were generated using the Kaplan-Meier method. Survival comparisons were made using the log-rank test. Binomial comparisons were made using the Fisher exact test, and the Kruskal-Wallis test was used to compare medians.

Postoperative complications have been defined in a previous publication.\(^5\) In brief, a *pancreatic fistula* was defined as drainage of more than 30 mL/d of amylase-rich fluid from intraoperatively placed drains after postoperative day 7 or as the continued use of an intraoperatively placed drain at the time of discharge (regardless of postoperative day or amount). *Wound infection* was defined as culture-positive, purulent drainage from the postoperative wound that required packing. An *intraabdominal abscess* was defined as
culture-positive, purulent drainage obtained from a percutaneous or operative intervention. *Intraabdominal collections* were those in which the drainage was nonpurulent and culture negative. Length of stay was calculated from the day of surgery even if the patient was hospitalized pre-operatively.

The World Health Organization classification system for pancreatic endocrine tumors was used to categorize histopathologic findings. We determined that all patients with malignant findings, whether low grade or high grade, had malignant disease, although those with well-differentiated tumors but no characteristics of malignant disease were divided into benign and uncertain tumor groups.

Patients who underwent resection of symptomatic, nonfunctioning PETs were identified from the institutional database as a comparative group. Similar data regarding tumor characteristics, operative details, and postoperative outcomes were collected for the incidentally identified tumors. Patients whose lesions were detected via active surveillance for known multiple endocrine neoplasia were also included in this group.

**RESULTS**

From May 1, 1977, to July 31, 2009, 139 patients underwent resection of an incidentally identified PET. Thirty resections were performed from 1977 to 2000 and 109 after 2000. Figure 1 shows the number of patients who underwent resections per year. No sex predilection was observed in this series (51.1% women), and the median patient age was 56 years (range, 21–85 years). The indication for obtaining the axial imaging that revealed the incidental lesion was available for 71 patients (51.1%) (Table 1). The indication for imaging could not be confidently determined in the remaining patients. Tumor size ranged from 0.4 to 17.0 cm (median, 3.0 cm). One hundred tumors (71.9%) were larger than 2 cm.

Tumors were most commonly found in the tail of the pancreas (46.8%), with 30.2% in the head or uncinate process. Seventy-four patients (53.2%) underwent distal pancreatectomy, 39 (28.1%) underwent pancreaticoduodenectomy, 17 (12.2%) underwent middle segmental pancreatic resection, and 9 (6.5%) underwent enucleation. Clear surgical margins were obtained in 121 patients (87.1%), and lymph node metastases were identified in 28 patients (20.1%). Fifteen patients (10.8%) had distant metastases at the time of initial surgery, all in the liver. Three of the patients with synchronous metastases had nonanatomic hepatic resections at the time of pancreatectomy, and 1 patient had a subsequent formal hepatectomy for a synchronous metastasis. One patient had a wedge resection of a liver metastasis before pancreatic surgery. Twenty-six patients (18.7%) had benign histologic findings, but 72 (51.8%) had uncertain and 39 (28.1%) had malignant findings. We were unable to confidently classify 2 tumors due to lack of information regarding mitotic rate in the pathology report. No relationship was observed between age and histopathologic findings, with median ages of 55, 56, and 57 years for patients with benign, uncertain, or malignant disease, respectively (P=0.67).

No perioperative deaths were reported. Median length of stay was 7 days. One or more perioperative complications occurred in 61 patients (43.9%) (Table 2). One patient required a subsequent operation in the perioperative period for debridement of peripancreatic necrosis and abscess after a distal pancreatectomy that resulted in an uncontrolled pancreatic leak. A total of 16 patients (11.5%) patients underwent postoperative chemotherapy, radiotherapy, or both.

Complete follow-up was available for 112 patients (80.6%), with a median follow-up of 34.2 months. Five-year and 10-year actuarial survival rates were 88.8% and 67.7%, respectively, among those with benign disease, 92.5% and 77.8%, respectively, for those
with tumors of uncertain biology, and 49.8% and 16.6%, respectively, for those with malignant tumors (P=.01 overall, P=.03 for benign vs malignant, P=.001 for uncertain vs malignant, and P=.27 for benign vs uncertain). Tumor-related 5-year and 10-year mortality rates were 7.1% and 7.1% for the benign group, 6.1% and 14.0% for the uncertain group, and 35.9% and 78.6% for the malignant group. Overall survival data stratified by World Health Organization classification are depicted in Figure 2 and Figure 3. Late metastasis, tumor recurrence, or disease progression was seen in 1 patient (3.8%) with tumors initially classified as benign, 8 patients (11.1%) with tumors initially classified as uncertain, and 15 patients (38.5%) with tumors initially classified as malignant (P<.001). Negative margin status was associated with improved 5-year survival rates (91.2% vs 55.0%, P=.001), as was negative lymph node status (94.1% vs 55.1%, P=.001). Among patients without positive lymph node status, no significant association was found between number of lymph nodes analyzed and survival, using a univariate Cox proportion hazards regression model (hazard ratio, 1.05; 95% confidence interval, 0.93–1.18; P=.45). Tumor size as a dichotomous variable (<2 vs ≥2 cm) was a predictor for disease progression or metastasis, with an odds ratio of 5.00 (95% confidence interval, 1.12–22.35; P=.04). However, 3 of 39 patients (7.7%) with a resected tumor no larger than 2 cm developed metastatic disease and eventually died of disease. Figure 4 illustrates the distribution of tumors by size.

During the same period, 30 patients underwent resection for symptomatic, nonfunctioning PETs. These patients comprise 17.8% of the total group of patients with nonfunctioning PETs. When compared with the patients with incidentally discovered PETs, no difference was observed in sex (50.0% vs 48.9% men in the incidental group), median age (55 vs 56 years), frequency of malignant histopathologic findings (30.0% vs 28.1%), or surgical complications (46.7% vs 44.0%). Also, no significant difference was observed in median size of tumor (3.5 vs 3.0 cm, respectively; P=.48). Nonincidental tumors were more likely to be found in the head (36.7% vs 28.8%), but this finding did not reach statistical significance (P=.39). Five-year and 10-year overall survival rates were 81.7% and 65.4%, respectively, in the symptomatic group compared with 82.8% and 65.1% for patients with incidentally identified tumors (P=.27) (Figure 5).

COMMENT

Management of incidentally identified lesions poses a quandary to health care professionals, especially when they represent rare conditions, such as PETs. The true incidence of these lesions is not well known, with widely variable rates reported in population-based studies. 

Epidemiologic studies suggest a low incidence of clinically significant disease, with 1 large registry reporting an annual incidence of only 2 per million, but autopsy studies report much higher rates of incidental tumors.

To our knowledge, ours is the largest single-institution series of incidentally discovered, nonfunctioning PETs. Although intuitively we would anticipate better outcomes and perhaps less need for formal pancreatic resection because of the earlier discovery, most of these tumors were larger than 2 cm and only 18.7% were classified as benign. We were surprised to find that 28 patients (20.1%) had lymph nodes that tested positive and 15 (10.8%) had distant metastases at the time of surgery. Also, the 5-year and 10-year survival rates for the 39 patients (28.1%) classified as having malignant tumors (well or poorly differentiated) were 49.8% and 16.6%, respectively, although this finding includes 10 patients who had known metastatic disease left in situ at the time of initial resection. Furthermore, this series shows that small tumor size, although a predictor of decreased likelihood of disease progression or metastasis, did not guarantee a good outcome because 3 of 39 patients (7.7%) with tumors 2 cm or smaller eventually had disease recurrence and died of their
disease, including 1 patient with disease initially classified as benign. One patient with a tumor smaller than 1 cm was found to have malignant disease. Clearly, asymptomatic, nonfunctioning PETs are potentially lethal lesions even when small and, as shown in this series, have long-term outcomes almost identical to those of patients who underwent resection for symptomatic, nonfunctioning tumors.

Our results also show that when pancreatic surgery is performed in a specialized center, the morbidity and mortality rates can be acceptably low. Depending on their location and size, these tumors require a variety of types of resection. Notably, 25 patients (18.0%) were treated with enucleation or a middle pancreatectomy, operations that typically do not include lymph nodes in the resection. Although most of the tumors in this group were small, the effect of the lack of lymphadenectomy cannot be determined, and of the 25 patients in this group, 2 had recurrence or progression. However, among the 87 patients who underwent formal pancreatic resection and had negative lymph node results, 13 (14.9%) had recurrence or progression, but 12 of 29 patients with positive nodes (41.4%) were alive without evidence of disease at last follow-up. In addition, no significant relationship was observed between the number of lymph nodes resected and patient survival. These findings suggest that tumor biology may play as important a role as lymph node excision.

This study cannot demonstrate that surgical resection alters the natural history of nonfunctioning PETs or improves survival. Its retrospective nature and the lack of a control group of patients who did not undergo resection preclude this conclusion. However, it is unrealistic to envision that such a study ever could be conducted. Although inevitably, some patients will not be favorable surgical candidates or will refuse surgery, their survival will be hampered by other factors; randomization of fit patients to observation vs resection would be unethical given our lack of counterbalance regarding the benefit of surgery. Accumulation of more cases with focus on the analysis of smaller tumors will help us understand the significance of such tumors. If indeed the risk of malignancy or progression is diminished in this group, perhaps we can develop strategies to allow us to identify tumors with an increased risk of malignant behavior. This research will be particularly relevant as refinements in axial imaging and endoscopic ultrasonography detect increasing numbers of small lesions.

This study also confirms the difficulties in the pathologic evaluation of PETs. Multiple systems of clinical pathologic staging have been proposed to identify characteristics of malignant behavior in these tumors. These systems have proven to be of moderate value in distinguishing between aggressive and benign tumors, and a significant risk of tumor-related death or disease progression continues to exist, even among those patients with benign tumors on histopathologic review. Although patients with PETs have much improved survival compared with those with adenocarcinoma of the pancreas, a notable burden of morbidity and mortality still is associated with these lesions and, as demonstrated herein, even with a benign diagnosis after surgical extirpation, long-term surveillance for recurrence is necessary.

In summary, resection should be offered to surgically fit patients with incidentally identified PETs. No size cutoff exists beyond which malignancy can be safely excluded. Furthermore, all patients who undergo resection should receive long-term surveillance, including those with tumors the World Health Organization classification system labels as benign. Patients with positive margins or lymph node metastases should be followed up especially closely. Additional study is needed to optimize the pathologic classification and treatment of these rare tumors and to better understand the role of lymphadenectomy in operative therapy.
References


Figure 1.
Year of resection. The 2009 column includes those patients on whom operations were performed between January 31 and July 1 only.
Figure 2.
Overall survival of patients after resection of an incidentally identified, nonfunctioning pancreatic endocrine tumor (N=139). Crosshatch marks indicate date of censure.
Figure 3.
Overall survival stratified by histopathologic classification after resection of an incidentally identified, nonfunctioning pancreatic endocrine tumor. Crosshatch marks indicate date of patient censure. The difference in survival between patients with benign (n=26) and malignant (n=39) lesions was statistically significant (P=.03), as was the difference between patients with uncertain (n=72) compared with benign lesions (P<.001). No significant difference in survival was found between patients with benign or uncertain lesions.
Figure 4.
World Health Organization pathologic classification by tumor size. Number of tumors with each classification are shown for each size interval.
Figure 5.
Overall survival from date of surgery comparing patients with incidentally identified lesions (n=139) with those with nonincidental lesions (n=30) (P=.27).
Table 1

Indication for Abdominal Imaging

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. (%) of Patients (n=71)</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>21 (29.6)</td>
</tr>
<tr>
<td>Genitourinary symptoms</td>
<td>12 (16.9)</td>
</tr>
<tr>
<td>Laboratory result abnormalities</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>Thoracic symptoms</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>Lower gastrointestinal tract symptoms</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Other cancer surveillance</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (15.5)</td>
</tr>
</tbody>
</table>

*Patients were included only when a concrete indication for imaging was noted in the medical record. The remaining patients were noted in the medical records to have incidental tumors, but the records did not show a clear indication for the reason of investigation.

b Only includes patients with abdominal pain deemed unlikely to be related to the pancreas.
Table 2
Postoperative Complications Within 30 Days of Resection of Incidentally Identified Pancreatic Endocrine Tumors$^a$

<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>No. (%) of Patients (N=139)</th>
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<tbody>
<tr>
<td>Pancreatic fistula</td>
<td>21 (15.1)</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Intestinal fistula</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Other complication</td>
<td>25 (18.0)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Any complication</td>
<td>61 (43.9)</td>
</tr>
</tbody>
</table>

$^a$Two tumors are not classified by the World Health Organization system owing to lack of information regarding mitotic rate in the pathology report; information regarding these tumors is included in the aggregate analysis.