PAPER

Morbidity and Mortality of Aggressive Resection in Patients With Advanced Neuroendocrine Tumors

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Background: There is considerable controversy about the treatment of patients with malignant advanced neuroendocrine tumors of the pancreas and duodenum. Aggressive surgery remains a potentially efficacious antitumor therapy but is rarely performed because of its possible morbidity and mortality.

Hypothesis: Aggressive resection of advanced neuroendocrine tumors can be performed with acceptable morbidity and mortality rates and may lead to extended survival.

Design: The medical records of patients with advanced neuroendocrine tumors who underwent surgery between 1997 and 2002 by a single surgeon at the University of California, San Francisco, were reviewed in an institutional review board–approved protocol.

Main Outcome Measures: Surgical procedure, pathologic characteristics, complications, mortality rates, and disease-free and overall survival rates were recorded. Disease-free survival was defined as no tumor identified on radiological imaging studies and no detectable abnormal hormone levels. Proportions were compared statistically using the Fisher exact test. Kaplan-Meier curves were used to estimate survival rates.

Results: Twenty patients were identified (11 men and 9 women). Of these, 10 (50%) had gastrinoma, 1 had insulinoma, and the remainder had nonfunctional tumors; 2 had multiple endocrine neoplasia type 1, and 1 had von Hippel-Lindau disease. The mean age was 55 years (range, 34-72 years). In 10 patients (50%), tumors were thought to be unresectable according to radiological imaging studies because of multiple bilobar liver metastases (n=6), superior mesenteric vein invasion (n=3), and extensive nodal metastases (n=1). Tumors were completely removed in 15 patients (75%). Surgical procedures included 8 proximal pancreatectomies (pancreatoduodenectomy or whipple procedure), 3 total pancreatectomies, 9 distal pancreatectomies, and 3 tumor enucleations from the pancreatic head. Superior mesenteric vein reconstruction was done in 3 patients. Liver resections were done in 6 patients, and an extended periaortic node dissection was performed in 1. The spleen was removed in 11 patients, and the left kidney was removed as a result of tumor metastases in 2. Eighteen patients had primary pancreatic tumors, and 2 had duodenal tumors; 2 patients with multiple endocrine neoplasia type 1 had both pancreatic and duodenal tumors. The mean tumor size was 8 cm (range, 0.5-23 cm). Of the patients, 14 (70%) had lymph node metastases and 8 (40%) had liver metastases. The mean postoperative hospital stay was 11.5 days (range, 6-26 days). Six patients (30%) had postoperative complications. There was a significantly greater incidence of pancreatic fistulas with enucleations compared with resections ($P=.04$). There were no operative deaths. The mean follow-up period was 19 months (range, 1-96 months); 18 patients (90%) are alive, 2 died of progressive tumor, and 12 (60%) are disease-free. The actuarial overall survival rate is 80% at 5 years, and disease-free survival rates indicate that all tumors will recur by the 7-year follow-up visit.

Conclusions: Aggressive surgery including pancreatectomy, splenectomy, superior mesenteric vein reconstruction, and liver resection can be done with acceptable morbidity and low mortality rates for patients with advanced neuroendocrine tumors. Although survival rates following surgery are excellent, most patients will develop a recurrent tumor. These findings suggest that conventional contraindications to surgical resection, such as superior mesenteric vein invasion and nodal or distant metastases, should be reconsidered in patients with advanced neuroendocrine tumors.

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THE TREATMENT of patients with advanced neuroendocrine tumors of the pancreas and duodenum has caused considerable controversy[1-4] for many reasons. First, these tumors are rare, with an incidence of approximately 1 to 2 per million people; therefore, no single investigator or surgeon will have a large amount of experience with them, and prospective randomized studies are not possible.[5] Second, the pathologic characteristics of these tumors are confusing; pathologists often cannot be certain whether an individual neuroendocrine tumor is benign or malignant, primary or metastatic, or multifocal or unifocal, nor can they always determine the

subtype of tumor based on immunohistochemistry (insulinoma, gastrinoma, somatostatinoma, or glucagonoma).[6] Third, the natural history of these tumors is indolent, so patients may live for years with untreated metastatic disease.[7] Fourth, 2 distinct life-threatening issues with these tumors require effective treatment: excessive hormonal secretion and the malignant tumoral process.[4] For example, in patients with malignant gastrinoma or insulinoma, life-threatening symptoms occur as a result of excessive uncontrolled hormone secretion and dissemination of metastases. Treatment strategies must be designed to meet both problems; the acid hypersecretion and hypoglycemia must be managed, and the tumor metastases and invasion must be controlled. Fifth, neuroendocrine tumors of the pancreas occur both sporadically (noninherited form) and in families (inherited), and the disease process may be very different in the 2 forms.[8] For example, patients who develop Zollinger-Ellison syndrome (ZES) in the sporadic form have a 40% long-term cure rate with surgery, whereas those who develop the same disease in the setting of multiple endocrine neoplasia type 1 (MEN 1) have a 0% long-term cure rate. Thus, treatment of the same tumor may be different in sporadic vs familial forms. Furthermore, some physicians argue that surgery is not indicated even for patients with sporadic ZES because treatment of the acid secretion with proton pump inhibitors is outstanding and the surgical cure rate is low.[3,9] Finally, most patients with nonfunctional neuroendocrine tumors initially develop either locally advanced or metastatic tumors, resulting in a more difficult surgical procedure and higher morbidity rate.[4]

The role of cytoreductive surgery remains controversial,[1-3] with some physicians arguing that attempted surgical resection is not indicated in patients with advanced tumor burdens but that instead it should be reserved for those who have nonmetastasizing disease with a single lesion.[3] These reservations are due in part to the high projected morbidity and mortality rates of such procedures. However, it has recently been shown that complex surgical procedures such as pancreatoduodenectomy (Whipple procedure) can be performed safely in high-volume university centers.[10,11] Surgery is the only potentially curative treatment for these tumors because chemotherapy and radiation therapy have not demonstrated significant antitumor effects.[4,7] Furthermore, if all of the tumor can be removed with extensive surgery, the duration and quality of life may be greatly enhanced.[4,7]

In our experience, aggressive surgery to remove locally advanced and metastatic neuroendocrine tumors can improve the duration and quality of life.[12,13] Therefore, we advocate technically advanced surgical procedures to try to remove all of the tumor even if it involves significant structures such as the superior mesenteric vein, portal vein, liver, and kidney. Resection of tumors at distant sites and pancreatic resection have been combined in an attempt to remove all gross tumors. In this study, we analyze our results in 20 consecutive patients with locally advanced, recurrent, or metastatic neuroendocrine tumors of the pancreas and duodenum to determine the results of surgery. Our hypothesis is that this type of aggressive surgery can be performed with acceptable morbidity and mortality rates and may lead to extended survival.

METHODS

Between 1997 and 2002 at the University of California, San Francisco, the results of surgery by a single surgeon (J.A.N.) in patients with locally advanced and/or metastatic duodenal or pancreatic neuroendocrine tumors were reviewed according to an institutional review board–approved protocol. Superior mesenteric vein reconstruction was done by vascular surgery (T.C. and D.S.).

Patients' medical records were reviewed to identify pancreatic or duodenal neuroendocrine tumors with direct invasion, local recurrence, or lymph node and distant (liver and other organs) metastases. The diagnosis of ZES was based on studies of acid secretion, measurement of fasting serum levels of gastrin, and results of secretin and calcium stimulation tests.[14] The diagnosis of insulinoma was based on a diagnostic fast during which fasting serum levels of glucose and insulin were determined at the time of neuroglycopenic symptoms. Serum levels of proinsulin and C-peptide were also measured.[15] The diagnosis of MEN 1 was based on standard criteria that have been described elsewhere.[8] Similarly, the diagnosis of von Hippel-Lindau disease has been described previously.[16]

The localization and extent of duodenal and pancreatic neuroendocrine tumors were determined using high-resolution spiral computed tomography (CT) of the abdomen with a pancreas and liver protocol.[17] Somatostatin receptor scintigraphy was performed as described previously.[18]

At exploration, an extensive search was performed for neuroendocrine tumors. The gastrocolic ligament was divided to expose the lesser sac. The body and tail of the pancreas were dissected by incising along the inferior border of the pancreas. The right colon was completely mobilized, and a Kocher maneuver was performed to assess the duodenum and head of the pancreas. The ligaments of the liver were divided, and the liver was also mobilized. Palpation of organs and intraoperative ultrasonography were performed on all patients using a high-resolution 5- to 7.5-MHz transducer. For patients with ZES, we performed a 3-cm-long duodenotomy centered on the anterolateral surface of the second portion of the duodenum to identify duodenal tumors. Solitary tumors in the pancreatic head and duodenum were enucleated. Multiple or large (>3 cm) tumors in the pancreatic head and duodenum or those associated with bulky lymph node metastases were treated with pancreatoduodenectomy if the patient gave informed consent. Distal or subtotal pancreatectomy with splenectomy was performed for large tumors in the body and tail of the pancreas. Total pancreatectomy with splenectomy was performed for tumors in the body of the pancreas that extended into the pancreatic head near the common bile duct. Adjacent lymph nodes were removed along with resection specimens. If enucleation of the tumor was performed, detailed inspection and removal of peripancreatic, periduodenal, and hepatic portal lymph nodes were carried out. If the superior mesenteric or portal vein was invaded with a tumor, it was resected along with the specimen and reconstructed with autologous vein, usually the common femoral vein. If liver metastases were present, the extent of the tumor was better delineated with intraoperative ultrasonography, and the liver tumors were treated with resection with a 1-cm margin. Either wedge resection of the liver or hepatic lobectomy was performed based on the location of the tumor. Small tumors deep within the liver were treated with radiofrequency ablation guided by intraoperative ultrasonography. Two patients had tumors that metastasized to the left kidney and underwent radical nephrectomy after CT determined the function of the contralateral kidney.

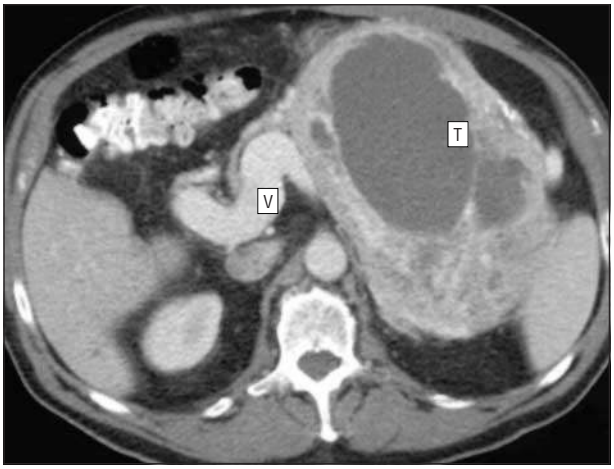

Figure 1. Large neuroendocrine tumor (T) in the tail of the pancreas. The tumor was palpable on physical examination and is obstructing the splenic vein at the junction of the superior mesenteric vein (V). It was completely resected using subtotal pancreatectomy with splenectomy.

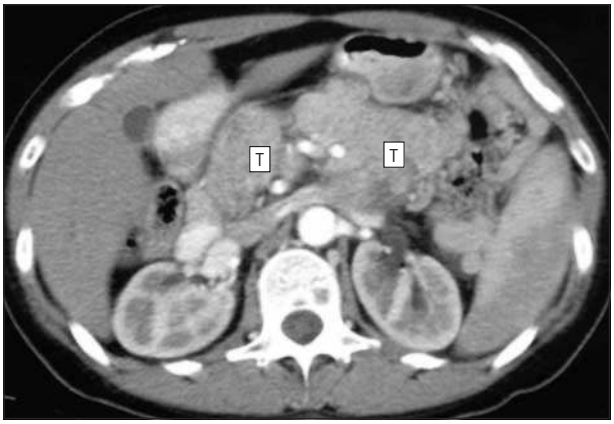

Figure 2. Large neuroendocrine tumor (T) of the entire pancreas. It is abutting the left renal vein and is surrounding the splenic artery and the superior mesenteric artery. It was completely resected using total pancreatectomy with splenectomy.

The main outcome measures were surgical procedure, pathologic characteristics, complications, operative mortality rates, and disease-free and overall survival rates. Disease-free survival was defined as no detectable tumor on postoperative radiological imaging studies and no hormonal evidence of a recurrent or persistent tumor. For nonfunctional neuroendocrine tumors, serum levels of pancreatic polypeptide or chromogranin A were used as the hormonal marker of recurrence. The actuarial probabilities of survival were calculated and plotted according to the Kaplan-Meier method.[19] Proportions were compared statistically with the Fisher exact test.[20]

RESULTS

Twenty patients were identified who had locally advanced (**Figure 1** and **Figure 2**), locally recurrent, or distant metastatic neuroendocrine tumors of the pancreas and duodenum. There were 11 men and 9 women, and the mean age was 55 years (range, 34-72 years). Ten patients (50%) had ZES, and 2 patients (10%) had both ZES and MEN 1. Nine (45%) apparently had nonfunctional neuroendocrine tumors. One patient had von Hippel-Lindau disease, and 1 had a malignant insulinoma (**Table 1**).

Table 1. Demographics of 20 Patients With Malignant Neuroendocrine Tumors*

Characteristic	
Male	11 (55)
Age, mean (range), y	55 (34-72)
MEN 1	2 (10)
VHL	1 (5)
ZES	10 (50)
Insulinoma	1 (5)
Nonfunctional tumors	9 (45)

Abbreviations: MEN 1, multiple endocrine neoplasia type 1; VHL, von Hippel-Lindau disease; ZES, Zollinger-Ellison syndrome.
*Data are presented as number (percentage) of patients unless otherwise indicated.

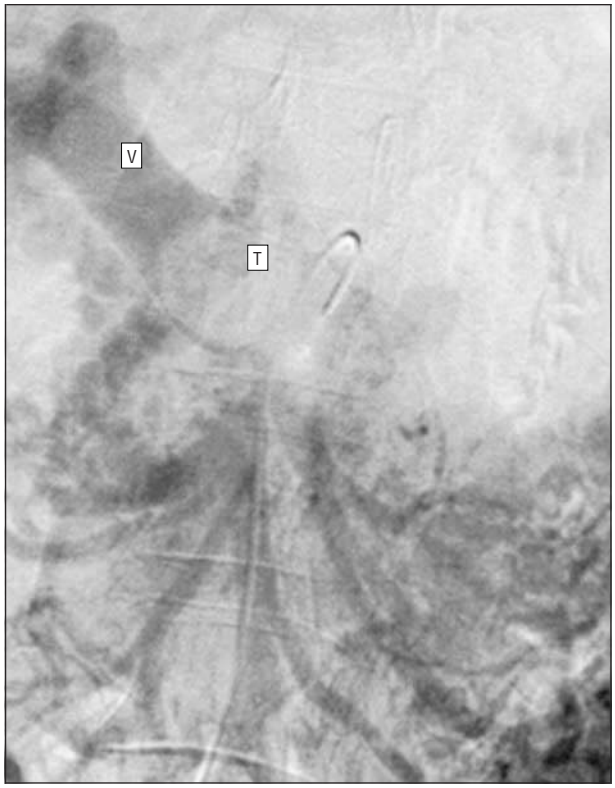

Figure 3. Venous phase of an arteriogram demonstrating a tumor (T) invading the proximal portal vein (V). This tumor was completely resected using total pancreatectomy with reconstruction of the superior mesenteric vein.

The location of the primary or metastatic neuroendocrine tumor was correctly identified in all patients using CT. In patients with ZES, somatostatin receptor scintigraphy accurately identified the extent of the tumor. However, CT suggested that the tumor was not resectable in 10 patients (50%) because of bilobar liver metastases in 6, superior mesenteric vein invasion in 3 (**Figure 3** and **Figure 4**), and extensive retroperitoneal nodal metastases in 1 (**Table 2**). All gross identifiable tumors were removed in 15 patients (75%). In cases in which the tumor was not completely resected, the liver was the only site of residual disease.

Surgical procedures included pancreatoduodenectomy in 8 patients (40%), distal pancreatectomy and sple-

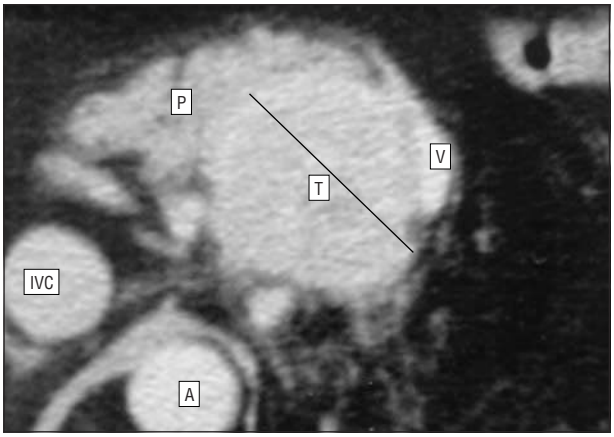

Figure 4. Recurrent gastrinoma (T) in the head of the pancreas (P) following previous distal pancreatectomy with splenectomy. The aorta (A) and inferior vena cava (IVC) are also shown. The tumor is invading the superior mesenteric vein (V) at the proximal portal vein. Because the patient was concerned about developing diabetes, this tumor was enucleated with reconstruction of the portal vein. The patient developed a complication from a pancreatic fistula that eventually healed.

Table 2. Preoperative Radiological Assessment of Tumor Resectability for Malignant Neuroendocrine Tumors*

Characteristic	No. (%)
Resectable	10 (50)
Unresectable	10 (50)
Bilobar liver metastases	6 (30)
Superior mesenteric vein invasion	3 (15)
Extensive retroperitoneal nodal metastases	1 (5)
All gross tumor removed	15 (75)
Tumor debulked	5 (25)

*N = 20.

nectomy in 9 (45%), and total pancreatectomy and splenectomy in 3 (15%). Three patients had enucleation of the tumor from the head of the pancreas, and each underwent distal pancreatectomy, 2 concomitantly and 1 previously. Concomitant liver resection was performed in 6 patients (30%), with radiofrequency ablation in 2 (10%). Superior mesenteric vein reconstruction was performed in 3 patients (15%). An extensive periaortic lymph node dissection including the hila of both kidneys and the iliac nodes (50 of 57 lymph nodes had tumor metastases) was performed in 1 patient (5%) with bulky retroperitoneal nodal disease. Two patients (10%) underwent left nephrectomy for parenchymal kidney metastases (**Table 3**).

Pathologic results demonstrated that 18 patients had primary pancreatic neuroendocrine tumors and 2 patients had primary duodenal tumors. The 2 patients with ZES and MEN 1 had both duodenal and pancreatic tumors. The pancreatic tumors had a mean size of 8 cm (range, 2-23 cm). The duodenal tumors had a mean size of 2 cm (range, 0.5-3.0 cm). Fourteen patients (70%) had lymph node metastases, 8 (40%) had liver metastases, and 2 (10%) had kidney metastases. The development of lymph node and liver metastases did not appear to be different based on the type of tumor. For example, gastrinomas, malignant insulinomas, and nonfunctional neuroendocrine tumors all had a similar proportion of lymph node and liver metastases (**Table 4**).

Table 3. Extent of Surgery for Malignant Neuroendocrine Tumors in 20 Patients

Procedure	No. (%)
Proximal pancreatectomy (pancreatoduodenectomy)	8 (40)
Distal pancreatectomy with splenectomy	9 (45)
Total pancreatectomy with splenectomy	3 (15)
Enucleation from pancreatic head	3 (15)*
Liver resection	6 (30)†
Radiofrequency ablation for liver metastasis	2 (10)
Superior mesenteric vein reconstruction	3 (15)
Nephrectomy	2 (10)‡
Extensive nodal dissection§	1 (5)
Transverse colectomy	2 (10)
Partial gastrectomy	1 (5)

*Two patients had distal pancreatectomies with enucleation of the tumor from the head of the pancreas.

†One patient had a subsequent second liver resection 4 years after the first.

‡Two patients had nephrectomies for metastatic neuroendocrine tumors of the kidney.

§Extensive nodal dissection means dissection of the periaortic nodes including the iliac nodes and nodes in the retroperitoneum.

The mean postoperative length of stay was 11.5 days (range, 6-26 days). Six patients (30%) had significant complications, but there were no operative deaths. Complications were divided according to pancreatic procedure. The complication rate was 25% with pancreatoduodenectomy and 13% with distal pancreatectomy; there were no complications with total pancreatectomy. In all cases, enucleation of the tumor from the pancreatic head resulted in pancreatic fistula. Enucleation was associated with a significantly greater probability of pancreatic fistula than either pancreatoduodenectomy or distal pancreatectomy ($P = .04$). Each fistula eventually healed with adequate drainage, although 1 required a pancreatic duct stent. Superior mesenteric vein reconstruction was associated with no complications, and follow-up CT demonstrated that each superior mesenteric vein graft was patent (**Table 5**). The 3 patients who underwent total pancreatectomy required insulin and digestive enzyme replacement; no other patient required these treatments. The mean follow-up period was 19 months (range, 1-96 months); 18 patients (90%) are alive, 2 (10%) have died of progressive disease, and 12 (60%) are disease-free (**Figure 5** and **Figure 6**). The actuarial plot of overall survival suggests that 80% of these patients will be alive at 5 years. Disease-free survival rates suggest that each patient will develop a recurrent tumor by approximately 7 years of follow-up (Figure 6).

COMMENT

Significant advances have been made in the treatment of functional gastrointestinal neuroendocrine tumors. Potent gastric antisecretory agents (proton-pump inhibitors or histamine type 2 blockers) effectively control long-term acid hypersecretion in gastrinomas,[3,4,9,21] and somatostatin analogues and/or interferon control the symptoms of carcinoid syndrome, vipomas, and other

Table 4. Pathologic Results of Malignant Neuroendocrine Tumors*

Group	Sample Size	Pancreatic Tumor		Duodenal Tumor		Lymph Node Metastases, No. (%)	Liver Metastases, No. (%)	Kidney Metastases, No. (%)
		No. of Patients	Mean Size, cm	No. of Patients	Mean Size, cm			
All	20	18	8	4	2	14 (70)	8 (40)	2 (10)
Gastrinoma	10	7	4	4	2	8 (80)	5 (50)	1 (10)
Nonfunctional	9	9	7	NA	NA	4 (44)	2 (22)	NA
Insulinoma	1	1	6	NA	NA	1 (100)	1 (100)	1 (100)
MEN 1	2	2	5.5	2	2.5	1 (50)	1 (50)	NA

Abbreviations: MEN 1, type 1 multiple endocrine neoplasia; NA, not applicable.
*Two patients with gastrinoma and MEN 1 had both duodenal and pancreatic primary tumors.

Table 5. Complications of Surgery for Malignant Neuroendocrine Tumors*

Group	Sample Size	Hospital Stay, Mean (Range), d	Morbidity, No. (%)	
			Pancreatic Fistula	Abscess
All	20	11.5 (6-26)	4 (20)	2 (20)
Proximal pancreatectomy	8	14.3 (8-26)	1 (13)	1 (13)
Distal pancreatectomy with splenectomy	9	10 (7-20)	1 (13)	0
Total pancreatectomy	3	9 (6-11)	0	0
Enucleation from pancreatic head	3	15 (12-19)	3 (100)†	0
Superior mesenteric vein reconstruction	3	15 (6-19)	1 (33)	0

*For all procedures, the mortality rate was 0.
†Significantly greater than pancreatic fistula following proximal or distal pancreatectomy; $P = .04$ using a Fisher exact test.

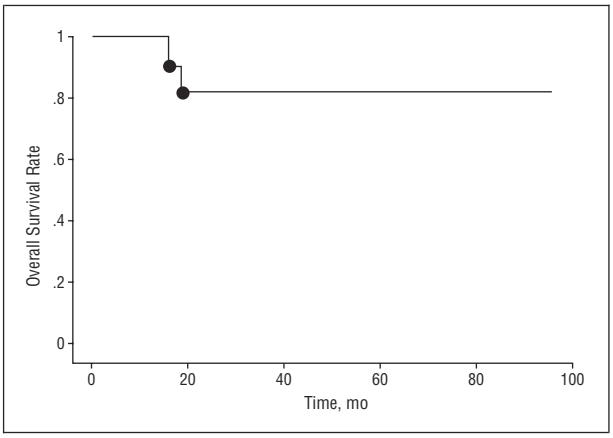

Figure 5. Kaplan-Meier overall survival curve following surgical resection of a malignant pancreatic or duodenal neuroendocrine tumor.

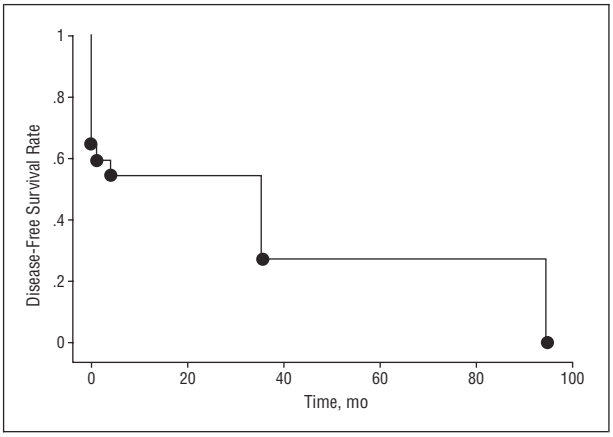

Figure 6. Kaplan-Meier disease-free survival curve following surgical resection of a malignant pancreatic or duodenal neuroendocrine tumor.

functional neuroendocrine tumors.[22] Increasingly, survival is being determined by the natural history of these tumors.[9,23,24] Except for insulinoma, neuroendocrine tumors are malignant in more than 50% of cases.[4,24] In various studies, 50% to 80% of patients with advanced disease have died within 5 years of tumor progression.[23,24] At present, medical treatments alone (chemotherapy, biotherapy, and hepatic embolization) have had limited success in prolonging survival and can be associated with significant adverse effects.[4] The role of aggressive surgical resection in these patients has remained controversial for many reasons.[1-4] First, these tumors are uncommon, most series are small and retrospective in nature, and no controlled trials exist. Second, carcinoid tumors are often included with neuroendocrine tumors, and their pathologic characteristics can differ.[4,24] Third, series often include both functional and nonfunctional neuroendocrine tumors, and the effects of cytoreductive surgery on symptoms of hormone excess may not be evaluated separately from effects of surgical resection on tumor progression. Fourth, the ability to resect all gross tumors in patients with advanced disease in conjunction with an acceptable morbidity rate has received limited study. Therefore, varying criteria for tumor extent are used as contraindicators to surgery. This latter point is of particular importance because patients with advanced disease are frequently asymptomatic and have a life expectancy measurable in years; therefore, there is a reluctance to recommend aggressive resection. The major issue addressed in this study concerns the effects of extensive surgery to remove advanced pancreatic and metastatic tumors. Our hypothesis is that this type of surgery can be performed with acceptable morbidity and low mortality rates and will result in extended long-term disease-free and overall survival.

Pathologic results demonstrated that tumors in all patients in our study were malignant with invasion and/or metastases. The mean size of the 18 primary pancreatic tumors was 8 cm. Previous studies have demonstrated

that tumors greater than 3 to 4 cm in diameter are nearly always malignant.[7] Furthermore, 70% of our patients had lymph node metastases, 40% had liver metastases, and 10% had kidney metastases. Lymph node and distant metastases are a hallmark of malignant neuroendocrine tumors, and studies have shown that liver metastases limit the survival rate.[7] This means that patients do not die of pancreatic neuroendocrine tumors unless liver metastases are present. These findings document that patients in our study had advanced disease caused by these tumors.

At outside institutions, most of these patients were believed to have unresectable tumors based on the extent of disease on a preoperative CT scan. This assessment was made because 6 patients had multiple bilobar liver metastases, 3 had invasion of the superior mesenteric vein (Figures 3 and 4), 1 had extensive retroperitoneal lymph node metastases, and 1 had a tumor involving the entire pancreas and abutting the major vessels in the upper abdomen (Figure 2). The magnitude of the surgery was significant. There were 8 pancreatoduodenectomies, 9 distal pancreatectomies, 3 total pancreatectomies, 3 concomitant enucleations of the tumor from the pancreatic head, 6 liver resections, 3 superior mesenteric vein reconstructions, 2 nephrectomies, 1 extensive nodal dissection, 2 transverse colectomies, and 1 partial gastrectomy. Despite the extent of these procedures, there were no operative deaths, the mean hospital stay was 11.5 days, and only 6 patients had significant complications that included abscess and pancreatic fistula. These findings are similar to those demonstrated in other studies of cytoreductive surgery in patients with gastrointenstinal neuroendocrine tumors[1,23,25,26] and pancreatic adenocarcinoma, which documents that major aggressive surgical resections for these tumors can be performed safely in centers experienced with these procedures.[9,10] In our study, most pancreatic resections were not associated with complications; however, enucleation of the tumor from the head of the pancreas always resulted in a pancreatic fistula. The probability of pancreatic fistula was higher for enucleations than for proximal or distal pancreatectomies. Nevertheless, the pancreatic fistula associated with enucleation eventually resolved without complications in all cases. The diet was not modified, and the leak slowly closed with time (15-30 days). Often these patients were discharged home with the drain in place. These results demonstrate that extensive resections can be performed with acceptable morbidity and low mortality rates.

Fifteen (75%) of 20 patients had all identifiable tumors removed. For those who did not, part of the tumor remained in the liver. All extrahepatic neuroendocrine tumors were removed in all patients. Following surgery, patients did not have any additional treatment but received careful follow-up using serum markers and CT scans. Serum levels of chromogranin A and pancreatic polypeptide have been used to detect the recurrence of nonfunctional neuroendocrine tumors. Two patients who did not have all of their tumor removed had rapid progression and died 20 months postoperatively (Figure 5). Although all other patients are alive and have remained asymptomatic, approximately 50% had evidence of tumor recurrence at the 30-month follow-up visit; long-term actuarial follow-up suggests that all tumors will recur by 7 years. No patient with this type of extensive tumor burden is cured by surgery alone, suggesting that some tumor remains after each procedure even though we think we are removing all of the identifiable tumor. Either the tumor is too extensive for complete resection or some of the tumor is missed in the liver or pancreas. Nevertheless, the actuarial survival curve demonstrating that 80% of patients will be alive at 5 years suggests that major surgery may be beneficial. These results are in general agreement with those of other cytoreductive studies in patients with advanced neuroendocrine tumors, which report a 5-year postresection survival rate of 70% to 80%.[1,25,26]

In conclusion, our findings suggest that conventional contraindications to surgical resection, such as superior mesenteric vein invasion and nodal or distant metastases, should be redefined in patients with advanced neuroendocrine tumors. Surgical debulking, even in patients with extensive disease, should be increasingly considered if all gross tumors can be safely removed. Because extensive surgical debulking can be performed with acceptable morbidity rates in these patients, its use coupled with adjuvant medical treatments (somatostatin analogues, radiolabeled somatostatin analogues, or chemotherapy) should be systematically studied. This combination may result in enhanced survival rates compared with either procedure alone.

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DISCUSSION

Sean J. Mulvihill, MD, Salt Lake City, Utah: Thank you for the privilege of opening the discussion of this very fine paper written by Dr Norton and colleagues describing operative morbidity and survival in a radical approach to resection of islet cell tumors of the pancreas. Dr Norton is an acknowledged expert in this field.

Developing evidence-based treatment strategies for patients with neuroendocrine tumors is difficult because of their rarity and the differences in presentation that make each patient nearly an anecdote unto himself or herself. Our thinking has changed over the years, however, from preoccupation with control of the endocrine syndrome—the ulcer diathesis, for example, in gastrinoma—to concern regarding control of metastasis and long-term survival of patients with these peculiar neoplasms.

Years ago these lesions were thought of as islet cell adenomas, benign lesions, and when the metabolic characteristics of the cells were recognized, the term *apudoma* was popularized, and this term also implied a benign nature. Although these tumors do not have highly malignant cellular characteristics such as anaplasia and high mitotic activity, when examined microscopically, we now recognize that about 70% of vipomas and glucagonomas, 50% of gastrinomas, and 10% of insulinomas present with metastases and must be considered malignant. My first questions to Dr Norton relate to this issue: Are all neuroendocrine tumors malignant, or are some benign, and if so, can we reliably recognize the difference by features such as tumor size, hormonal secretion, or biopsy findings at the time we plan treatment? This is an important issue because our strategy for small localized lesions historically has been enucleation. If these tumors are all malignant, should a more radical approach such as pancreatectomy and/or duodenectomy to achieve negative margins be considered for all patients?

Dr Norton has described admirable outcomes, including no mortality, in this small group of patients in which he included not only pancreatic and duodenal resection but often splenectomy, liver resection, portal vein resection, nephrectomy, colectomy, and node dissection to achieve grossly negative margins. We know that such an aggressive approach is unlikely to achieve long-term survival in the more common patient with ductal adenocarcinoma of the pancreas, but his data suggest an 80% 5-year survival rate in patients with neuroendocrine tumors. In my view, his philosophy might be extended to patients with 3 other unusual pancreatic neoplasms: solid/cystic papillary neoplasm, intraductal papillary tumors, and mucinous cystic neoplasms. In each of these situations, grossly negative margins can generally be achieved with radical resection, and rates of long-term survival are high. However, with large tumors such as these, microscopically positive margins are common. Jeff, you did not report microscopic margins in the manuscript, but I would be interested in knowing this data and if you believe margin status contributed to the relatively high recurrence rate observed in your series.

Finally, one of the quality measures we have used in assessing the outcome of pancreatic surgery is the need for blood transfusion, as evidence suggests that the known immunosuppressive effect of transfusion may decrease long-term survival in patients with malignancy. We know that pancreatectomy can generally be performed without transfusion, but combining liver resection, vein resection, and the like is another matter. Dr Norton, what proportion of patients in your series required transfusion, and did this correlate with recurrence?

This paper is an important contribution to the evolution of our treatment strategies for patients with these unusual lesions. Thank you for sharing your data with us.

Theodore X. O'Connell, MD, Los Angeles, Calif: I think Dr Russell emphasized in his talk the importance of evidence-based guidelines to tell us what to do in the future and to abide by that. My problem with the paper is that I don't know if the evidence is really there. Obviously it is a very aggressive surgery, but many of these tumors can be very indolent, and we all know that patients with metastases can live many years. I am a little worried that there are no controls in this study, even retrospectively matched controls, to show that this very aggressive surgery really makes a difference in outcome.

Orlo H. Clark, MD, San Francisco, Calif: I have 2 questions:

Are there any patients with neuroendocrine tumors who are not candidates for resection? In other words, when would you not recommend resection?

Do you use intraoperative ultrasound examination to determine the relationship of the neuroendocrine tumor and the pancreatic duct?

Howard A. Reber, MD, Los Angeles: I certainly understand the focus on the surgical approach to the problem, but I wonder if you could tell us something about adjuvant therapy. Did you use chemotherapy in an effort to downstage some of

these tumors before you took the patients to the operating room, and once you operate on them, are these patients then put into some sort of an adjuvant program?

Rodney F. Pommier, MD, Portland, Ore: Dr Norton, I enjoyed your paper very much. We are fortunate that all these tumors, even the nonfunctional ones, produce chromogranin A. Chromogranin A is a more reliable marker than serum hormone levels produced by these tumors, as chromogranin A correlates much better with actual tumor volume. Do you have any data on the serum chromogranin A levels in these patients after complete resection? Were complete resections also a biochemical cure as indicated by a return to a normal chromogranin A level? Do the magnitudes of chromogranin A levels after operation predict the time to recurrence? I know that you don't believe in using octreotide to prevent pancreatic fistulas after operation because in your randomized trial you showed that it had no effect. Would you give octreotide as an adjuvant therapy in patients with incomplete resection or in patients with a complete resection who still have an elevated postoperative chromogranin A level? Octreotide will often suppress elevated chromogranin A levels or even suppress them back down to normal, indicating that there is a tumor suppression response to this agent.

Juan Asensio, MD, Los Angeles: Trauma surgeons don't know a lot about endocrine surgery, but I just wanted to ask Dr Norton, How did you reconstruct the superior mesenteric vein?

Dr Norton: First, I want to thank each of the discussants for the important and insightful questions. In response to Dr Mulvihill, the most important way we can distinguish malignant neuroendocrine tumors is the presence of metastases. At the time of surgery, it is important to explore for lymph node and liver metastases. Insulinomas are almost always benign and are enucleated. The probability that an insulinoma is malignant is only 10%. If we obtain a preoperative CT scan and identify a large insulinoma or liver metastases, it may be malignant. The remainder of the pancreatic neuroendocrine tumors have malignant potential. We also use serum levels of chromogranin A as a marker for malignancy, similar to Dr Pommier's remarks. Approximately 90% of malignant pancreatic neuroendocrine tumors have elevated serum levels of chromogranin A. Size is the final important criterion. If pancreatic neuroendocrine tumors are greater than 3 cm, they have a 40% probability of having liver metastases. So the 3 best criteria for malignancy are lymph node or liver metastases, size, and serum chromogranin A elevations.

In response to Dr O'Connell, it is true that we do not have a randomized control group for these patients. The primary objective for this study is to establish that this type of aggressive surgery can be done with acceptable morbidity and mortality. However, a control group may be identified from previous studies in the literature. These studies suggest that the 5-year survival rate for patients with unoperated metastatic neuroendocrine tumors is 20%. The actuarial long-term survival rate in this study with aggressive surgery is 80%. This study suggests that if you can remove locally advanced and metastatic neuroendocrine tumors, patients do better. This leads to Dr Clark's question about who is not an operative candidate. The key to determining who is an operative candidate is if the surgeon can conceive of a plan to remove all tumors based on the results of imaging studies. Furthermore, if a patient with a neuroendocrine tumor has a local complication of the tumor that can be corrected by surgery, like gastric variceal bleeding from an obstructed splenic vein, the pancreatic tumor and spleen should be removed even if all liver metastases could not be removed.

We used intraoperative ultrasound on every single patient to image both the liver and the pancreas. Intraoperative ultrasound has allowed us to plan resections during the surgery and to identify some tumors that may be missed without it. It appears to be a significant advance for these procedures.

In response to Dr Reber, there is no effective adjuvant chemotherapy for these patients. Doxorubicin, 5-fluorouracil, and streptozotocin are active agents, but the response rate is only 30%. There are no complete responses. There is no improvement in survival with chemotherapy. As Dr Pommier suggested, Octreoscan is useful in imaging both primary and metastatic pancreatic neuroendocrine tumors. If tumors are imaged by Octreoscan, the long-acting form of Sandostatin may be a good treatment. Sandostatin is an inhibitory hormone that may inhibit both neuroendocrine tumor cell function and growth. This treatment has been associated with the development of gallstones, so it is important to do a cholecystectomy at the time of surgery. Patients must be treated for a short time interval (7 days) with the short-acting drug octreotide to be certain that it is well tolerated prior to treatment with the long-acting form. If it is well tolerated, then you can treat with long-acting Sandostatin, 20 to 30 mg IM [intramuscularly], every 3 weeks. This regimen is well tolerated. There is evidence that long-acting Sandostatin decreases serum levels of chromogranin A and may prolong survival. However, results are preliminary, and studies do not prove that it prolongs survival.