Resection of Pancreatic Neuroendocrine Tumors

Results of 70 Cases

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Hypothesis: Neuroendocrine tumors of the pancreas can be managed surgically with excellent outcomes.

Design: Retrospective case series.

Setting: Academic medical center.


Interventions: Pancreatoduodenectomy, distal pancreatectomy, or enucleation.

Main Outcome Measures: Postoperative morbidity, mortality, and long-term survival.

Results: Of the 70 patients, 50 (71.4%) had nonfunctional tumors. Thirty-seven patients (52.9%) had neuroendocrine carcinomas and 13 (18.6%) had benign islet cell neoplasms. Twenty patients had functional tumors. Of these 20 patients, 16 had insulinomas, 2 had glucagonomas, and 2 had gastrinomas. Twenty-seven patients underwent pancreaticoduodenectomy, 32 had distal pancreatectomy, and 11 underwent enucleation. Patients undergoing enucleation as compared with those not undergoing enucleation were younger (mean age, 39 vs 51 years, respectively; \( P = .009 \)) and had smaller tumors (mean tumor size, 2 vs 5 cm, respectively; \( P < .001 \)). Postoperative complications occurred in 13 patients (48.1%) after pancreaticoduodenectomy, in 4 patients (12.5%) after distal pancreatectomy, and in 0 patients after enucleation. There were no perioperative mortalities. With a median follow-up of 50 months, the 5-year actuarial survival for the patients with malignant neuroendocrine carcinomas (\( n = 37 \)) was 77%, and all of the patients with functional tumors were alive. The presence of lymphovascular invasion closely approached significance when survival was evaluated (\( P = .06 \)). Lymph node status, perineural invasion, and liver metastasis did not impact survival.

Conclusions: This single-institutional case series demonstrates that pancreatic neuroendocrine tumors can be safely resected without mortality and with minimal morbidity. The presence of lymphovascular invasion can be used to classify neuroendocrine tumors as malignant, and this appears to predict survival. Patients with malignant tumors can expect long-term survival even in the setting of metastatic disease.

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Neuroendocrine tumors of the pancreas are the most common abdominal endocrine neoplasms. Functional tumors secrete ectopic hormones (eg, insulin, gastrin, glucagon, vasoactive intestinal peptide, corticotropin) that can cause distinct clinical syndromes.\(^1\) The first functional pancreatic neuroendocrine tumor, an islet cell neoplasm, was described in 1902 by Nicholls.\(^2\) The first resection was performed in 1929 when an insulinoma was enucleated.\(^3\) However, most pancreatic neuroendocrine tumors are nonfunctional, and they are generally not diagnosed until symptoms develop from a mass effect or from metastatic disease in those tumors that are malignant. In many patients, the tumor is noted incidentally on an abdominal imaging study and the patients are asymptomatic.\(^4\)

Patients with neuroendocrine pancreatic cancers have a significantly better prognosis than those with the more common ductal pancreatic adenocarcinoma, but the two may be impossible to distinguish preoperatively.\(^4,10\) As with exocrine cancers, resection is the only chance for cure, and the type of resection that is required depends on the location of the tumor. To evaluate our own experience with these neoplasms, we conducted a retrospective review of the patients treated at the University of California, Los Angeles, Medical Center who underwent resection for pancreatic neuroendocrine tumors over the last 15 years, and we analyzed short- and long-term outcomes and factors influencing survival.
Table 1. Resected Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfunctional</td>
<td>50 (71.4)</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>37 (52.9)</td>
</tr>
<tr>
<td>Benign islet cell tumor</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>Functional</td>
<td>20 (28.6)</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
</tr>
</tbody>
</table>

STATISTICAL ANALYSIS

Data are presented as mean±SEM unless otherwise indicated. Differences in the continuous variables of demographics, operative data, and length of hospitalization were analyzed using analysis of variance and t tests. Differences in discrete variables were analyzed with the Fisher exact test and Mann-Whitney rank sum test. Survival estimates were generated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Statistical significance was achieved at P<.05. Statistical analyses were performed using SAS statistical software (SAS Institute, Inc, Cary, NC).

RESULTS

PATIENT CHARACTERISTICS AND OPERATIVE RESULTS

From January 1, 1990, to December 31, 2005, 70 pancreatic resections were performed at the University of California, Los Angeles, Medical Center for a variety of neuroendocrine tumors (Table 1). Most of these were done for neuroendocrine carcinomas (in 37 patients [52.9%]). Twenty patients (28.6%) had functional tumors, mostly insulinomas. Based on tumor size and relationship to the pancreatic duct, 27 patients (38.6%) underwent pancreaticoduodenectomy (PD), 32 (45.7%) had distal pancreatectomy (DP), and 11 (15.7%) underwent enucleation. All of the enucleations were performed for functional tumors. Four DP s were performed laparoscopically, and 4 patients underwent simultaneous liver resections for metastatic disease. The patients who received liver resection for metastatic disease were free of all gross tumor at the completion of the procedure.

The mean±SEM age for the entire cohort was 51.7±1.9 years, but patients undergoing enucleation (mean±SEM age, 39.1±4.0 years; P=.02) and those with functional tumors (mean±SEM age, 40.7±3.3 years; P=.001) were significantly younger. Operative time and blood loss were significantly greater for PD compared with DP and enucleation (all P<.001). Malignant and/or nonfunctional tumors were significantly larger than benign and/or functional tumors (mean tumor size, 5 vs 2 cm, respectively; P<.001). Accordingly, patients undergoing PD or DP had significantly larger tumors (P<.001). Demographic and operative data are presented in Table 2.

POSTOPERATIVE OUTCOMES

There were no perioperative deaths. Postoperative complications occurred in 13 patients (48.1%) after PD, in 4 patients (12.5%) after DP, and in 0 patients after enucleation (P<.001). Specific postoperative complication data are presented in Table 3. The most common complications after PD were delayed gastric emptying (5 patients [18.9%]) and pancreatic fistula (3 patients [11.1%]); after DP, the most common complication was pancreatic fistula (3 patients [9.4%]).

With a median follow-up of 50 months, the overall 5-year actuarial survival of all of the patients (n=70) was 89%. To date, no patient in this series undergoing resection for a benign or functional tumor has died. All of the deaths in this series (n=8) have occurred in patients with neuroendocrine carcinomas. For patients with neuroendocrine carcinomas (n=37), the 5-year actuarial survival is 77% (71% actual survival), which is significantly less than the survival for patients with benign and/or functional tumors (n=33) (P=.001) (Figure 1). The presence of lymphovascular invasion noted on pathological examination very closely approached significance (P=.06).
when survival was evaluated (Figure 2). Only 3 patients in this series had a positive resection margin, so this did not statistically impact survival. All of these 3 patients had nonfunctioning neuroendocrine carcinomas. Positive lymph nodes, perineural invasion, and liver metastasis did not significantly impact survival ($P = .85$, $.34$, and $.11$, respectively). Pathological factors and their effect on survival are presented in Table 4.

### Comment

Although neuroendocrine tumors of the pancreas are often discussed together because of their endocrine origin, they are in fact a heterogeneous group of neoplasms with different characteristics. Our own institutional experience certainly reflects that. Thus, we saw a minority of functional tumors (in 20 of 70 patients), of which 16 were insulinomas, 2 were gastrinomas, and 2 were glucagonomas. All of these tumors were sporadic, and contrary to the usual experience with both gastrinoma and glucagonoma, they were all benign. In all of these patients, the diagnosis had been made and the tumors had been localized preoperatively. Preoperative evaluation of patients with these lesions involves biochemical analysis of clinically relevant hormones and tumor localization. More than 50% of functioning tumors produce more
tic cytology. Somatostatin receptor scintigraphy may with fine-needle aspiration, which provides characteris-
ing often fail to detect them. We have used endoscopic computed tomography and magnetic resonance imag-
ning of choice for evaluating these tumors, with reported sen-
It was often useful when reviewing imaging studies. Dual-phase, thin-cut, helical computed tomography is currently our initial modality of choice for evaluating these tumors, with reported sensitivities up to 95%. Magnetic resonance imaging is also used by some, but there is no clear evidence that it is better than high-quality computed tomography. Because many of the functional tumors, especially insulinomas, are smaller than 2 cm at the time of presentation, computed tomography and magnetic resonance imaging often fail to detect them. We have used endoscopic ultrasonography to localize these lesions, and the diagnosis can be confirmed by endoscopic ultrasonography with fine-needle aspiration, which provides characteristic cytology. Somatostatin receptor scintigraphy may also be valuable.

Fifty of the 70 tumors were nonfunctional, and in this group, 37 were neuroendocrine carcinomas. Many of these tumors are larger than the functional ones at the time of diagnosis, and the patients are often asymptomatic. Because of the size of the lesions, they are often detected on computed tomography or magnetic resonance imaging. Preoperative localization is not an issue, but the differential diagnosis between an exocrine or endocrine neoplasm may be. The vascular nature of the lesion is often the only clue. If endoscopic ultrasonography with fine-needle aspiration is done, cytologic examination may reveal endocrine cells.

The basis for the pathological diagnosis of cancer in our patients warrants some discussion. Historically, the teaching has been that the diagnosis of invasive malignancy in pancreatic endocrine tumors requires histologic evidence of the direct invasion of an adjacent organ by the tumor, the presence of lymph node metastases, or distant spread to another organ, usually the liver. To our knowledge, even the recent surgical literature has classified patients with malignant neuroendocrine tumors according to those criteria. In the Armed Forces Institute of Pathology fascicle on the pathology of pancreatic tumors (1995), microscopic evidence of vascular invasion within the primary tumor is also considered sufficient to make the diagnosis of a malignant neoplasm, even in the absence of these other factors. Indeed, 21 of our patients had positive lymph nodes and 9 also had liver metastases. Of these 21 patients with positive nodes, 10 showed microscopic evidence of vascular invasion and 11 did not. Nevertheless, they were all viewed as having invasive cancer on the basis of nodal involvement. However, there were 10 patients with negative nodes and without any other distant metastases who had histologic evidence of vascular invasion. They were designated as having invasive cancer solely on that basis. It would be interesting to know whether the prognosis in this group of patients with microscopic vascular invasion but without metastatic disease was similar to the prognosis in those with metastatic disease with or without vascular invasion. We found no difference in our patients, but the small numbers would likely have obscured any difference. Future studies with larger numbers of patients will be required to address this issue.

Based on tumor location, size, index of suspicion of invasive cancer, and the relationship of the tumor to the pancreatic duct, 27 patients (38.6%) in our series underwent PD, 32 (45.7%) had DP with splenectomy, and 11 (15.7%) underwent enucleation. Enucleation was performed in patients with benign functional tumors that were some distance from the pancreatic duct. Intraoperative ultrasonography was used in all of the cases to clarify this. Patients who underwent enucleation for functional tumors were significantly younger and had smaller tumors compared with those who underwent PD or DP. As expected, operative time, blood loss, and length of hospital stay were significantly greater for patients who underwent PD compared with those who underwent DP and enucleation. Postoperative morbidity occurred at expected rates for each operation. Pancreatic fistula and delayed gastric emptying were the most prevalent complications, but these were managed by conservative measures in all of the cases. There were no perioperative deaths in our series, and postoperative morbidity was acceptable.

All of the deaths in this series occurred in patients with malignant neuroendocrine carcinomas. The 5-year actuarial survival for neuroendocrine carcinomas was 77%. This is an improvement over the 36% to 50% 5-year survival rates reported in other series. The reasons for this improvement are obscure but are likely multifactorial. Possibilities include more effective adjuvant therapy, more aggressive management including occasional resection of distant metastatic disease, and the inclusion of 10 patients with microscopic vascular invasion in the cancer group who had no metastatic disease (see earlier discussion). Past descriptions of patients with resected neuroendocrine tumors have suggested that positive resection margins and the presence of liver metastases are predictors of postoperative survival. Although we found

<p>| Table 4. Pathological Factors and Survival in Neuroendocrine Carcinoma in 37 Patients |
|----------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients, No. (%)</th>
<th>Mean Survival, mo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3 (8.1)</td>
<td>112</td>
<td>.78</td>
</tr>
<tr>
<td>Negative</td>
<td>34 (91.9)</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>21 (56.8)</td>
<td>120</td>
<td>.85</td>
</tr>
<tr>
<td>Negative</td>
<td>16 (43.2)</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6 (16.2)</td>
<td>137</td>
<td>.34</td>
</tr>
<tr>
<td>Absent</td>
<td>31 (83.8)</td>
<td>112</td>
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</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>20 (54.1)</td>
<td>59</td>
<td>.06</td>
</tr>
<tr>
<td>Absent</td>
<td>17 (45.9)</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Liver metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>9 (24.3)</td>
<td>153</td>
<td>.11</td>
</tr>
<tr>
<td>Absent</td>
<td>28 (75.7)</td>
<td>109</td>
<td></td>
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</tbody>
</table>

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REFERENCES


DISCUSSION

Jeffrey A. Norton, MD, Stanford, Calif: As you mentioned, pancreatic neuroendocrine tumors are very rare. The incidence is only about 1 per million in the population. This retrospective review from UCLA [University of California, Los Angeles] focuses primarily on the malignant nature of these tumors and the results of surgery for them. It is a relatively large experience, as 70 patients were identified. The 5-year survival of patients with malignant neuroendocrine pancreatic tumors was 77%, which is significantly higher than most other series.

This series identified significant factors that affected survival. These were tumor size (tumors > 5 cm were more likely to decrease survival), the presence of lymphovascular invasion noted on pathologic analysis, which has not really been described by others, and the presence of lymph node and liver metastases, which actually did not affect survival. Most prior studies have demonstrated that lymph node metastases for pancreatic neuroendocrine tumors have not decreased survival, but nearly every study that I know of has shown that liver metastases are the key step in survival for patients with malignant neuroendocrine tumors.

I have 3 specific questions for the authors. First, other than metastases, there are few clear indications of malignancy for pancreatic neuroendocrine tumors. (1) How did you clearly identify malignant tumors? (2) Did you have any small tumors, say for example, less than 3 cm, that were malignant? The complication rate for proximal pancreaticoduodenectomy was nearly 50%, which was significantly higher than for distal pancreatectomy and tumor enucleation. Is this rate higher than expected? For example, would this be higher than seen in patients with malignant adenocarcinoma of the pancreas? If so, why? (3) We have previously reported the value of aggressive surgery for liver metastases combined with concomitant pancreatic surgery for neuroendocrine tumors. What type of pancreatic surgery was performed in the 9 patients with liver resections, and was all tumor able to be removed in each case? Do you feel that it is necessary to remove all tumor before undertaking aggressive surgery for the primary tumor and liver metastases?

Bruce E. Stabile, MD, Torrance, Calif: This is an interesting series, and it does point out some differences with some of the other series, as Dr Norton has alluded to. Most principally, the seemingly benign nature of liver metastasis is probably a function of duration of follow-up. Virtually all other series show that the one high-quality predictor of mortality from the disease is liver metastases, and I noted that all of the patients who ultimately died in this series were patients with neuroendocrine carcinomas. I would assume that at least some of those had liver metastases. Do the authors confirm or repudiate the notion that liver metastasis is the modus of exit for these patients with neuroendocrine carcinomas?

The other observation I would make is that MEN [multiple endocrine neoplasia] syndrome was not mentioned in the presentation. I wonder how many MEN patients there were in this series and how the authors managed those patients with multiple pancreatic tumors as compared to sporadic cases in which tumors tend to be single. Would the authors comment on that? Lastly, regarding the functional tumors and their tumor markers, were there hormone levels present in the serum that could be used for follow-up of these patients and for determination of recurrence? This is more problematic in the nonfunctional.
tumors, and I wonder what tumor markers, if any, were found to be useful by the authors. Specifically, did they use chromogranin A or pancreatic polypeptide or others, and were octreotide scans useful in the follow-up of patients with suspected recurrence?

Quan-Yang Duh, MD, San Francisco, Calif: I have questions specifically about the nonmalignant, well-localized, solitary tumors. In many centers, insulinomas are resected laparoscopically. You mentioned 4 distal pancreatectomies that were done laparoscopically. I wonder about the enucleated cases. How many of these were done laparoscopically? How do you choose your patients within the group of neuroendocrine tumors for minimally invasive operations? What would be your criteria for having laparoscopic operations for insulinoma, for example?

A. Brent Eastman, MD, Rancho Santa Fe, Calif: My question is that you didn’t specifically reference the diagnosis and management of diffuse hyperplasia. In your pancreaticoduodenectomy cohort, did you include patients with diffuse islet cell hyperplasia?

Sean J. Mulvihill, MD, Salt Lake City, Utah: We don’t understand the natural history of these tumors very well. And, it’s evident that we are seeing an increasing number of incidentally identified small lesions in the pancreas through the use of CT [computed tomographic] scans for other reasons, both cystic lesions and occasionally hypervascular lesions. So, based on the information that you have from your survival data in this series, what would you advise when a patient is identified with a small, 1.5-cm, asymptomatic, hypervascular mass in the pancreas?

Dr Hines: This is a very heterogeneous mix of patients, and that unfortunately is the nature of this disease. But, this is an attempt to try and understand more about the natural history as was mentioned. We define malignant neuroendocrine tumors as those that exhibit lymphovascular invasion, nodal disease, or liver metastasis.

Dr Norton asked about the morbidity of the Whipple procedure and if these numbers were higher than what would be expected for patients who had adenocarcinoma and were undergoing a pancreaticoduodenectomy. Actually, the numbers are very consistent. If you look at the history of pancreaticoduodenectomy in the United States and in Europe, we have made big strides in the mortality rates, but we really haven’t significantly affected the morbidity rates. Patients are dying of the complications of the operation, but we still have fairly high morbidity rates in the 40- to 50-percentile range. Most large series report similar numbers to that.

With regard to the patients that had liver metastases, we actually had 4 patients who had liver metastases. Two of these patients had a distal pancreatectomy, and 2 of them have had a Whipple procedure. All of the patients with a positive margin had liver metastases—we had 3 patients who had a positive margin. One patient with a Whipple procedure had a retroperitoneal positive margin, and 2 of the distal pancreatectomies had a positive retroperitoneal margin.

We had 4 patients who underwent a liver resection: 2 lobectomies, 1 lateral segmentectomy, and 1 patient who had a wedge resection. One of those patients had a combined procedure at the same operation. The other 3 had subsequent operations.

With regards to the management of these, I do think that the patients need to have, as Dr Norton has written about, aggressive management of liver disease and local disease, and because it is a different entity than pancreatic adenocarcinoma, we are more aggressive with these in the operating room. For instance, in the patient who has pancreatic adenocarcinoma, we might not resect someone who has invasion of the transverse mesocolon, but in a patient with a neuroendocrine tumor, since these patients do so much better with resection, we are more aggressive.

Dr Stabile asked about liver metastases and whether or not this was the cause of their death. As we said, we only had 4 patients with liver metastases, and we really don’t have information as to the ultimate cause of the patient’s death because we got the death data from the social security data.

We have no information about the functional tumors with regards to the patients who had multiple neuroendocrine neoplasia. With regards to the functional tumors and using the hormones that they produce as tumor markers, none of those patients, like was stated, have died from their disease, and they have gone back to their primary care doctors for management and surveillance so we don’t have information about that, but obviously those are ways to predict recurrence, but none of them have died in this series.

The use of chromogranin A: we have used this over the past couple of years. All of the nonfunctioning tumors were confirmed as neuroendocrine tumors by staining with chromogranin A over the last 3 to 4 years by the pathology service.

Dr Duh had several questions about the nonmalignant functional tumors and the patients who underwent distal pancreatectomy laparoscopically and what criteria we used to try to determine whether or not it is appropriate to address these laparoscopically. None of the patients who have had an enucleation had a laparoscopic approach. The 1 insulinoma that was resected laparoscopically was performed by a splenic-preserving distal pancreatectomy with a laparoscope. The criteria that we would use for a laparoscopic approach are those that are typically cystic lesions that appear simple or small, or, like I stated earlier, hypervascular lesions seen on CT scan. If this is a functional tumor and is a small lesion, we would consider the possibility of performing a laparoscopic operation.

Really, the entire question about laparoscopic surgery and pancreatic surgery is yet to be answered. Like colon cancer, we need randomized trials to answer what the appropriate criteria are.

Dr Eastman asked about patients who have diffuse disease. We have had 1 patient who had multiple insulinomas, and that patient has done well and is alive.

Dr Mulvihill had a question about the natural history and asked specifically if we had a patient who had had a CAT [computed axial tomographic] scan with a small, 1-cm, hypervascular tumor. We think that needs to come out. This is a different question than a patient who has a cystic lesion of the pancreas. The evaluation of that would really be based upon not only CT imaging, but we almost always use EUS [endoscopic ultrasonography] and aspiration of a cystic lesion to evaluate for tumor markers.

Just a note on the natural history of this disease—we have 1 patient who has had a neuroendocrine carcinoma who is now 10 years out from having disease both in the liver and the lung resected. So, these patients can have long survivals, even though they have liver and lung disease. We think, like Dr Norton thinks, that these patients should be managed very aggressively because they can expect improved survival over what traditionally was poor survival for other pancreatic neoplasms.