Published in final edited form as:
Arch Surg. 2011 June ; 146(6): 724–732. doi:10.1001/archsurg.2011.129.

Major Vascular Abutment, Involvement or Encasement is not a Contraindication to Pancreatic Endocrine Tumor Resection

Jeffrey A. Norton[a], **E. John Harris Jr.**[b], **Yijun Chen**[a], **Brendan C Visser**[a], **George A Poultsides**[a], **Pamela C. Kunz**[c], **George A Fisher**[c], and **Robert.T. Jensen**[d]

[a]Division of General Surgery, Department of Surgery, Stanford University

[b]Division of Vascular Surgery, Department of Surgery, Stanford University

[c]Division of Medical Oncology of the Department of Medicine at Stanford University

[d]Digestive Diseases Branch of the National Institute of Diabetes and Digestive and Kidney Diseases

Abstract

Background—There is considerable controversy about the treatment of patients with malignant functional or nonfunctional pancreatic endocrine tumors (PETs). Aggressive surgery with dissection and/or reconstruction of major vascular structures is a potentially efficacious antitumor therapy, but is rarely performed, and considered a contraindication to surgery by many.

Hypothesis—Aggressive resection of locally advanced PETs in which preoperative studies suggest major vascular involvement can be performed with acceptable morbidity and mortality rates and may lead to extended survival.

Design—The combined databases of the prospective NIH study on PETs (gastrinomas) (from 1982) and Stanford (all PETs)(from 2004) were queried. All patients with possible involvement of major vascular structures were reviewed and preoperative studies, operative findings and surgical results/outcomes correlated.

Main Outcome Measures—Surgical procedure, pathologic characteristics, complications, mortality rates, and disease-free and overall survival rates.

Results—Of 273 patients with PETs, 46 (17%) had preoperative CT evidence of major vascular involvement. There were 21 men (45%). Mean age was 42 years (range 24-76). 32 (57%) had functional tumors with 30 gastrinomas and 2 glucagonomas; the remainder (n=14) had nonfunctional PETs. 12 patients (26%) had MEN-1. 44 of 46 underwent surgery. The mean size for the primary PET on preoperative CT was 5.8 cm. The involved major vessel was as follows: portal vein (n=20, 43%), SMV or SMA (n=16, 35%), IVC (n=4, 9%), splenic vein (n=4, 9%) and heart (n=2, 4%). 42 (91%) patients had PET removed: 12 (27%) primary only, 30 (68%) with lymph nodes, and 18 (41%) with liver metastases. PETs were removed by either enucleation (n=5, 12%) or resection (n=36, 86%). Resections included distal or subtotal pancreatectomy in 23 (55%), Whipple in 10 (23%) and total in 2 (5%). 19 (45%) patients had concomitant liver resection: 10 (23%) wedge resection and 9 (21%) anatomic resections (lobectomy or trisegmentectomy). 9 (21%) had vascular reconstruction: each had reconstruction of the SMV and portal vein, while 1 had concomitant reconstruction of the SMA. There were no deaths, but 12 (28%) had complications. 18 (42%) were immediately disease-free and 5 recurred with follow-up leaving 14 (33%) long-term disease-free. The 10-year overall survival was 60%. Functional tumors had a better overall survival ($p<0.0001$), and liver metastases decreased overall survival ($p<0.0001$).

Conclusions—Aggressive surgery including superior mesenteric vein reconstruction, and liver resection can be done with acceptable morbidity and mortality rates for patients with advanced

PETs. Although survival rates following surgery are excellent, most patients will develop recurrence. These findings suggest that surgical resection is indicated even in PETs with vascular invasion and nodal or distant metastases. Distant metastases decrease the probability of long-term survival, still 60% are alive at 10 years and one third remain disease-free.

Introduction

Malignant pancreatic endocrine tumors (PETs), if resectable, can have a good prognosis [1-7]. Unfortunately, a proportion may present late with tumors that encase or invade adjacent major blood vessels [8-10]. A number of studies have shown vascular invasion in both patients with pancreatic adenocarcinomas and advanced PETs is associated with decreased survival [2, 4, 11-15]. The surgical approach to this group of patients is controversial. Based on analogies to pancreatic adenocarcinomas and limited experience with attempted surgical resection with this group of patients with advanced PETs, for many, involvement of the superior mesenteric vein (SMV), inferior vena cava (IVC), portal vein (PV), splenic vein with extensive varices (SV), superior mesenteric artery (SMA), aorta or heart is considered a contra-indication to surgery [11, 14, 16].

Recent surgical series in pancreatic adenocarcinoma suggest that there are reasons to question this approach [11, 14, 17-19]. The operability of pancreatic tumors is usually defined by the results of CT or other imaging studies [9-11, 14, 20, 21]. However, these studies may not always give an accurate image for determining operability [14]. For example, in patients with adenocarcinoma of the pancreas, when preoperative CT suggests that the tumor involves the SMV, SMA or portal vein, in the past, most would say that the tumor is inoperable [11, 14, 17]. However, recent studies dispute this thinking and suggest that these locally advanced tumors may be resectable for benefit [11, 14, 17, 22-24]. Yet this is controversial because patients may not benefit in terms of disease-free and overall survival. We have recently demonstrated that vascular surgery techniques can be used to remove sarcomas that were previously thought to be inoperable with acceptable morbidity and good survival [25]. Because PETs are rare, there has been no systematic studies of the ability to surgically resect malignant PETs thought to abut or involve major vascular structures, with most reports being isolated case reports or involving only a few PET patients [9, 10, 26-33]. In this study we report our long-term results with PETs that abut or involve major vascular structures including the PV, SMV, SMA, inferior vena cava, splenic vein with large collaterals and the heart (interventricular septum). The findings suggest that possible/definite major vascular involvement on preoperative imaging studies should not be a contraindication to PET resection.

Methods

Since 1982 at the National Institutes of Health (NIH), and 2004 at Stanford University hospitals, 195 patients with Zollinger-Ellison syndrome (ZES) and 78 patients with either other functional or nonfunctional pancreatic PETs were involved in a prospective plan to perform surgical exploration for cure as described previously [34-41]. All patients at the NIH, after confirming the diagnosis, underwent detailed imaging studies (CT scan with intravenous contrast, MRI with gadolinium, ultrasound, somatostatin receptor scintigraphy since 1994 [using [^{111}In-DTPA-DPhe^{1}]-octreotide (6 mCi) with whole body, planar, and SPECT views [42-45]], and in selected cases selective abdominal angiography) to determine operability as described previously [34, 36, 46]. All patients at Stanford underwent CT plus additional studies as deemed necessary. Patients were invited to undergo surgery to remove the tumor if they had no co-morbid medical condition markedly limiting life expectancy, had apparently operable tumor, and if MEN1 was present, had tumor ≥2.5 cm in diameter [35-37, 40, 47-49]. Patients were also included with limited liver metastases, which were potentially completely resectable, as described previously [38, 39, 50]. 46 (17%) patients

described in detail here were identified on preoperative imaging either CT or MRI or both to have a PET that involved a major vascular structure. This included all patients, in which the PET by imaging studies involved the heart [51]; IVC; either abutted (Figure 1) or involved the SMV or portal vein at or near the confluence (Figure 2) or the SMA; or invaded the splenic vein with large short gastric collateral vessels.

The diagnosis of ZES was based on acid secretory studies, measurement of fasting serum level of gastrin as well as the results of secretin and calcium provocative tests [52-54]. Basal and maximal acid output (BAO, MAO) was determined for each patient using methods described previously [54]. Doses of oral gastric antisecretory drug were determined as described previously [55-57]. The diagnosis of glucagonoma (the only other functional PET in this study) was based on the presence of a characteristic rash and elevated fasting plasma levels of glucagon [58].

A detailed past history of disease was taken at first admission including symptoms related to ZES and past medical/surgical procedures as described previously [53, 59]. Time from onset of the disease to exploration was determined for all patients with ZES [35, 52, 52, 60, 60]. The time of diagnosis of ZES was the time the diagnosis was first established by appropriate laboratory studies or when a physician established the diagnosis based on clinical presentation [35, 53].

All patients referred with a diagnosis of possible ZES underwent an evaluation to establish the diagnosis of ZES and to determine whether MEN1 was present [35, 37, 52, 53, 59] and studies to determine the suitability of surgical exploration for cure [35, 37, 38, 52]. These latter studies included tumor localization studies, studies to determine the presence or absence of MEN1 [35, 59, 61] and studies to determine the presence of other disease that might make surgery contraindicated. MEN1 was established by assessing plasma hormone levels (PTH [intact, mid-molecule], prolactin, insulin, proinsulin, glucagon), serum calcium (ionized, total) and glucose as well as from personal and family history [37, 48, 59, 61].

44 of 46 patients who fit this study for possible vascular involvement underwent a surgical exploration for potential cure. The operative techniques have been described previously [35, 36, 47, 62, 63]. Tumors in the pancreatic head were enucleated. Tumors in the pancreatic body and tail were resected. If large pancreatic head tumors were present and could not be enucleated, a pancreaticoduodenectomy was performed [64]. A detailed inspection for peripancreatic, periduodenal, or portohepatic lymph nodes was carried out, and these were routinely removed [34, 65]. If liver metastases were present and localized, they were wedge-resected with a 1-cm margin, if possible; if this was not possible and they were localized, a segmental resection or lobectomy was performed [38, 39, 50]. If the superior mesenteric vein was resected and reconstructed, it was done with either the proximal femoral vein or the jugular vein [25, 39]. The superior mesenteric artery was reconstructed with the saphenous vein [25, 39]. Postoperatively, patients underwent evaluation for disease-free status immediately after surgery (i.e., 2 weeks post-resection), within 3 to 6 months post-resection, and then yearly [35, 43, 52, 62]. Yearly evaluations included conventional imaging studies (CT, ultrasound, MRI, and angiography, if necessary); somatostatin receptor scintigraphy (SRS) since 1994; assessment of functional disease status (in gastrinomas-acid secretory studies, fasting gastrin determinations, secretin provocative test; in glucagonomas-plasma glucagon levels); and assessment of endocrine status (parathyroid, pituitary, adrenal function) [35, 43, 52, 62]. To compare the results with functional and nonfunctional PETs, disease-free status was defined as no evidence of tumor on conventional imaging studies usually CT. For patients with functional PETs (gastrinoma, glucagonoma), complete disease-free status assessed by plasma hormone levels and secretin provocative testing (gastrinomas) as described previously [35, 36, 52] and was defined as a normal fasting plasma gastrin/glucagon

level, and negative secretin test (gastrinoma), and no tumor on imaging studies A recurrence post-resection was defined as occurring in a patient who was initially disease-free post-resection of the PET, but then lost disease-free status on follow-up evaluation by developing positive imaging studies (Nonfunctional-PETs, functional PETs) as well as recurrent fasting hormone/provocative test results with negative imaging in functioning PETs [35, 36, 52, 66]. Recurrent disease was treated with chemotherapy or somatostatin analogues with or without alpha interferon as described previously [67-69].

The Fisher's exact test was used for two-group comparisons. All continuous variables were reported as mean ± standard error of the mean. The probabilities of survival were calculated and plotted according to the Kaplan-Meier method [70].

Results

Demographics

46 (17%) patients were identified on preoperative imaging studies to have pancreatic PETs either involving the IVC, heart, PV or abutting or encasing the SMV (Figures 1 and 2), SMA or splenic vein with extensive collateral veins (Tables 1 and 2). There were 21 men (45%) and 39 were Caucasian (85%) (Table1). The mean age was 42 years with a range of 24 to 76 years. 32 (57%) had functional tumors with 30 gastrinomas and 2 glucagonomas; the remainder (n=14) had nonfunctional PETs. 30 functional PET patients presented with symptoms related to ZES (peptic ulcer disease, GERD and diarrhea) and 2 glucagonoma patients presented with a rash that was later called necrolytic migratory erythema. While the nonfunctional tumor patients each presented with pain, some (n=6) functional PET patients also had pain as a presenting symptom (Table 1). 12 patients (26%) had MEN-1. For the patients with functional PETs, symptoms were present for approximately 5 years before the diagnosis was made. The median gastrin increase for the ZES patients was 12 fold (Table 1).

Preoperative Imaging

The mean size for the primary pancreatic PET on preoperative CT was 5.8 cm (Table 2). Some patients had more than one primary so the mean number of tumors per patient was 1.5. 27 primary tumors were located within the head of the pancreas or the duodenum (59%). 17 were either in the pancreatic body (n=9, 20%) or tail (n=8, 17%). The other 3 were ectopic: two in the interventricular septum of the heart and the other within the wall of the right hepatic duct abutting the right portal vein (Figure 3). On preoperative imaging 35 patients were found to have metastases (76%) with 27 having lymph node metastases (59%) and 14 liver spread (30%). On the preoperative imaging studies the involved major vessels were as follows: portal vein (n=20, 43%), SMV or SMA (n=16, 35%), IVC (n=4, 9%), splenic vein (n=4, 9%) and heart (n=2, 4%) (Table 2).

Surgical Findings and Results

44 of the 46 patients underwent surgery (2 patients refused surgery) and in 42 patients the primary tumor was resected (91%) (Table 3). The mean age at the time of surgery was 49 years and it had been an average of 5 years since diagnosis. The primary PET was located within the pancreas in 30 (68%) patients, the duodenum in 12 (27%) and the remainder (n=5, 11%) had ectopic locations (bile duct n=1), liver n=2, heart n=1 and lymph node n=1) (Table 3). The average tumor size at surgery was 5 cm, and the largest tumor was 15 cm. At surgery, 31 (70%) patients had lymph node metastases and 18 (41%) had liver metastases. Eight patients had only a primary tumor found (18%), 31 had a primary tumor with lymph node involvement (70%), 20 had liver involvement (48%) and 15 had vascular encasement including the heart (n=1), cava (n=1), SMA (n=1) and the portal vein or SMV (n= 12) (Table 3).

42 patients had PETs removed: 12 (27%) a primary only, 30 (68%) with lymph node metastases, and 18 (41%) with liver metastases (Table 4). The pancreatic primary PET was removed by either enucleation n=5 (12%) or resection n=36 (86%). Resections included partial pancreatectomy either distal or subtotal pancreatectomy in 23 (55%), Whipple proximal pancreaticoduodenectomy in 10 (23%) and total pancreatectomy in 2 (5%). 19 (45%) patients had concomitant liver resection: 10 (23%) had wedge resections and 9 (21%) had anatomic resections (lobectomy or trisegmentectomy) (Table 4). 9 (21%) had vascular reconstruction: each had reconstruction of the SMV and portal vein, while 1 patient had concomitant reconstruction of the SMA. There were no deaths due to surgery, but 12 (28%) had complications including pancreatitis, abscess, wound infection, bile duct injury, leak at pancreaticojejunostomy and ischemic bowel.

Follow-up and Outcome

18 (42%) were immediately disease-free and 5 recurred with follow-up leaving 14 (33%) long-term disease-free assessed by serial imaging studies (Table 4). 7 patients with gastrinomas immediately postoperatively and 6 on follow-up had normal imaging studies but an elevated fasting gastrin and/or provocative test. The long-term 10 year overall survival is 60% and the disease-free survival is 33% (Figure 4). Possible prognostic factors were examined to determine if they affected long-term and disease-free survival. Most variables did not affect disease-free survival (Table 5). Patients with functional tumors had a greater long-term overall survival than nonfunctional tumors, but the disease-free survival was similar (p=0.0001) (Figure 5). The presence of lymph node metastases did not decrease disease-free survival. However, the presence of liver metastases decreased disease-free survival from 66% to 20% (p= 0.002), and the use of liver resection decreased disease-free survival from 66% to 25% (p=0.007). The use of vascular reconstruction did not affect disease-free survival (Table 5). The use of other anti-tumor treatment following surgery did not affect disease-free survival (Table 5).

Discussion

PETs are uncommon neoplasms with a clinical incidence of approximately 1-3 per million [71]. The patients described here are those with the PET on extensive preoperative imaging studies likely or actually invading major vascular structures either by abutting and/or encasing the vascular structure or thought to invade a major vascular structure. We found that such patients comprised 17% (44 patients) of our total surgical population of 273 patients with PETs. This is the first series of PET patients that has systemically investigated such a large group of such patients. Our frequency of preoperative vascular involvement is similar to results in smaller series of patients with PETs where a 13-16% frequency of likely vascular involvement was reported in two radiologic studies [8, 10] of patients with PETs and 26% reported in the radiological study of 30 PET patients [9] with large, malignant PETs. These results demonstrate that possible vascular involvement on preoperative imaging studies is not an uncommon occurrence in patients with PETs, although it is less common than the 44% (mean -13 series, 891 patients) seen with pancreatic adenocarcinoma [24]. These results support the importance of the present study, because they demonstrate that if vascular involvement is used as a contra-indication to surgical resection for PET patients, approximately 20% of all PET patients will be excluded from surgery.

This paper focuses on the role of surgery to remove PETs abutting, invading or encasing a major blood vessel, usually the superior mesenteric vein or portal vein (Figures 1 and 2), as well as removing the primary, lymph nodes and any limited, liver metastases in these patients. This study was undertaken for a number of reasons. First, a proportion of PETs show aggressive, malignant growth, which is associated with decreased survival, and the medical treatment of these large, advanced tumors is generally only marginally effective [67,

[71-73]. Second, a number of studies have shown vascular invasion in both patients with pancreatic adenocarcinomas and advanced PETs is associated with decreased survival [2, 4, 11-15]. Third, there are a number of surgical reports by different groups that resection of distant metastatic PETs, including within the liver, may improve survival, improve symptom control and even render some patients disease-free [38, 50, 74-77]. However, there has never been a controlled study establishing this, because these patients are uncommon, most believe that this type of surgery is helpful when it can be done in patients with limited liver metastases, and in a recent consensus statement it is recommended it be performed whenever possible [3, 38, 50, 71, 74, 75, 78]. Fourth, similar to PETs, until recently most studies with pancreatic adenocarcinoma, considered involvement of major vascular structures a contra-indication to surgery [11, 14, 16]. However, recent studies in patients with exocrine adenocarcinoma of the pancreas suggest that these tumors, even when invading venous structures, may be resected with acceptable morbidity and this may be of benefit [11, 14, 17-19]. Similarly, we have recently reported that this aggressive approach to resection of invasive sarcomas of the extremity and retroperitoneum that involved or replaced major blood vessels, results in some cases, in the complete removal of tumors thought previously to be inoperable [27]. Furthermore, numerous case reports and small series suggested a similar approach might be feasible and perhaps beneficial in patients with advanced functional [9, 28, 79-81] and nonfunctional PETs [9, 29, 30, 33, 82-84], although no study has systematically examined this issue until the present study. Fifth, despite the fact that PETs can result in death and shorten the life-expectancy of an individual patient, an aggressive PET can also cause dramatic life-threatening complications like massive bleeding due to the formation of vascular shunts [27] or from the development of short gastric varices in the setting of splenic vein occlusion by tumor [80, 83-86].

In our study we found that the PETs were resectable in 91% of our patients, even though the tumors were usually large (mean size-5.5 cm) and associated with advanced disease in most cases, with metastases present in three-fourths of the patients, including to lymph nodes (68%) and the liver (41%). Even though preoperative imaging studies suggested vascular involvement in all patients, at surgery, the PET was found to have invaded and/or encased a major vascular structure in less than one-half the patients (40%), and in the remaining cases, the PET showed either only partial vascular involvement or vascular abutment without encasement and/or invasion of a major vascular structure. This result is similar to those in a study [9] of patients with advanced, large PETs in which 50% of the patients thought to have vascular involvement from preoperative studies, were found at surgery, to not have vascular encasement and/or invasion of major vessels. CT and MRI scanning are reported to have excellent sensitivity for detecting vascular involvement and are the standard imaging modalities used to determine vascular involvement in patients with either pancreatic exocrine adenocarcinomas or and PETs [3 9-11, 14]. In the present study both modalities were used in the gastrinoma patients and CT in the nonfunctional PET patients. With pancreatic adenocarcinomas, preoperative CT is reported to have excellent sensitivity for identifying involvement of major vessels, however, similar to our results in PETs, it can also have false positives in pancreatic adenocarcinoma, with specificity as low as 50% in some studies [11, 14]. The difference between our surgical results and the preoperative imaging results in PET patients is likely explained by our surgical findings and suggests that PETs differ from pancreatic adenocarcinomas in this regard. Our results demonstrate that with PETs, radiological abutment or even possible vascular involvement is not frequently synonymous with vascular involvement at surgery. The PET was found frequently to be encroaching, abutting, or distorting the major vascular structure, without encasing it and/or invading it. That CT may falsely suggest vessel involvement, has been reported in a small number of patients with PETs in other studies [9, 87]. In pancreatic adenocarcinoma false positives imaging results for vascular involvement occur, especially in the portal vein, where in some studies, up to 50% of the tumors thought to involve the portal vein, on histological

evaluation showed no tumor involvement, but the radiological changes were due to inflammatory adhesions [14].

In our study only 9 of the 42 patients (15%) undergoing PET resections required vascular reconstruction demonstrating that in most PET patients, even if the radiological evaluation suggests vascular involvement and at surgery, the PET is found to partially encase or involve the vessel, the PET can be removed with careful dissection without requiring vascular reconstruction. These results differ from pancreatic adenocarcinoma where venous resection is usually required with tumor involvement and where the percentage of the patients with potentially resectable disease having major vascular involvement is much lower [14, 17, 23, 24].

In our study, despite the extensive tumor involvement, post surgical resection, both the long-term survival rate and the disease-free survival rates at 5-years were high (77% and 50%, respectively). An important prognostic factor associated with a decreased disease-free survival was the presence of liver metastases, which is in agreement with the results a number of studies that show the presence of liver metastases are one of the most important factors in patients with PETS associated with decreased either disease-free or total survival [4-7, 71, 88]. In contrast, disease-free survival was not affected by either the extent or type of vascular involvement (i.e. by the presence of vascular invasion or encasement of a major vessel by the PET, the need for vascular reconstruction at surgery, the type of vascular involvement) or by the presence of other factors which have prognostic significance for disease-free or total survival in other studies of PET patients [i.e. lymph node metastases, the presence of MEN1, high tumor marker levels or the presence of a large primary PET (i.e. >3 cm)][2, 4, 6, 7, 71, 88]. In our study patients with nonfunctional PETs with possible vascular involvement on preoperative imaging studies had a significantly decreased ($p<0.001$) survival compared to similar patients with functional PETs. In previous reports patients with nonfunctional PETs have a poorer survival than patients with functional PETs in many studies [1, 4, 5, 7, 89] but not all [2, 6]. The decreased survival of patients with nonfunctional PETs is reported to be likely due to their more aggressive behavior or the fact that these patients characteristically present later in their disease course with more advanced disease than patients with functional PETs [1, 7] In our study the extent of disease in the patients with functional and nonfunctional tumors was comparable, so this supports the proposal that these patients have more aggressive tumors. [1, 7]

Unfortunately, our study, like many other surgical studies of patients with advanced PETs including those with liver metastases, because of the low patient numbers available, the study design does not clearly establish the value of the surgical approach taken [76-78, 90]. Nevertheless, a number of findings in our study are suggestive of surgical benefit and encouraging for future studies. First, despite the decreased survival of patients with vascular involvement and/or liver metastases with malignant PETs [2, 4, 12, 13, 71, 72], in our series, the results suggest that the long-term survival rate was 77% at 5 years and our results suggest surgery was beneficial as 42% were immediately disease-free and 33% long-term disease-free. These data are encouraging, because in historic controls of patients with metastatic PETs who remained untreated and with potentially resectable disease, as is our group because of their vascular involvement, the five-year survival rates were 30-40% [89, 91]. Second, in our study these results were obtained in the setting of major pancreatic resection in most patients (86%) plus liver resection in 45%. Furthermore, tumor removal required dissection an/or removal of PETs adjacent or partially involving major vessels in all patients, and vascular reconstruction in 21%. Despite this extent of surgical resection, there was no surgical mortality and the surgical complication rate (28%) was well within the range of that reported in studies with PET resections, usually involving less extensive resections than in these patients with and without vascular involvement [1, 92, 93]. Third, in

the present study five patients presented with upper gastrointestinal hemorrhage from gastric varices secondary to splenic vein occlusion by the PET and the bleeding was totally ameliorated by removal of the tumor with the spleen. This experience is similar to that reported in a small number of case reports [8, 83, 85-87, 94-96]. These results suggest the resection of the PET despite vascular involvement is of particular benefit in this group of PET patients. Fourth, medical therapies of advanced PETs have provided only modest benefits, with many studies reporting short term disease stabilization and a small percentage of partial responses [71-73, 97]. Therefore, it has generally not been possible to downsize extensive disease in a patient with a malignant PET to make it surgically resectable, as has been done in some other tumors [71-73, 98, 99]. However, one patient on a novel chemotherapy protocol with capecitabine, oxaliplatin and bevacizumab became operable after his upfront chemotherapy treatment suggesting that this and other protocols may increase operability in the future. Therefore, at present, surgical resection is recommended for these patients, even by consensus conference, whenever it is possible. Our data suggests that major vascular involvement should not be a contra-indication to surgery, thus increases the possible number of patients in whom surgical resection should be considered, because this occurs in 20% of patients with advanced PETs.

Acknowledgments

This study was partially supported by intramural funds of NIDDK, NIH.

Reference List

1. Phan GQ, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA, Cameron JL. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. J Gastrointest Surg. 1998 September; 2(5):472–82. [PubMed: 9843608]
2. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. J Clin Oncol. 2002 June 1; 20(11):2633–42. [PubMed: 12039924]
3. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg. 2004; 240(5):757–73. [PubMed: 15492556]
4. Jensen, RT. Natural history of digestive endocrine tumors. In: Mignon, M.; Colombel, JF., editors. Recent advances in pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris, France: John Libbey Eurotext Publishing Co.; 1999. p. 192-219.
5. Madeira I, Terris B, Voss M, et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. Gut. 1998; 43:422–7. [PubMed: 9863490]
6. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer. 2005 December; 12(4):1083–92. [PubMed: 16322345]
7. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res. 2008 December 1; 14(23):7798–803. [PubMed: 19047107]
8. Bok EJ, Cho KJ, Williams DM, Brady TM, Weiss CA, Forrest ME. Venous involvement in islet cell tumors of the pancreas. AJR Am J Roentgenol. 1984 February; 142(2):319–22. [PubMed: 6320613]
9. Hellman P, Andersson M, Rastad J, et al. Surgical strategy for large or malignant endocrine pancreatic tumors. World J Surg. 2000; 24:1353–60. [PubMed: 11038206]
10. Johnson DBS, Francis IR, Eckhauser FE, Knol JA, Chang AE. Dual-phase helical CT of nonfunctioning islet cell tumors. J Comput Assist Tomogr. 1998 January; 22(1):59–63. [PubMed: 9448762]
11. Wray CJ, Ahmad SA, Matthews JB, Lowy AM. Surgery for pancreatic cancer: recent controversies and current practice. Gastroenterology. 2005 May; 128(6):1626–41. [PubMed: 15887155]

12. La Rosa S, Rigoli E, Uccella S, Novario R, Capella C. Prognostic and biological significance of cytokeratin 19 in pancreatic endocrine tumours. Histopathology. 2007 April; 50(5):597–606. [PubMed: 17394496]
13. Deshpande V, Fernandez-Del Castillo C, Muzikansky A, et al. Cytokeratin 19 is a powerful predictor of survival in pancreatic endocrine tumors. Am J Surg Pathol. 2004; 28(9):1145–53. [PubMed: 15316313]
14. Buchs NC, Chilcott M, Poletti PA, Buhler LH, Morel P. Vascular invasion in pancreatic cancer: Imaging modalities, preoperative diagnosis and surgical management. World J Gastroenterol. 2010 February 21; 16(7):818–31. [PubMed: 20143460]
15. Ballian N, Loeffler AG, Rajamanickam V, Norstedt PA, Weber SM, Cho CS. A simplified prognostic system for resected pancreatic neuroendocrine neoplasms. HPB (Oxford). 2009; 11(5): 422–8. [PubMed: 19768147]
16. Evans DB, Skibber JM, Lee JE, et al. Nonfunctioning islet cell carcinoma of the pancreas. Surgery. 1993 December; 114(6):1175–81. [PubMed: 7903005]
17. Martin RC, Scoggins CR, Egnatashvili V, Staley CA, McMasters KM, Kooby DA. Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. Arch Surg. 2009 February; 144(2):154–9. [PubMed: 19221327]
18. Glanemann M, Shi B, Liang F, et al. Surgical strategies for treatment of malignant pancreatic tumors: extended, standard or local surgery? World J Surg Oncol. 2008; 6:123. [PubMed: 19014474]
19. Siriwardana HP, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. Br J Surg. 2006 June; 93(6):662–73. [PubMed: 16703621]
20. Zhao WY, Luo M, Sun YW, et al. Computed tomography in diagnosing vascular invasion in pancreatic and periampullary cancers: a systematic review and meta-analysis. Hepatobiliary Pancreat Dis Int. 2009 October; 8(5):457–64. [PubMed: 19822487]
21. Noone TC, Hosey J, Firat Z, Semelka RC. Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. Best Pract Res Clin Endocrinol Metab. 2005 June; 19(2):195–211. [PubMed: 15763695]
22. Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection. Ann Surg. 1996 September; 224(3):342–7. [PubMed: 8813262]
23. Tseng JF, Tamm EP, Lee JE, Pisters PW, Evans DB. Venous resection in pancreatic cancer surgery. Best Pract Res Clin Gastroenterol. 2006 April; 20(2):349–64. [PubMed: 16549332]
24. Ramacciato G, Mercantini P, Petrucciani N, et al. Does portal-superior mesenteric vein invasion still indicate irresectability for pancreatic carcinoma. Ann Surg Oncol. 2009 April; 16(4):817–25. [PubMed: 19156463]
25. Song TK, Harris EJ Jr, Raghavan S, Norton JA. Major blood vessel reconstruction during sarcoma surgery. Arch Surg. 2009 September; 144(9):817–22. [PubMed: 19797105]
26. Obuz F, Bora S, Sarioglu S. Malignant islet cell tumor of the pancreas associated with portal venous thrombus. Eur Radiol. 2001; 11(9):1642–4. [PubMed: 11511884]
27. Handa M, Nakada T, Kajitsuka S, Hirose M, Sato Y. Portosystemic A-V fistula and portal hypertension associated with islet-cell tumor of the pancreas. Nippon Geka Gakkai Zasshi. 1985 August; 86(8):953–8. [PubMed: 2997591]
28. Rusher AH, Henson K. Metastatic malignant insulinoma: debulking for palliation of symptoms. J Ark Med Soc. 1991 November; 88(6):267–9. [PubMed: 1724774]
29. Sakamoto E, Hasegawa H, Ogiso S, et al. Curative resection for a pancreatic endocrine carcinoma involving the portal vein. Hepatogastroenterology. 2004 November; 51(60):1849–51. [PubMed: 15532841]
30. Kawakami H, Kuwatani M, Hirano S, et al. Pancreatic endocrine tumors with intraductal growth into the main pancreatic duct and tumor thrombus within the portal vein: a case report and review of the literature. Intern Med. 2007; 46(6):273–7. [PubMed: 17379993]

31. Akatsu T, Aiura K, Shimazu M, et al. Successful pancreatectomy with en-bloc resection of the celiac artery and portal vein for pancreatic endocrine carcinoma. Hepatogastroenterology. 2007 June; 54(76):1269–71. [PubMed: 17629086]
32. Yamato H, Kawakami H, Kuwatani M, et al. Pancreatic carcinoma associated with portal vein tumor thrombus: three case reports. Intern Med. 2009; 48(3):143–50. [PubMed: 19182424]
33. Bedirli A, Patiroglu TE, Sakrak O, Aritas Y. Portal vein resection for a portal vein thrombus caused by nonfunctioning islet cell carcinoma: report of a case. Surg Today. 2004; 34(9):802–4. [PubMed: 15338361]
34. Norton JA, Alexander HA, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Possible primary lymph node gastrinomas: occurrence, natural history and predictive factors: A prospective study. Ann Surg. 2003; 237(5):650–9. [PubMed: 12724631]
35. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med. 1999; 341(9):635–44. [PubMed: 10460814]
36. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Jensen RT. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases or survival in patients with Zollinger-Ellison syndrome (ZES)? Ann Surg. 2004; 239(5):617–26. [PubMed: 15082965]
37. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg. 2001; 234(4):495–506. [PubMed: 11573043]
38. Norton JA, Doherty GD, Fraker DL, et al. Surgical treatment of localized gastrinoma within the liver: A prospective study. Surgery. 1998; 124(6):1145–52. [PubMed: 9854596]
39. Norton JA, Kirlen MA, Li M, Schreiber D, Chuter T, Jensen RT. Morbidity and mortality of aggressive resections in patients with advanced neuroendocrine tumors. Arch Surg. 2003; 138:859–66. [PubMed: 12912744]
40. Fraker DL, Norton JA, Alexander HR, Venzon DJ, Jensen RT. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. Ann Surg. 1994; 220:320–30. [PubMed: 7916560]
41. Norton JA. Surgical treatment and prognosis of gastrinoma. Best Pract Res Clin Gastroenterol. 2005 October; 19(5):799–805. [PubMed: 16253901]
42. Termanini B, Gibril F, Reynolds JC, et al. Value of somatostatin receptor scintigraphy: A prospective study in gastrinoma of its effect on clinical management. Gastroenterology. 1997; 112:335–47. [PubMed: 9024287]
43. Alexander HR, Fraker DL, Norton JA, et al. Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger-Ellison syndrome. Ann Surg. 1998; 228(2):228–38. [PubMed: 9712569]
44. Gibril F, Reynolds JC, Chen CC, et al. Specificity of somatostatin receptor scintigraphy: a prospective study and the effects of false positive localizations on management in patients with gastrinomas. J Nucl Med. 1999; 40:539–53. [PubMed: 10210211]
45. Krudy AG, Doppman JL, Jensen RT, et al. Localization of islet cell tumors by dynamic CT: Comparison with plain CT, arteriography, sonography and venous sampling. Am J Roentgenol. 1984; 143:585–9. [PubMed: 6087646]
46. Termanini B, Gibril F, Doppman JL, et al. Distinguishing small hepatic hemangiomas from vascular liver metastases in patients with gastrinoma: Use of a somatostatin-receptor scintigraphic agent. Radiology. 1997; 202:151–8. [PubMed: 8988205]
47. Sugg SL, Norton JA, Fraker DL, et al. A prospective study of intraoperative methods to diagnose and resect duodenal gastrinomas. Ann Surg. 1993; 218:138–44. [PubMed: 8342993]
48. MacFarlane MP, Fraker DL, Alexander HR, Norton JA, Jensen RT. A prospective study of surgical resection of duodenal and pancreatic gastrinomas in multiple endocrine neoplasia-Type 1. Surgery. 1995; 118:973–80. [PubMed: 7491542]
49. Norton JA, Fraker DL, Alexander HR, et al. Surgery increases survival in patients with gastrinoma. Ann Surg. 2006; 244(3):410–9. [PubMed: 16926567]
50. Norton JA, Warren RS, Kelly MG, Zurek MB, Jensen RT. Aggressive surgery for metastatic liver neuroendocrine tumors. Surgery. 2003; 134(6):1057–65. [PubMed: 14668741]

51. Noda S, Norton JA, Jensen RT, Gay WA Jr. Surgical resection of intracardiac gastrinoma. Ann Thorac Surg. 1999; 67:532–3. [PubMed: 10197684]
52. Fishbeyn VA, Norton JA, Benya RV, et al. Assessment and prediction of long-term cure in patients with Zollinger-Ellison syndrome: the best approach. Ann Intern Med. 1993; 119:199–206. [PubMed: 8323088]
53. Roy P, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome: clinical presentation in 261 patients. Medicine (Baltimore). 2000; 79(6):379–411. [PubMed: 11144036]
54. Roy P, Venzon DJ, Feigenbaum KM, et al. Gastric secretion in Zollinger-Ellison syndrome: correlation with clinical expression, tumor extent and role in diagnosis - A prospective NIH study of 235 patients and review of the literature in 984 cases. Medicine(Baltimore). 2001; 80(3):189–222. [PubMed: 11388095]
55. Raufman JP, Collins SM, Pandol SJ, et al. Reliability of symptoms in assessing control of gastric acid secretion in patients with Zollinger-Ellison syndrome. Gastroenterology. 1983; 84:108–13. [PubMed: 6128284]
56. Jensen RT, Niederle B, Mitry E, et al. Gastrinoma (duodenal and pancreatic). Neuroendocrinology. 2006; 84(3):173–82. [PubMed: 17312377]
57. Termanini B, Gibril F, Sutliff VE III, Yu F, Venzon DJ, Jensen RT. Effect of long-term gastric acid suppressive therapy on serum vitamin B^{12}levels in patients with Zollinger-Ellison syndrome. Am J Med. 1998; 104:422–30. [PubMed: 9626024]
58. Norton JA, Kahn CR, Schiebinger R, Gorschboth C, Brennan MF. Amino acid deficiency and the skin rash associated with glucagonoma. Ann Intern Med. 1979; 91:213–5. [PubMed: 111595]
59. Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. A prospective study of 107 cases and comparison with 1009 patients from the literature. Medicine (Baltimore). 2004; 83(1):43–83. [PubMed: 14747767]
60. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology. 1995; 108:1637–49. [PubMed: 7768367]
61. Benya RV, Metz DC, Venzon DJ, et al. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type 1. Am J Med. 1994; 97:436–44. [PubMed: 7977432]
62. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome: Results of a 10-year prospective study. Ann Surg. 1992; 215:8–18. [PubMed: 1531004]
63. Norton JA. Intraoperative methods to stage and localize pancreatic and duodenal tumors. Ann Oncol. 1999; 10:182–4. [PubMed: 10436817]
64. Norton JA. Surgical treatment of neuroendocrine metastases. Best Pract Res Clin Gastroenterol. 2005 August; 19(4):577–83. [PubMed: 16183528]
65. Arnold WS, Fraker DL, Alexander HR, Weber HC, Jensen RT. Apparent lymph node primary gastrinoma. Surgery. 1994; 116:1123–30. [PubMed: 7985097]
66. Jaskowiak NT, Fraker DL, Alexander HR, Norton JA, Doppman JL, Jensen RT. Is reoperation for gastrinoma excision in Zollinger-Ellison syndrome (ZES) indicated? Surgery. 1996; 120(6):1057–63.
67. von Schrenck T, Howard JM, Doppman JL, et al. Prospective study of chemotherapy in patients with metastatic gastrinoma. Gastroenterology. 1988; 94:1326–34. [PubMed: 2966088]
68. Shojamanesh H, Gibril F, Louie A, et al. Prospective study of the anti-tumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinomas. Cancer. 2002; 94:331–43. [PubMed: 11900219]
69. Pisegna JR, Slimak GG, Doppman JL, et al. An evaluation of human recombinant alpha interferon in patients with metastatic gastrinoma. Gastroenterology. 1993; 105:1179–83. [PubMed: 8405864]
70. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–81.
71. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors:; Pancreatic endocrine tumors. Gastroenterology. 2008; 135:1469–92. [PubMed: 18703061]

72. Yu F, Venzon DJ, Serrano J, et al. Prospective study of the clinical course, prognostic factors and survival in patients with longstanding Zollinger-Ellison syndrome. J Clin Oncol. 1999; 17:615–30. [PubMed: 10080607]
73. Strosberg JR, Kvols LK. A review of the current clinical trials for gastroenteropancreatic neuroendocrine tumours. Expert Opin Investig Drugs. 2007 February; 16(2):219–24.
74. Eriksson J, Stalberg P, Nilsson A, et al. Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumors. World J Surg. 2008 May; 32(5):930–8. [PubMed: 18324347]
75. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. Surg Oncol Clin North Am. 2003; 12(1):231–42.
76. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003; 197(1):29–37. [PubMed: 12831921]
77. Steinmuller T, Kianmanesh R, Falconi M, et al. Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2008; 87(1):47–62. [PubMed: 18097131]
78. Gurusamy KS, Ramamoorthy R, Sharma D, Davidson BR. Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases. Cochrane Database Syst Rev. 2009; (2):CD007060. [PubMed: 19370671]
79. Pachera S, Yokoyama Y, Nishio H, et al. A rare surgical case of multiple liver resections for recurrent liver metastases from pancreatic gastrinoma: liver and vena cava resection. J Hepatobiliary Pancreat Surg. 2009; 16(5):692–8. [PubMed: 19267257]
80. Geehan DM, Kapcala LP, Saberinia M, Scovill WA. Intravascular tumor: a previously unreported finding of glucagonoma. South Med J. 1997 July; 90(7):743–7. [PubMed: 9225901]
81. Gold RP, Black TJ, Rotterdam H, Casarella WJ. Radiologic and pathologic characteristics of the WDHA syndrome. AJR Am J Roentgenol. 1976 September; 127(3):397–401. [PubMed: 183523]
82. Fortner JG, Kim DK, Cubilla A, Turnbull A, Pahnke LD, Shils ME. Regional pancreatectomy: en bloc pancreatic, portal vein and lymph node resection. Ann Surg. 1977 July; 186(1):42–50. [PubMed: 195543]
83. Metz DC, Benjamin SB. Islet cell carcinoma of the pancreas presenting as bleeding from isolated gastric varices. Report of a case and review of the literature. Dig Dis Sci. 1991; 36:241–4. [PubMed: 1846333]
84. Ait-Ali A, Sall I, El-Kaoui H, et al. Medial pancreatectomy for a neuroendocrine tumor invading the splenic artery and vein. JOP. 2010; 11(1):75–7. [PubMed: 20065560]
85. Okuno M, Sakaguchi S, Nagayama M, et al. Nonfunctioning islet cell carcinoma presenting bleeding gastric varices and splenomegaly. Jpn J Surg. 1984 May; 14(3):244–7. [PubMed: 6087001]
86. Yamaguchi T, Takahashi H, Kagawa R, et al. Nonfunctioning pancreatic endocrine tumor presenting with hemorrhage from isolated gastric varices. Am Surg. 2005 December; 71(12): 1027–30. [PubMed: 16447473]
87. Chellappa M, Yee CK, Gill DS. Left-sided portal hypertension from malignant islet cell tumour of the pancrease: review with a case report. J R Coll Surg Edinb. 1986 August; 31(4):251–2. [PubMed: 3023606]
88. Bettini R, Boninsegna L, Mantovani W, et al. Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. Ann Oncol. 2008 May; 19(5):903–8. [PubMed: 18209014]
89. Thompson GB, Van Heerden JA, Grant CS, Carney JA, Ilstrup DM. Islet cell carcinomas of the pancreas: a twenty-year experience. Surgery. 1988; 104:1011–7. [PubMed: 2904180]
90. Fendrich V, Waldmann J, Bartsch DK, Langer P. Surgical management of pancreatic endocrine tumors. Nat Rev Clin Oncol. 2009 July; 6(7):419–28. [PubMed: 19506584]
91. Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. J Clin Oncol. 1987; 5:1502–22. [PubMed: 2443618]

92. Fendrich V, Langer P, Celik I, et al. An Aggressive Surgical Approach Leads to Long-term Survival in Patients With Pancreatic Endocrine Tumors. Ann Surg. 2006 December; 244(6):845–53. [PubMed: 17122609]

93. Kazanjian KK, Reber HA, Hines OJ. Resection of pancreatic neuroendocrine tumors: results of 70 cases. Arch Surg. 2006 August; 141(8):765–9. [PubMed: 16924083]

94. Wolf JH, Long RJ, Miller FJ Jr, Jeffries GH. Pancreatic islet cell tumor presenting as bleeding gastric varices secondary to splenic vein occlusion. Am J Dig Dis. 1977 July; 22(7):652–5. [PubMed: 195464]

95. Maclean N, Falconer CW, Gilmour IE, Webb FN. Islet cell tumours of the pancreas with portal varices and gastrointestinal haemorrhage. J R Coll Surg Edinb. 1970 July; 15(4):206–12. [PubMed: 4318001]

96. Watase M, Sakon M, Monden M, et al. A case of splenic vein occlusion caused by the intravenous tumor thrombus of nonfunctioning islet cell carcinoma. Surg Today. 1992; 22(1):62–5. [PubMed: 1312375]

97. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008 January; 9(1):61–72. [PubMed: 18177818]

98. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010 January; 11(1):38–47. [PubMed: 19942479]

99. Thomas AA, Rini BI, Stephenson AJ, et al. Surgical resection of renal cell carcinoma after targeted therapy. J Urol. 2009 September; 182(3):881–6. [PubMed: 19616232]

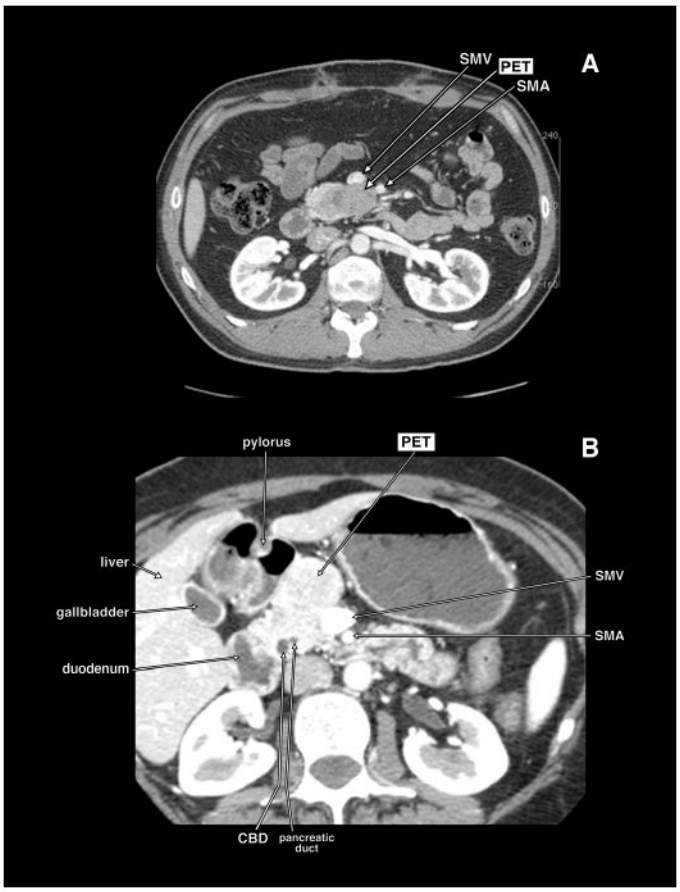

Figure 1.

Computed tomography (CT) scans of 2 different patients with pancreatic endocrine tumor (PET) in the head of the pancreas abutting the mesenteric vessels. In panel A, the PET is in the uncinate portion of the pancreatic head and lies abutting the posterior surface of the superior mesenteric vein (SMV) and superior mesenteric artery (SMA). In panel B, the PET is in the anterior portion of the head of the pancreas abutting the anterior and lateral wall of the SMV. These patients could have the PET dissected off the SMV.

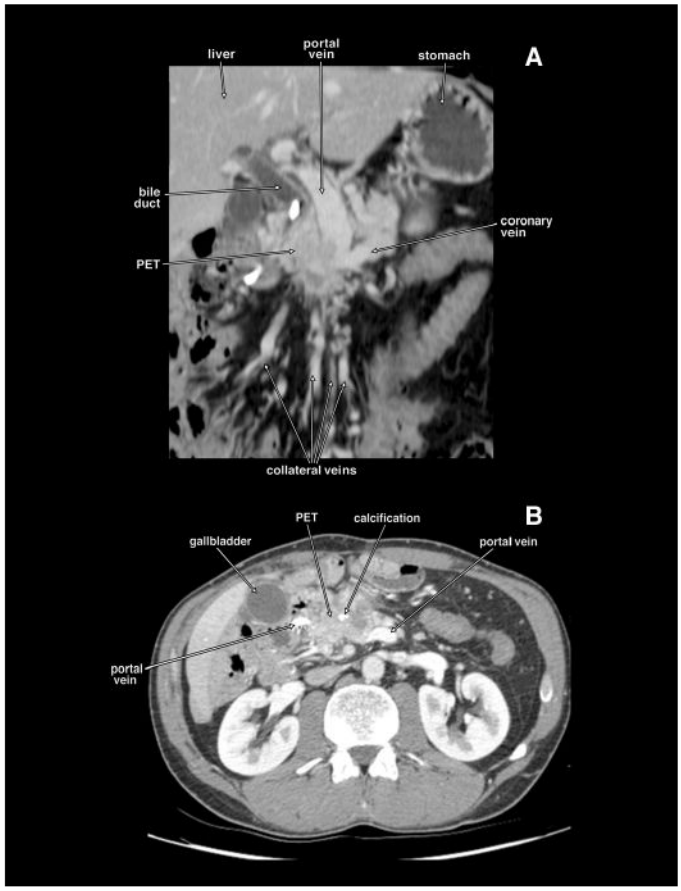

Figure 2.
Coronal planar reformation (panel A) and axial tomogram (panel B) of a computed tomography of the same patient with a locally invasive non-metastatic pancreatic endocrine tumor (PET) obstructing the proximal portal vein. The PET has calcifications. There are extensive collateral veins because of the portal vein obstruction. This patient had the portal vein resected and reconstructed with autologous femoral vein.

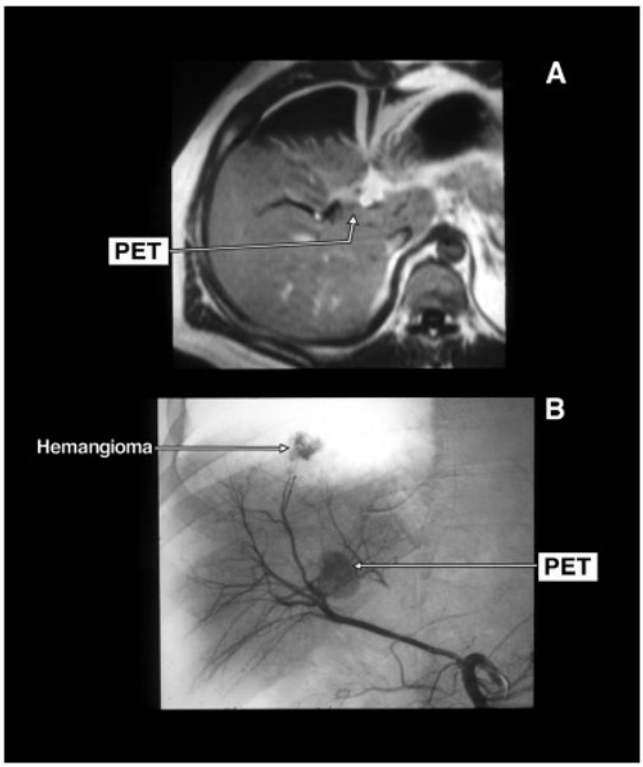

Figure 3.
Gadolinium enhanced magnetic resonance imaging (MRI) (panel A) and selective arteriogram (panel B) of a pancreatic endocrine tumor (PET) that was in the wall of the right hepatic duct. The tumor was abutting the right portal vein. There is a second liver tumor shown on the hepatic arteriogram (panel B) as a liver hemangioma. The PET was locally resected with the right hepatic duct. The tumor was dissected off the portal vein.

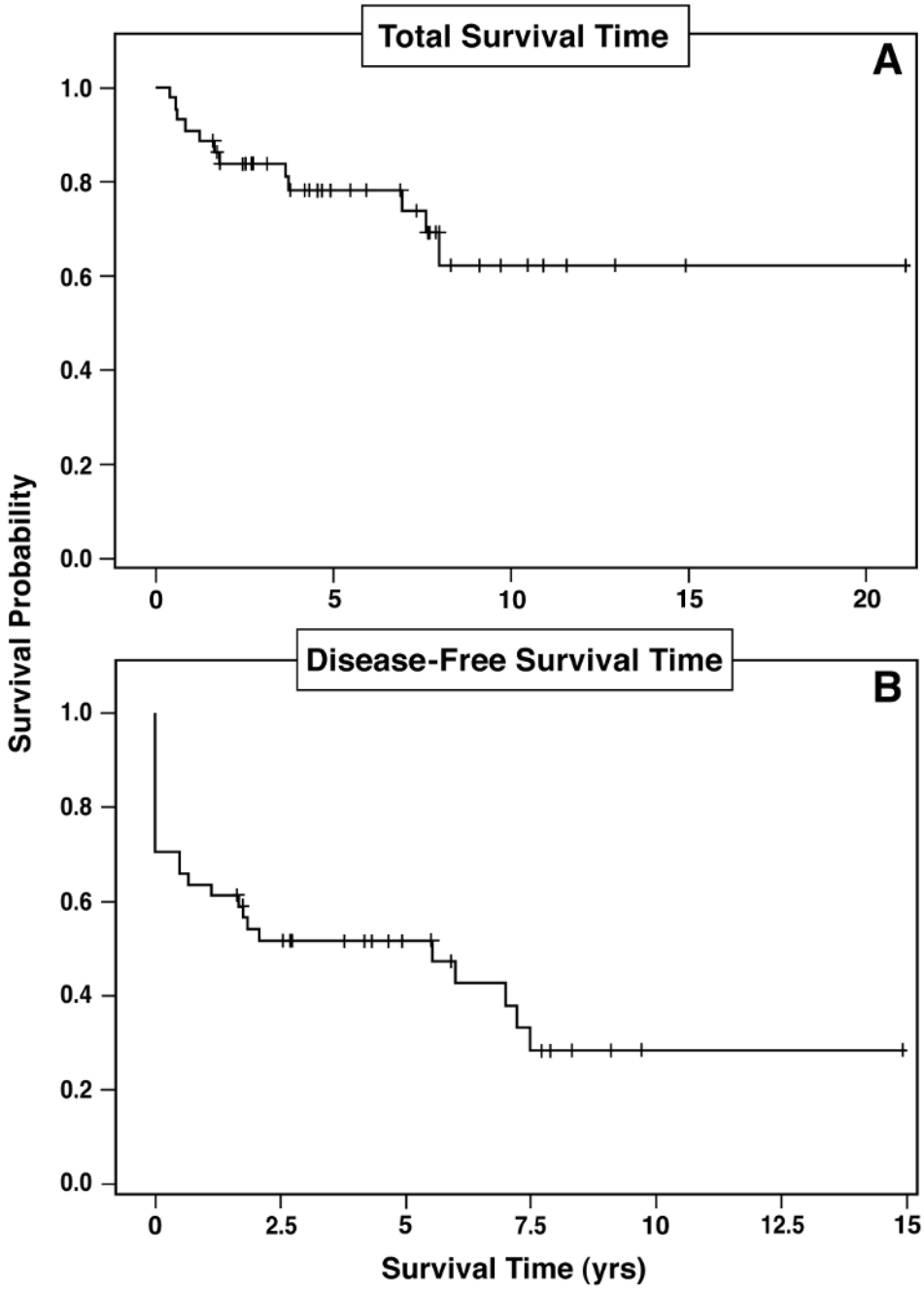

Figure 4.

Kaplan Meier plot of total survival (upper panel) and disease-free survival (lower panel) of the 44 patients with pancreatic endocrine tumors (PET) involving major vascular structures who had the tumor removed surgically. The 10-year total survival was 60 % and the 10-year disease-free survival was 33%.

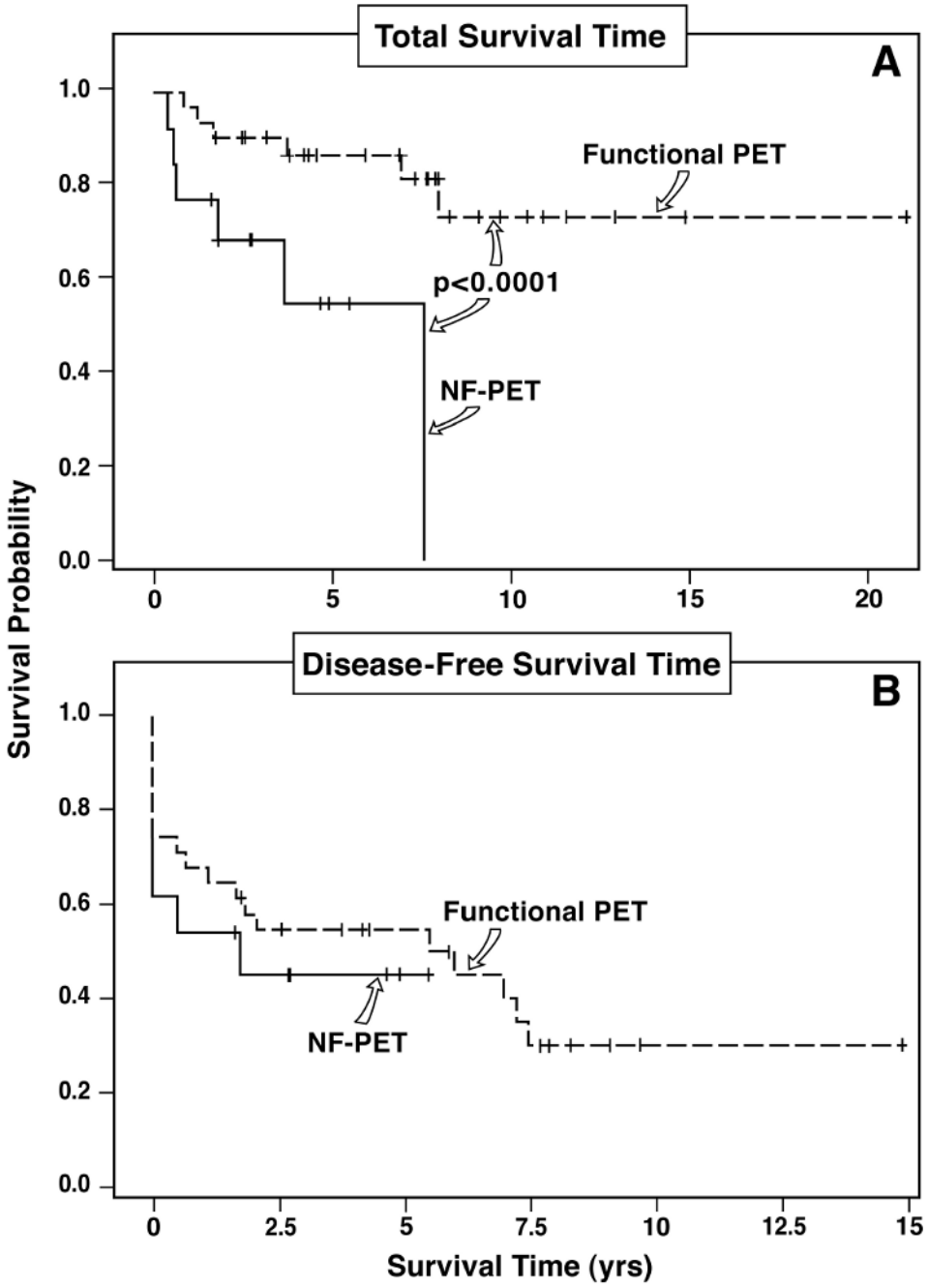

Figure 5.

Kaplan Meier plot of total survival (upper panel) and disease-free survival (lower panel) based on the clinical production of a hormone (gastrin and glucagon); that is, defined as functional vs non-functional pancreatic endocrine tumor (NF-PET). Functional PET had a significantly better total survival than NF-PET ($p<0.001$, upper panel), but there was no difference in disease-free survival (lower panel).

Table 1

Patient demographics and clinical characteristics preoperatively.

Characteristic	Number (%)
Total number	46
Male	21 (45%)
Race (Caucasian)	39 (85%)
Age Diagnosis (yrs)	
Mean ± SEM	41.7 ± 2.1
[range]	[24-76]
Type PET	
NF-PET	14 (43%)
Functional PET	32 (57%)
Gastrinoma (glucagonoma)	30 (2)[a]
Presenting symptom	
Due to functional PET	32 (70%)[b]
Due to pain	20 (30%)
MEN1 present	12 (26%)
Duration of symptoms at diagnosis (yrs) (Functional PETs)	
Mean ± SEM	5.0 ± 0.9
[range]	[0.25-17.9]
Hormone elevation (fold increase)	
median	12[c]
Mean ± SEM	292 ± 213
[range]	[3-5500]

[a] Six patients with gastrinomas with MEN1 also had NF-PETs identified preoperatively. Two patients had glucagonoma.

[b] All patients with functional PETs presented with symptoms due to hormone excess state.

[c] Gastrin elevation in the 30 patients with gastrinomas preoperatively

Table 2

Preoperative tumoral features assessed by imaging studies.

Tumoral characteristic	Number (%)
Primary tumor	
Largest size	
Mean ± SEM	5.8 ±0.5
[range]	[2-13]
Number	
Mean ± SEM	1.5 ± 0.2[a]
[range]	[1-5]
Preoperative primary location	
Pancreatic head/duodenum	27 (59%)[b]
Pancreatic body	9 (20%)
Pancreatic tail	8 (17%)
Other	2 (4%)
Metastases present	35 (76%)
Lymph node metastases present	27 (59%)
Liver metastases (limited)	14 (30%)[c]
Vessels involved/abuts	46(100%)
Portal vein or tributary	20 (43%)
SMV/SMA	16 (35%)
IVC	4 (9%)
Splenic vein	4 (9%)
Heart	2 (4%)

[a] Six patients with gastrinomas with MEN1 had multiple primary PETs Identified preoperatively.

[b] Imaging studies could not clearly differentiate whether in pancreatic head or duodenum.

[c] Limited liver metastases refer to patients without diffuse liver metastases and liver metastatic disease thought completely resectable.

Abbreviations; SMV/SMA-superior mesenteric artery/vein; IVC-inferior vena cava;

Table 3

Surgical findings

Characteristic	Number (%)
Patient numbers	
Total number patients entered	46
Number undergoing surgery	44 (100%)[a]
Number tumor resected	42 (91%) [b]
Age surgery (yrs)	
Mean ± SEM	49 ± 2
[range]	[27.5-81)
Duration diagnosis to surgery (yrs)	
Mean ± SEM	5.3 ± 1.1
[range]	[0.1-18.8]
Primary PET location/size (surgery)	
Location	
Pancreas	30 (68%)
Duodenum	12 (27%)
Other	5 (11%)[c]
Largest Primary size (cm)	
Mean ± SEM	5 ± 0.6
[range]	[0.4-15]
Metastases found at surgery	
Lymph node involvement	31 (70%)
Liver metastases	18 (41%)[d]
Tumor extent at surgery	
Primary only	8 (18%)
Primary plus lymph node involvement	31 (70%)
With liver involvement	20 (48%)[d]
Invasion/encasement of major vessel	15 (36%)[e]

[a] Two patients refused surgery.

[b] Two patients with gastrinomas had unresectable disease. One with diffuse peritoneal implants/diffuse small liver metastases and the second with complete encasement of the IVC/portal vein with arterial invasion with bleeding. The number of patients undergoing surgery was used as 100% in this table.

[c] Other refers to 1 patient with a primary gastrinoma in the bile duct (n=1), liver (n=2), heart (n=1) and lymph node (n=1).

[d] Two patients had primary gastrinoma of the liver.

[e] One patient had invasion of the heart by a gastrinoma, twelve encasement of the SMV or PV, one SMA and one involvement of the IVC.

Table 4

Type and result of surgery, follow-up and complications

Result	Number (%)
Tumor resected	42 (95%)[a]
Primary only	12 (27%)
With lymph node metastases	30 (68%)
With liver metastases	18 (41%)
Type Primary surgery	
Enucleation	5 (12%)
Resection	36 (86%)
Partial pancreatectomy	23 (55%)
Whipple resection	10 (23%)
Total pancreatectomy	2 (5%)
Liver resection	19 (45%)
Wedge resection	10 (23%)
Lobectomy	9 (21%)[b]
Vascular reconstruction	9 (21%)
SMV-portal vein	9 (21%)
SMA	1 (2%)
Surgical complications	
Surgical death	0 (0%)
Complications	12(28%)[c]
Surgical result	
Immediate tumor free	18 (42%)[d]
Recurrence	5 (12%) [d]
Time to recurrence years	
Mean ± SEM	1.7 ± 0.6
[range]	[0.5-3]
Long term disease-free	14 (33%)[d]
Status Last follow-up	
Alive	34 (77%)
Dead	10 (23%)
Years surgery to death	
Mean ± SEM	5.5 ± 0.3
[range]	[3-8]
Duration of follow-up (yrs)	
Time from surgery	
Mean ± SEM	5.7 ± 1.0
[range]	[1.3-21.2]

Result	Number (%)
Time from diagnosis	
Mean ± SEM	12.7 ± 1.2
[range]	[3.9-25.8]
Other anti-tumor treatment	18 (43%)
Chemotherapy	12 (28%)
Other	10 (23%)[e]

[a] Percentage based on 24 patients who underwent surgical exploration. Two patients had unresectable disease. See Table 3 footnote.

[b] Include a trisegmentectomy (n=1), l hepatic lobe resection(n=4), and segmentectomy (n=4)

[c] Complications include postoperative pancreatitis (n=1), abscess (n=4), wound infection (n=3), bile duct injury (n=1), leak at pancreaticojejunostomy (n=2) and ischemic bowel (n=1).

[d] Disease free status and recurrence based on serial imaging studies as described in Methods

[e] Patients treated with alpha-interferon (n=2), somatostatin analogues (n=9) or PRRT (n=1). Two that received alpha-interferon also got somatostatin analogues

Table 5

Possible prognostic factors for prolonged disease-free survival postresection

	Number (%)		
	Disease-free last follow-up		
Variable present	**Yes (n=20)**	**No (n=24)**	**Significance**
General features			
Male gender	10/20 (50%)	10/24 (41%)[a]	ns
Caucasian race	19/20 (95%)	19/24 (79%)	ns
NF-PET present	9/20 (45%)	7/24 (29%)	ns
MEN-1 present	5/20 (25%)	7/24 (29%)	ns
Hormone elevation >11.6 fold	8/20 (40%)	8/24 (33%)	ns
Pre-operative imaging			
Primary>3.7 cm	11/20 (55%)	17/24 (71%)	ns
Primary: pancreatic head/duodenum	13/20 (65%)	17/24 (71%)	ns
Possible Portal vein involvement	14/20 (70%)	20/24(83%)	ns
Possible liver metastases present	6/20 (30%)	12/24 (50%)	ns
Surgical findings			
Age surgery>47 yrs	14/20 (70%)	11/24 (46%)	ns
Primary tumor: pancreas	14/20 (70%)	16/24 (66%)	ns
Primary size>3 cm	11/20 (55%)	15/24 (63%)	ns
Lymph node metastases present	14/20 (70%)	19/24 (79%)	ns
Liver metastases found	2/20 (10%)	16/24 (66%)	<0.0001
Invasion/encasement of vessel	7/20 (35%)	8/24 (33%)	ns
Surgical treatment/result			
Liver resection	3/20 (15%)	16/24 (66%)	<0.001
Vascular reconstruction	5/20 (25%)	4/24 (17%)	ns
Immediate postoperative = tumor free	20/20 (100%)	11/24 (46%)	0.0001
Surgical followup			
Alive last follow-up	20/20 100%)	14/24 (58%)	<0.0001
Last follow-up>7.5 yrs from surgery	6/20 (30%)	11/24 (45%)	ns
Other antitumor treatment postoperative	0/20 (0%)	16/24 (66%)	<0.0001

*(a)*Proportions compared by Fisher's exact test.