Journal of Surgical Oncology 2007;96:397–403

Surgery in Malignant Pancreatic Neuroendocrine Tumors

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Background: Because of their rarity and indolent nature, optimal management of malignant pancreatic neuroendocrine tumors remains controversial. The purpose of this study is to review a series of patients with these tumors and investigate the role of surgery in the treatment.

Methods: A retrospective study of 73 patients (ages 24–86 years; 36 women) undergoing treatment at a tertiary academic medical center was performed. Patient demographics, diagnostic tests, operations, pathologic findings, adjuvant treatments, and survival were reviewed.

Results: Seventy-four percent of patients had advanced disease with hepatic metastases and 30% had functional tumors. Fifty-seven percent of the patients underwent pancreatic resections. Two 60-day mortalities occurred and the post-operative complication rate was 27%. Overall 5-year survival rate was 44%. There was no difference in survival between patients with functional and nonfunctional tumors. Patients undergoing resection, even in metastatic disease, had better survival than patients who had no resection (60% vs. 30%, $P = 0.025$). Recurrence occurred in 20% of patients who underwent a curative resection.

Conclusion: Patients with malignant pancreatic neuroendocrine tumors commonly present with advanced disease. Although, curative resection is not frequent, survival benefit may be obtainable with aggressive surgical management even in the face of metastatic disease.

J. Surg. Oncol. 2007;96:397–403.

KEY WORDS: **pancreas; neuroendocrine tumors; islet cell carcinoma**

INTRODUCTION

Pancreatic neuroendocrine tumors are rare, with an incidence of 0.4 per 100,000 [1]. Unlike pancreatic ductal tumors with resectability rates of less than 10%, endocrine pancreatic tumors have resectability rates as high as 65% and surgery remains the standard for cure [2]. The majority are malignant. These endocrine tumors pose numerous challenges, including difficult diagnosis with frequent nonspecific clinical symptoms, the presence of occult tumors, and the requisite for extensive operations due to bulky tumors and metastases.

Neuroendocrine pancreatic tumors can be classified as either functioning or nonfunctioning. Nonfunctional tumors form the largest group of these tumors and may produce symptoms related to their location, tumor bulk, or metastatic dissemination. Functional tumors are associated with clinical syndromes of hormonal excess and have distinctive metabolic and clinical manifestations. These tumors include insulinoma, gastrinoma, VIPoma, glucagonoma, carcinoid, somatostatinoma, pancreatic polypeptidoma, ACTHoma, and GHRHoma.

Surgery has traditionally been the mainstay of therapy for these tumors. In early disease, their indolent nature

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Received 9 May 2006; Accepted 2 March 2007
DOI 10.1002/jso.20824
Published online 27 April 2007 in Wiley InterScience (www.interscience.wiley.com).

allows a real opportunity for surgical cure. However, it is unclear if aggressive surgical resection is warranted in the management of metastatic disease. Nonoperative therapy such as systemic chemotherapy, radiotherapy, and biotherapy has demonstrated some palliation and survival benefit in select patients with advanced disease [3]. We feel aggressive surgery still remains an important therapy for patients with these tumors, even in advanced cases. This study reviews a large series of malignant pancreatic neuroendocrine tumors and evaluates the impact of surgery on survival. It is based on a high-volume practice at a tertiary referral care center. In addition, the recent literature regarding imaging and adjuvant therapy of these tumors is reviewed.

MATERIALS AND METHODS

The medical records of patients diagnosed with malignant pancreatic neuroendocrine tumors were identified within our Cancer Registry between 1989 and 1999. All patients who received medical or surgical treatment for pancreatic neuroendocrine tumors at the Mount Sinai Hospital were included. The tumors were considered malignant if metastases or tissue invasion were demonstrated at the time of diagnosis or during follow up. Patients without an apparent clinical syndrome and with normal hormonal levels were categorized as having nonfunctional neuroendocrine tumors. Records were reviewed with respect to patient demographics, clinical features, diagnostic modalities, operative details, response to treatment, and long-term survival. Pathology reports were reviewed to verify tumor histology and immunoperoxidase staining. The range of follow up for the patients was 2 months to 16 years (median: 41 months). Comparisons between treatment groups were made using Student's *t*-tests. Survival graphs were created using the Kaplan–Meier method and the logrank test was used to compare survival among the different treatment groups. Institutional review board approval was obtained for this study.

RESULTS

Demographics

Seventy-three patients were diagnosed with malignant pancreatic neuroendocrine tumors from January 1989 to January 1999. The study group included 37 men and 36 women, with a mean age of 53 (range: 24–86 years).

Patient Characteristics

Seventy percent (51/73) of the patients had nonfunctional tumors. The most common symptoms/signs in this group were abdominal pain (n = 22), followed by weight loss (n = 18), and a palpable abdominal mass (n = 9). Serum chromogranin A levels were routinely measured in the majority of patients. The 22 (30%) functioning tumors consisted of gastrinomas (n = 7), insulinomas (n = 6), VIPomas (n = 4), carcinoids (n = 2), glucagonomas (n = 2), and pancreatic polypeptidoma (n = 1). No patients had a mixed hormonal profile. One patient with a gastrinoma had multiple endocrine neoplasia type I and had undergone a parathyroidectomy in the past. No patients had multiple tumors in the pancreas. The majority of patients (74%) presented with advanced disease, as evidenced by hepatic metastases. Fifteen percent of patients presented with nodal metastases and 11% had only locally invasive disease at diagnosis.

Diagnostic Studies

The diagnostic methods used to successfully localize the tumors are shown in Figure 1. Computed tomography (CT) had the highest success rate, localizing tumors in 60 (83%) patients. Intraoperative ultrasound (US) was used to localize tumors in four patients. Other diagnostic studies included magnetic resonance imaging (MRI), octreotide scintigraphy, endoscopic retrograde cholangiopancreatography, selective celiac and mesenteric angiography, endoscopic ultrasound, and portal venous hormonal sampling.

Surgical Characteristics

Operations were performed in 57 (78%) patients (Fig. 2). Forty-two patients underwent tumor resection or debulking and 15 patients had explorations or bypass operations with no significant resection of tumor. Curative resections (R0) were successful in 20 (35%) patients. Nineteen of these patients had no liver involvement at the time of resection and one patient underwent a concomitant hepatic and pancreatic resection. For all patients, the most common operation was a distal

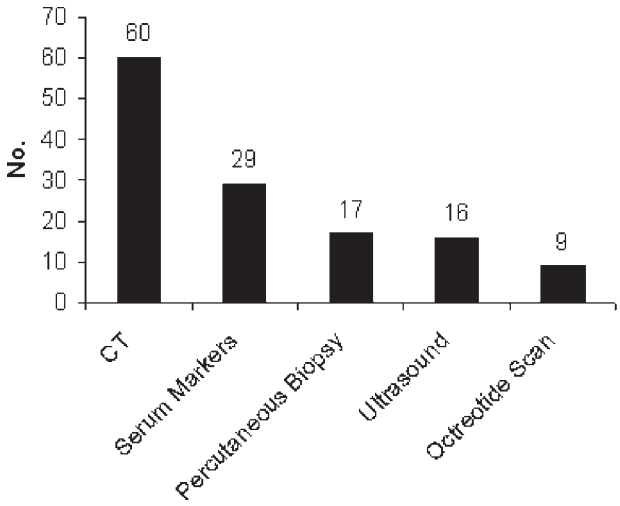

Fig. 1. Diagnostic modalities used to successfully diagnose tumors.

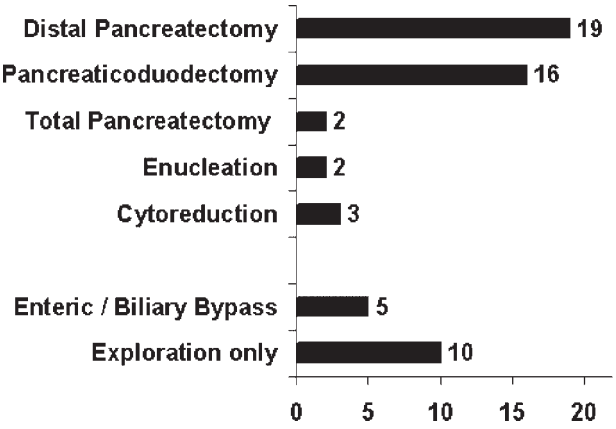

Fig. 2. Types of operations (n = 57).

pancreatectomy with splenectomy in 19 patients for tumors located in the tail of the pancreas followed by pancreaticoduodenectomy in 16 patients. Other procedures included limited resections and total pancreatectomies. Three patients underwent debulking operations with incomplete resections of tumor. Fifteen patients had unresectable tumors and underwent only explorations or bypass operations. Some patients with hepatic metastases were managed aggressively with pancreatic resections, including seven pancreaticoduodenectomies and 13 distal pancreatectomies. Two patients had hepatic lobectomies after their initial operation. Metastatic disease was managed by orthotopic liver transplant in three patients.

There were no operative mortalities. Two in-hospital deaths occurred during the second postoperative month secondary to respiratory failure and myocardial infarction. An overall complication rate of 27% was detected, the most common being pancreatic fistulas (seven), followed by delayed gastric emptying (three), and intra-abdominal abscess (two). No patient required reoperation. Patients' postoperative length of stay ranged from 1 to 55 days with a median of 8 days.

Treatments

Table I depicts the various treatment modalities. The majority of the patients underwent multimodality therapy with some combination of surgery, chemotherapy, biotherapy, radiation, and chemoembolization. The *Resection* group (n = 42) included all patients undergoing pancreatic resections and cytoreductive therapy. The *No Resection* group (n = 31) included patients who only had operative explorations, palliative biliary or enteric bypasses, or no surgery at all. A total of 55 (75%) patients underwent chemotherapy and 12 (16%) patients underwent radiation. A higher proportion of patients in the *No Resection* group underwent chemotherapy and received octreotide ($P < 0.05$, Student's *t*-test). Nineteen (26%) patients underwent hepatic artery chemoembolization for hepatic metastases. There was no significant difference between the *Resection* group and the *No Resection* group in terms of adjuvant treatment with radiation, chemoembolization, or interferon ($P > 0.05$, Student's *t*-test).

Survival

The overall actuarial survival rates at 5 and 10 years among the 73 patients with malignant pancreatic neuroendocrine tumors was 44% and 24%, with a median survival of 48 months (Fig. 3). There was no difference in survival when comparing patients with functional versus nonfunctional tumors (45% 5-year survival, both groups). Figure 4 demonstrates The *Resection* group had better 5-year survival than the *No Resection* group (55% versus 30%, $P = 0.01$). To minimize treatment selection bias, we recalculated survival after removing patients with early stage disease (local invasion or nodal metastases) from the *Resection* group. In the remaining patients, all with hepatic metastases, the 5-year survival was 60% in the *Resection* group and 30% in the *No Resection* group ($P = 0.025$) (Fig. 5).

In the 20 patients who underwent a curative resection, the actuarial 5-year survival was 46%. Four (20%) of these patients had recurrences, all within the liver. All underwent additional therapy with systemic chemotherapy or hepatic artery chemoembolization. Two patients had hepatic resections for their recurrences. Three were still alive at the time of the study at 70, 142, and 221 months, including the patients who had lobectomies.

TABLE I. Various Treatment Modalities

	Surgical resection[a] (%)	No surgical resection[b] (%)
Chemotherapy	27 (64)	27 (87)[c]
Radiation	7 (17)	5 (16)
Chemoembolization	12 (29)	7 (23)
Octreotide	3 (7)	8 (26)[c]
Interferon	5 (12)	2 (6)
Total	42	31

[a]Patients undergoing complete resections and debulking operations.
[b]Patients undergoing diagnostic exploration, palliative bypass, or no surgery at all.
[c]Statistically significant difference in comparison to *Surgical Resection* group ($P < 0.05$).

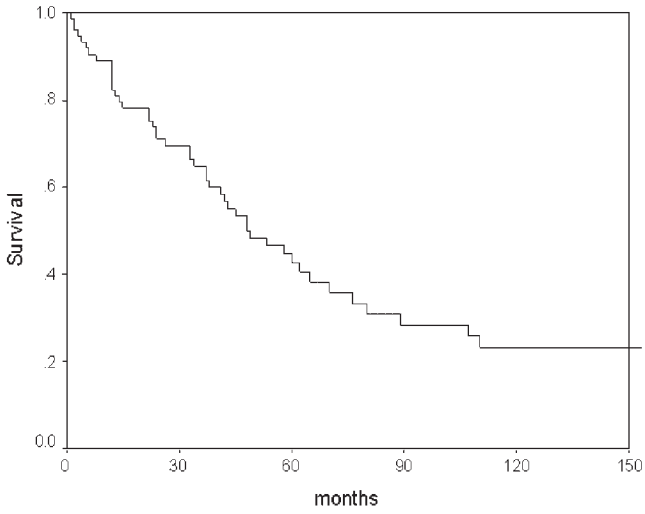

Fig. 3. Actuarial survival curve for entire cohort (n = 73). Five year survival: 44%; 10 year survival: 24%; median 48 months.

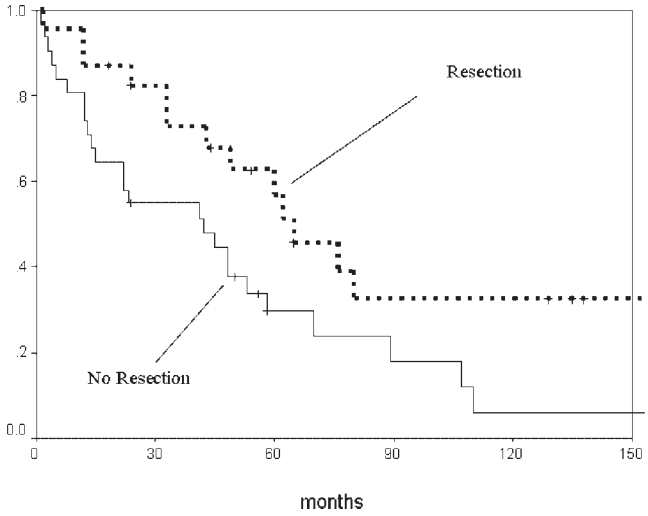

Fig. 5. Actuarial survival curves in patients with hepatic metastases. *Resection* and *No Resection* groups—5-year survival: 60% and 30%, respectively ($P = 0.025$).

Fifty-three (73%) of the patients had hepatic metastases at initial presentation. Twenty-two (42%) of these patients underwent resection or debulking therapy and the remaining had palliative bypasses, simple explorations, or no surgical therapy at all. Ninety-one percent of these patients underwent chemotherapy and some had radiation and chemoembolization. The 5-year survival for this group with hepatic metastases was 44%.

DISCUSSION

Despite advances in the diagnosis and pharmacological treatment of pancreatic neuroendocrine tumors, their management continues to pose a challenge and cure remains rare. In this retrospective review, 70% of patients had nonfunctional tumors and 74% had hepatic metastases. The atypical manifestations of these rare tumors cause a considerable diagnostic delay, accounting for the late stage which the majority of the patients were first evaluated. Due to their indolent nature, these tumors were usually amenable to resection. Surgery remains the most important therapeutic approach to these rare tumors and the low mortality and morbidity in our series indicate it can be performed safely. However, we must underscore the importance of seeking high-volume centers with surgical experience for optimal outcome.

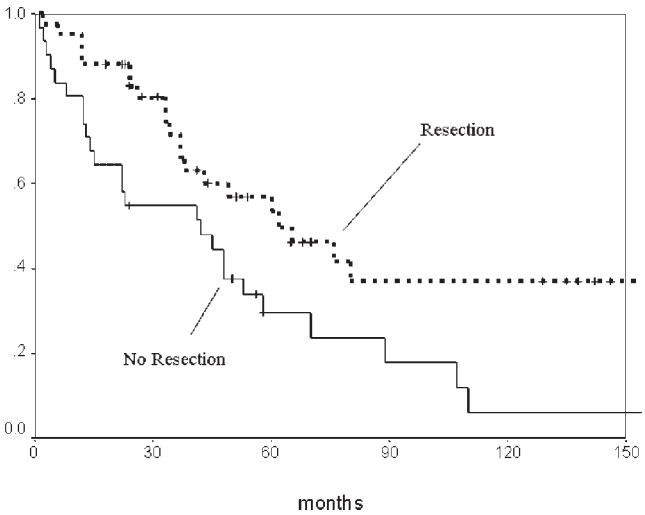

Fig. 4. Actuarial survival curves of *Resection* and *No Resection* groups. Five year survival: 55% and 30%, respectively ($P = 0.01$).

Our overall 5-year survival rate for all patients was 44%, with no difference between nonfunctional and functional tumors. This is comparable to others' large series [4–6]. These tumors fare better than ductal carcinoma, which average 5-year survival rates of 5–10%. A survival benefit was seen in patients who underwent any sort of resection versus the patients not undergoing any resection at all. In part, this may be attributed to the higher proportion of gastrinomas in the *Resection* group (5/7 gastrinomas were in the *Resection* group). Certainly, a treatment bias also exists as the *Resection* group includes the patients with the earliest stage tumors. Therefore, we reanalyzed our data with exclusion of the patients with early disease, without distant metastases. In these patients, all with advanced disease as evidenced by hepatic metastases, there was still a survival benefit found in the *Resection* group. In those resected, patients with hepatic metastases had better 5-year survival than patients without metastases (60% vs. 30%, $P = 0.025$). Although, selection bias likely plays a large role in the improved outcome of the *Resection* group, these results suggest patients with

advanced disease may still benefit from surgical resection. This is consistent with others' large series that demonstrate survival benefit from aggressive surgery [5–8]. We can conclude that these slow growing tumors do not preclude long-term survival, and surgical resection may be beneficial, even when metastases are present.

Patients with malignant pancreatic neuroendocrine tumors commonly develop recurrences. The recurrence rate after curative resection in this series was 20%. These patients were managed with additional systemic chemotherapy, chemoembolization, or hepatic resection. Three of the four patients with recurrences survived more than 5 years and were still alive at the time of this study, suggesting the possibility of long-term survival even after recurrence. Nevertheless, these patients require long-term surveillance for clinical signs of hormone excess with appropriate endocrine tests and follow up imaging. In our series, patients undergoing curative resection did not fare better than those who had incomplete or no resections. Although the number of curative resections in our series is small, this may suggest that debulking is just as important as curative resection in the management of these tumors.

In this series, only one patient underwent a concomitant hepatic resection and two others underwent liver resection at a later time. Most of the patients had advanced liver metastases and were not candidates for resection. These were treated with transplantation, hepatic artery chemoembolization, or medical therapy. Aggressive hepatic resection of metastases has been shown to be safe, achieve symptom control, and improve survival [9,10]. In addition, retrospective analyses of liver transplants have shown benefit with regard to symptomatic relief and long-term survival in selected patients. Furthermore, the role of multivisceral transplantation is evolving for neuroendocrine tumors [11]. Cryosurgery and radiofrequency ablation have been described for control of metastatic disease, although none of our patients underwent these treatment modalities [12,13].

Tertiary centers can provide the resources and expertize necessary for the evaluation and treatment of these complicated tumors. Biphasic CT is usually the initial imaging technique for detection, however magnetic resonance has been found to be similarly as effective [14]. Somatostatin scintigraphy successfully identified tumors in only 12% of the patients in our study. Likely, this was because the majority of our subjects were diagnosed in the earlier half of the 1990s, before this modality became popular. This technique is superior to conventional imaging methods (CT and US) in detecting primary lesions and hepatic metastases and is rapidly developing into the initial imaging modality of choice [15]. Endoscopic ultrasound is also becoming a primary diagnostic modality with reported localization sensitivity of 93% and specificity of 95% [16]. In our series, we also used US to detect small intraparenchymal lesions of the pancreas and liver in four patients. Most useful for insulinomas, US is almost always successful when combined with palpation [17]. Laparoscopic ultrasound is a newer imaging method, often used in laparoscopic resections of insulinomas [18]. Currently, positron-emission tomography (PET) using 11C-labeled L-dihydroxyphenylalanine (11C-L-dopa) and 11C-labeled 5-hydroxy-L-tryptophan (11C-5-HTP) is used to detect pancreatic endocrine tumors with reports of superior detection rates compared to CT or somatostatin scintigraphy [19,20]. Furthermore, PET scans are useful for following tumor progression response to therapies.

If patients were considered unresectable or high surgical risk, medical treatment was initiated for symptomatic relief. Pharmacotherapy with somatostatin analogs and interferon alfa is critical to the treatment and palliation of advanced cases of pancreatic neuroendocrine tumors. These drugs may enable patients to live for many years. Seven (10%) patients in this study received treatment with octreotide. Somatostatin analogs can control the clinical symptoms associated with hormonal hypersecretion and may also have some anti-proliferative actions [21]. Interferon alfa arrests tumor cells in the S phase of the cell cycle preventing tumor growth and secretion. Symptomatic responses are seen in 50% of patients, with significant tumor reduction in 10–15% [22]. The antiproliferative effects of these two therapies may be enhanced when used in combination. In our review, seven (10%) patients received interferon therapy with favorable results.

A high proportion (75%) of the patients in this study was treated with chemotherapy. Streptozocin based therapy, in combination with doxorubicin or 5-fluorouracil, have been the standard chemotherapeutic regimens for the treatment of pancreatic neuroendocrine tumors. A randomized controlled trial has demonstrated a superior response rate and a survival advantage of the streptozocin/doxorubicin combination, leading to its use as the front-line chemotherapy regimen [23]. Newer chemotherapeutic strategies warrant further investigation. In patients with hepatic-dominant disease, hepatic resection has been shown to provide effective palliation and prolong survival in selected patients [9,10]. Alternatively, hepatic arterial embolization or intraarterial injection of chemotherapy (chemoembolization) has been shown to provide significant symptomatic benefit, decrease tumor volume, and reduce hormonal markers [24]. At present, early evidence suggests that chemoembolization may prolong survival [25]. In this study, 19 (26%) of patients received chemoembolization and experienced some effective palliation. Neuroendocrine tumors were traditionally thought to be resistant to

radiotherapy. However, some reports suggest radiation may have a role in locally advanced resectable disease and metastatic disease [26]. Thirteen (18%) of our patients received radiation. Recently, radioactively labeled agents have been used to specifically target tumor cells. Treatment with ^{131}I labeled metaiodobenzylguanidine (^{131}I-MIBG) has achieved symptomatic, hormonal, and tumor response [27]. ^{90}Yttrium and ^{177}Lutetium labeled somatostatin analogs are also being investigated in phase I–II trials [28].

The limitations of this study center on its retrospective nature. A treatment selection bias undoubtedly exists, despite attempts to minimize it by reanalyzing the data to exclude patients with early disease. In addition, power calculations suggest that at least 800 total patients are needed to truly find a 20% survival difference between the two treatment groups (Power = 80%, $P = 0.05$). Nevertheless, the rarity of this tumor precludes prospective controlled trials comparing therapies. Therefore, we must depend on large retrospective studies, such as this, to assist in determining the optimal treatment for patients with these tumors. Another fault of this study lies in regard to adjuvant therapy. The treatment of these tumors follows a multimodality approach, and this study simply investigates the role of surgical resection on survival. The two treatment groups, *Resection* and *No Resection*, are comprised of patients who also underwent various other adjuvant therapies. The *No Resection* group had significantly more patients undergoing chemotherapy and octreotide than the surgical group, but still had poorer survival. This suggests surgery as a key element of therapy and these other modalities as less effective in terms of survival.

CONCLUSION

This review describes one of the largest series of malignant pancreatic neuroendocrine tumors reported in recent years. Long-term survival in these patients is possible given the indolent nature of these tumors, and the surgical and medical therapies available. It is advisable that patients seek care at tertiary centers with experienced multidisciplinary teams. This series demonstrates that these tumors can often be approached surgically with minimal perioperative mortality and acceptable morbidity. Despite low rates of curative resection, surgical therapy is an important component in the multimodality therapy contributing to improved survival. In advanced disease, surgical control with primary resection and management of hepatic metastases may contribute to long-term survival and palliation.

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