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ORIGINAL ARTICLE

Role and Operative Technique of Portal Venous Tumor Thrombectomy in Patients with Pancreatic Neuroendocrine Tumors

Laura Prakash[1] · Jeffrey E. Lee[1] · James Yao[2] · Priya Bhosale[3] · Aparna Balachandran[3] · Huamin Wang[4] · Jason B. Fleming[1] · Matthew H. G. Katz[1]

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Abstract

Introduction Venous tumor thrombi have been reported in as many as 33 % of patients with pancreatic neuroendocrine tumors (pNETs). Surgical thrombectomy is often used to manage tumor thrombi that develop in association with cancers of the liver or kidney. We have likewise used thrombectomy to extract portal venous tumor thrombi in selected cases of pNET.

Methods We describe all cases of portal venous thrombectomy that were performed at our institution between 2007 and 2014 and illustrate the thrombectomy techniques we used in detail. In addition, we report the results of a PubMed search for English-language articles that were published between 1990 and 2014 and that described surgical therapy for portal venous thrombus developing in association with pNETs.

Results Among 245 patients with pNET that underwent pancreatectomy at our institution, 26 (11 %) patients required surgical management of tumor involvement of the portal vein or its tributaries concomitant with pancreatectomy, including 9 (3.8 %) patients who underwent portal venous tumor thrombectomy. Eight cases describing surgical management of tumor thrombus including two additional cases of portal venous tumor thrombectomy were identified in the medical literature. Among patients with pNET who underwent thrombectomy at our institution, all nine had non-functioning tumors and eight (89 %) had tumors of the body and/or tail of the pancreas. Six (67 %) were treated with systemic therapy prior to pancreatectomy. Seven (78 %) patients are alive at a median follow-up of 33 months (range 3 to 97).

Conclusion Venous tumor thrombectomy may be used to safely and effectively extract thrombi from the portal venous system in selected patients with advanced pNET concomitant with pancreatectomy.

Keywords pNET · Tumor thrombus · Thrombectomy · Portal vein · Pancreatoduodenectomy · Distal pancreatectomy

✉ Matthew H. G. Katz
mhgkatz@mdanderson.org

[1] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Unit 1484, PO Box 301402, Houston 77230-1402, TX, USA

[2] Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3] Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[4] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction

Pancreatic neuroendocrine tumors (pNETs) account for approximately 10 % of pancreatic neoplasms.[1] In contrast to functional pNETs, which are generally diagnosed when they are small in the setting of clinical manifestations of hormone overproduction, non-functional pNETs, which do not produce clinically significant levels of hormones, are often identified only when they are quite large and present with mass effect, local invasion, or metastasis. In such cases, tumor thrombi may exist when the primary tumor has invaded through the wall of one or more adjacent venous structures.[2, 3]

Tumor thrombi are well described in hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC). Tumor thrombi have been reported in up to 34 % of cases of HCC, typically involve the right and left branches of the portal vein, and may extend distally to or beyond the confluence.[4] In such cases,

thrombi are associated with poor prognosis as they may lead to variceal hemorrhage, hepatic encephalopathy, jaundice, ascites, and liver failure.[5] Portal vein tumor thrombi in association with localized HCC may be addressed concomitantly with resection of the primary tumor by hepatectomy, en bloc vein resection and reconstruction of the vein, or tumor thrombectomy.[4, 5] In patients with RCC, involvement of the inferior vena cava (IVC) and renal vein by tumor is characteristic and has been reported in up to 10 % of patients. Nephrectomy with thrombectomy of IVC tumor thrombi may be performed in selected cases and may require cardiopulmonary bypass depending on the site and extent of the thrombus.[6, 7]

Although tumor thrombus in association with HCC and RCC is well described, the incidence of venous tumor thrombi associated with pNETs, the clinical impact of these thrombi, and the optimal surgical strategies to address them are unclear.[2, 8] In patients with pNET, tumor thrombi may develop secondary to direct invasion of the portal vein, invasion into the splenic vein with secondary extension into the portal vein, or invasion into smaller vessels.[2] In patients with tumor thrombi that arise within the splenic vein and extend past the portosplenic confluence into the main portal vein, we have performed thrombectomy to extract the venous component en bloc with the primary tumor safely and effectively and have used this technique successfully to remove locally advanced pNETs in selected patients without the need for segmental resection and reconstruction of the mesenteric vasculature. Herein, we present a series of nine cases performed at our institution, illustrate our technical approach to portal venous thrombectomy in detail, and report a comprehensive review of the literature describing surgical treatment of portal tumor thrombi arising in association with pNET.

Cases

Between 2007 and 2014, we performed pancreatectomy for 245 patients with pNET, of whom 26 (11 %) required surgical management of tumor involvement of the portal vein, superior mesenteric vein, or its first-order tributaries concomitant with pancreatectomy. Among all 245 patients, portal tumor thrombectomy was performed concomitant with pancreatectomy in 9 (3.8 %) patients. All nine had non-functioning tumors, and eight (89 %) had tumors confined to the distal pancreas. Six (67 %) were treated with systemic therapy using streptozocin, 5-fluorouracil (5-FU) with or without doxorubicin for a median of 7.5 cycles (range 2 to 15) prior to pancreatectomy. Seven (78 %) patients are alive at a median follow-up of 33 months (range 3 to 97); one died within a year and another 4 years after surgery. The clinical courses of three illustrative patients are described in detail below, and all cases are presented in Table 1.

Patient 1

A 54-year-old woman with a remote history of breast cancer presented with an 11.2×6.5 cm well-differentiated pNET in the pancreatic body in the setting of abdominal pain, early satiety, and weight loss (Fig. 1). On baseline imaging, the mass appeared to involve the posterior gastric wall and splenic flexure and tumor was found to invade into the splenic vein and extend into the splenoportal confluence. Nine cycles of induction chemotherapy with 5-fluorouracil and streptozocin were administered leading to Response Evaluation Criteria In Solid Tumors (RECIST) stable disease prior to distal pancreatectomy, partial gastrectomy, and segmental colectomy. At surgery, tumor thrombus within the portosplenic confluence was extracted via a longitudinal portal venotomy that was repaired primarily. Examination of the resected specimen showed a well-differentiated pNET with tumor extension into the peripancreatic tissue and lymphovascular invasion. Six of ten peripancreatic lymph nodes were positive for metastatic disease, and the tumor involved both the gastric and splenic vein margins. More than 50 % of tumor cells were viable. Her postoperative course was uncomplicated. Thirty-six months following surgery, the patient developed peritoneal carcinomatosis and was treated with everolimus and, later, sunitinib; she remains alive with recurrence 97 months after the operation.

Patient 2

A 46-year-old woman with multiple endocrine neoplasia type 1 (MEN I) presented with a 3.3-cm well-differentiated pNET of the pancreatic body that invaded into the splenic and portal veins in the setting of abdominal pain, chronic pancreatitis, and hypergastrinemia (Fig. 2). Distal pancreatectomy, splenectomy, left adrenalectomy, and extraction of tumor thrombus through the splenic vein orifice were performed primarily. Duodenotomy with excision of duodenal wall gastrinomas was performed concomitantly. Histopathologic analysis revealed an intermediate grade pNET; 1 out of 50 lymph nodes were positive for metastatic pNET. Postoperatively, she suffered from an International Study Group of Pancreatic Fistula (ISGPF) grade C pancreatic leak, GI bleeding requiring transfusion, cellulitis, and pancreatitis (maximum accordion grade of 4) but recovered completely. Thirty-three months following surgery, recurrence was identified in the liver and a right upper quadrant nodule was suspected; the patient opted to continue observation.

Patient 3

A 38-year-old woman complaining of diarrhea, weight loss, abdominal pain, nausea, and vomiting presented with a 15.7× 7.1 cm pNET of the pancreatic body that invaded the spleen,

Table 1 Clinical characteristics of patients who underwent portal tumor thrombectomy concomitant with pancreatectomy at MDACC between 2007 and 2014

Age/ gender	Presenting symptoms	Location of tumor	Type of pNET	Additional treatment with curative intent (cycles)	Surgical procedure	Tumor size (cm)	Ki-67[a] (%)	Mitotic index	AJCC stage	Margin status	First site of recurrence	Disease status
54/F	Abdominal pain, early satiety, weight loss	Body/tail	Non-functioning	Preoperative FS (9)	DP, en bloc splenectomy, segmental resection of the splenic flexure of the colon, and extraction of PVTT with primary repair	10	NR	NR	IIB	R1	Peritoneum	Recurrence 36 months, alive 97 months
46/F	Abdominal pain, chronic pancreatitis, hypergastrinemia	Body	Non-functioning	None	DP, splenectomy, duodenectomy, SMV-PV tumor thrombectomy with SMV venorrhaphy	2.7	4	2/10 HPF	IIB	R0	Liver, LUQ soft tissue nodule	Recurrence 33 months, alive 33 months
67/F	None	Body/tail	Non-functioning	None	DP, left adrenalectomy, splenectomy, extraction of PVTT with SMV-PV lateral venorrhaphy	12	20–30	9/10 HPF	IIB	R1	Liver, pleural fluid	Recurrence 5 months, dead 11 months
38/F	Diarrhea, weight loss, abdominal pain, n/v	Body/tail	Non-functioning	Preoperative FAS, FS (12, 3)	DP, left adrenalectomy, splenectomy, total gastrectomy, en bloc extraction and resection of PVTT	6.5	4.70	NR	IIB	R0	NA	NED, alive 23 months
38/M	Epigastric discomfort	Body/tail	Non-functioning	None	TP, radical lymphadenectomy, splenectomy, venotomy, and thrombectomy of the splenoportal venous confluence with primary venous repair	3.4	5.10	3/10 HPF	IIB	R0	NA	NED, alive 3 months
49/F	None	Body with metastasis to the liver	Non-functioning	Preoperative FAS, FS (7, 4)	1st step: DP and splenectomy, resection of splenic portal vein confluence with embolectomy, and patch venoplasty using internal jugular vein 2nd step: left hepatectomy and resection of segments	1.6, 4	NR	NR	IV	R1	Liver	Recurrence 4 months, dead 48 months
66/M	None	Head with metastasis to the liver	Non-functioning	Preoperative FAS (2)	1st step: extended pancreaticoduodenectomy, tumor extraction from SMV-PV confluence with primary venous repair 2nd step: liver segment resection	6.3, 2.1	NR	NR	IV	R0	Liver	Recurrence 26 months, alive 97 months
59/M	None	Body/tail	Non-functioning	Preoperative FAS (5)	DP, en bloc splenectomy, excisional biopsy of lesion in the left lateral segment of liver, extraction of PVTT with SMV-PV reconstruction using a saphenous vein patch	8	NR	<1/10 HPF	IIB	R1	Retroperitoneal lymph node	Recurrence 25 months, alive 76 months
39/F	Abdominal pain, n/v, weight loss	Body/tail	Non-functioning	Preoperative FAS (6)	DP, splenectomy, extraction of PVTT with SMV-PV reconstruction using a saphenous vein patch	5	3–5	<2/10 HPF	IIB	R0	NA	NED 8 months, alive 23 months

F female; *M* male; *n/v* nausea and vomiting; *FS* 5-fluorouracil and streptozocin; *FAS* 5-fluorouracil, doxorubicin (adriamycin), and streptozocin; *DP* distal pancreatectomy; *TP* total pancreatectomy; *PV* portal vein; *PVTT* portal vein tumor thrombus; *SMV* superior mesenteric vein; *NR* not reported; *HPF* high-power fields; *R0* negative margin of resection; *R1* positive margin of resection; *LUQ* left upper quadrant; *NA* not applicable; *NED* no evidence of disease

[a] Proliferative index

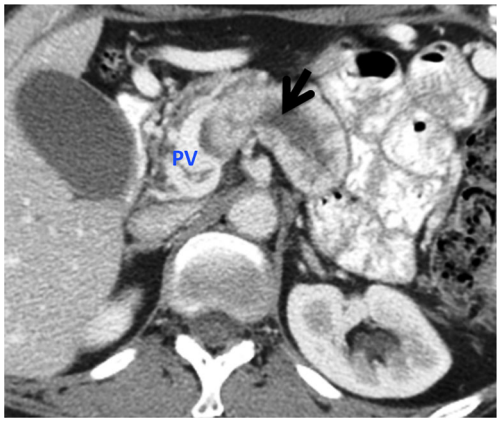

Fig. 1 Preoperative CT image from a 54-year-old woman who had received induction chemotherapy for a locally invasive pNET of the pancreatic body. The primary tumor (*arrow*) replaced the body and tail of the pancreas and directly invaded into the portosplenic venous confluence (*PV*) through the splenic vein

the posterior wall of the stomach, and the portosplenic confluence via the splenic vein (Fig. 3). Induction chemotherapy with 12 cycles of 5-FU, doxorubicin, and streptozocin followed by 3 cycles of 5-FU and streptozocin was administered leading to RECIST stable disease. A distal pancreatectomy with en bloc gastrectomy, splenectomy, left adrenalectomy, cholecystectomy, and venotomy with extraction of portal venous tumor thrombus was subsequently performed (Fig. 4). Histopathologic examination revealed an intermediate grade pNET with perineural and lymphovascular invasion and metastatic pNET in 2 of 32 lymph nodes. The postoperative course was uneventful, and she is free of disease 23 months after surgery.

Venous Thrombectomy: How We Do It

Tumor thrombus of the portal vein in the setting of pNETs of the pancreatic body often arises secondary to tumor invasion

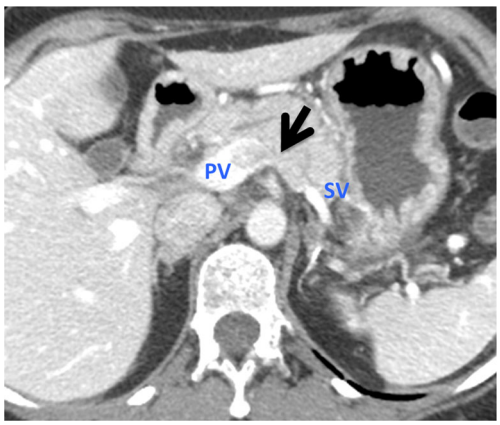

Fig. 2 CT image from a 46-year-old woman depicting a pNET of the body of the pancreas (*arrow*) that invaded the splenic vein (*SV*) and extended into the portal vein (*PV*)

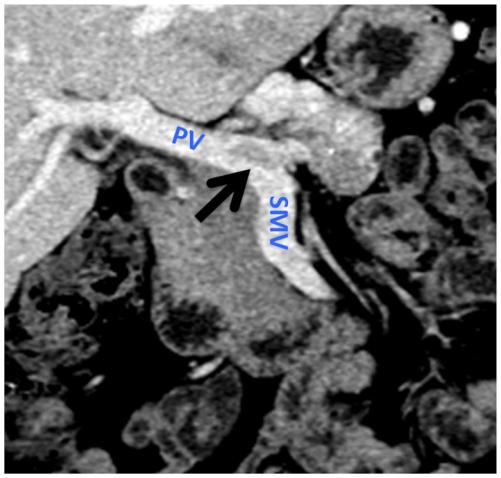

Fig. 3 Preoperative CT image from a 38-year-old woman following the administration of neoadjuvant chemotherapy. A pNET in the pancreatic body extends posteriorly along the splenic vein into the confluence of the portal vein (*PV*) and superior mesenteric vein (*SMV*)

of the splenic vein and extension into the confluence and main portal vein as a mobile appendage (Fig. 4). Thrombectomy may be safely accomplished in this circumstance by extraction of the tumor through the splenic vein orifice following complete control of the venous system (Fig. 5). Initial dissection is carried out cephalad to the neck of the pancreas to expose the bifurcation of the hepatic and splenic arteries as well as the portal vein as it emerges posteriorly. The splenic artery is ligated, and lymph nodes are swept to the left to be included in the specimen. Ligation and division of the gastroduodenal artery and cephalad retraction of the common hepatic artery may facilitate acquisition of vascular control on the portal vein; care must be taken to avoid injury to the coronary vein during this dissection. Control of the superior mesenteric vein is acquired caudally. The body and tail of the pancreas are completely mobilized, and then the pancreatic neck is

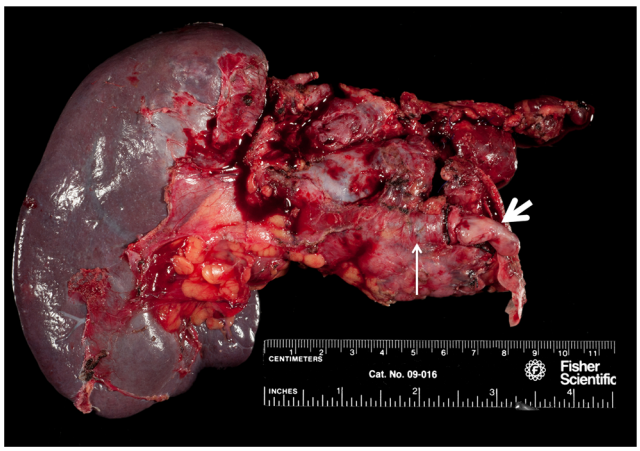

Fig. 4 Posterior view of the surgical specimen following distal pancreatectomy with en bloc splenectomy. The tumor thrombus emerges from the splenic vein (*thin arrow*) as a mobile appendage (*thick arrow*) that was extracted from the portosplenic confluence

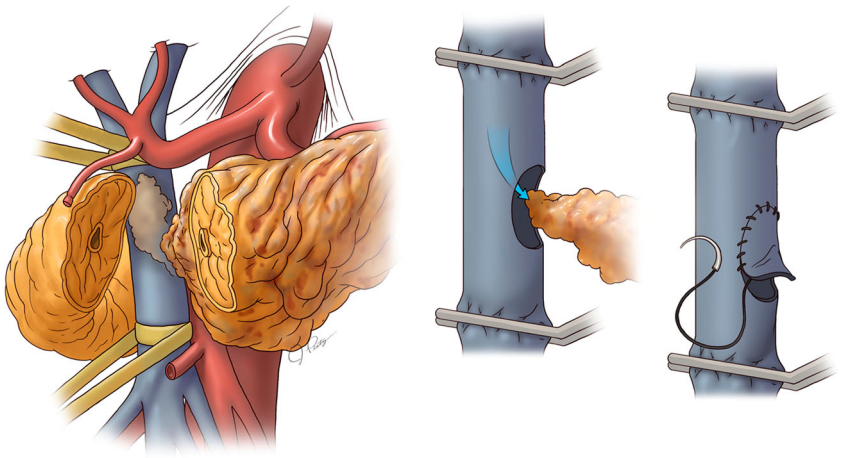

Fig. 5 Extraction of the tumor thrombus is accomplished through the splenic vein orifice following complete vascular isolation of the portosplenic confluence. The venorrhaphy may often be repaired primarily or—as in this case—using a vein or bovine pericardial patch

carefully divided over the portosplenic confluence. Palpation of the veins is used to confirm a mobile thrombus that is not affixed to the vein walls. Following intravenous administration of 5000 units of heparin, vascular clamps are placed on the PV and SMV above and below the palpable thrombus, the anterior wall of the confluence is opened to deliver the tumor thrombus through the open venotomy, and then the posterior wall of the vein is divided and the specimen passed off the fortable histopathologic evaluation. Repair of the portal vein or splenic vein may most commonly be accomplished primarily, or with a patch graft obtained from the saphenous vein or internal jugular vein, or fashioned from a small sheet of bovine pericardium, using 5-0 Prolene sutures. Prophylactic dose of Lovenox is administered for 28 postoperative days (as it is for all patients who undergo pancreatectomy in our practice); aspirin is also administered to these and other patients who have undergone resection of the portal vein or its major tributaries.

Literature Review

Methods

A search of the English-language literature with search string ("tumor thrombus" [MeSH] and "islet cell tumor" [MeSH] or "pancreatic neuroendocrine tumor" [MeSH] or "pNET" [MeSH]) was performed using PubMed. Relevant publications were also identified from searching reference lists. Studies were included for complete review if they described resection of venous tumor thrombus in association with pNET using any surgical technique.

Results

Only eight previously published manuscripts that described surgical management of portal venous thrombi that developed in association with pNET—all case reports—were identified in the literature.[3, 9–15] Patients reported therein had a median age of 53.5 years (range 33–68). The primary tumor was confined to the distal pancreas in six (75 %) patients. The tumor thrombus involved the portal vein (n=4),[3, 10, 11, 15] splenic vein (n=2),[12, 13] or both (n=2).[9, 14] Only two reported patients underwent thrombectomy,[9, 12] one operation was aborted due to disease extension,[11] four patients underwent vein resection and reconstruction,[3, 10, 14, 15] and the method of thrombus removal was unspecified for one.[13] Of the six patients with available survival data, five (83.3 %) were alive with no radiologic or chemical evidence of recurrence at a median follow-up of 25 months (range 9–60).[9, 10, 13–15] The characteristics, clinical features, therapy, surgery, pathology, and outcomes of the patients reviewed in the previously published literature are presented in Table 2.

Discussion

Here, we report the management of nine patients with pNET who underwent portal tumor thrombectomy concomitant with pancreatectomy, illustrate the surgical procedure we used in detail, and describe the results of a comprehensive review of the relevant literature. Although uncommonly performed, the surgical technique we described may be used safely to extract select tumor thrombi from the portal system that develop in association with locally advanced pNET without the need for segmental resection and reconstruction of the mesenteric vasculature. The technique therefore represents an important technical approach in the armamentarium of surgeons who routinely operate on pNETs.

Venous thrombi are broadly classified into bland, and malignant types depending on their composition and discrimination between the two may have important therapeutic implications. Bland thrombi are blood clots that are typically treated with anticoagulants or thrombolysis.[16] In contrast, malignant tumor thrombi develop secondary to local tumor

Table 2 Clinical characteristics of patients reported in the English-language literature between 1990 and 2014 to have undergone surgical therapy—using any technique—for portal venous thrombus concomitant with pancreatectomy

Reference	Age/ gender	Presenting symptoms	Location of tumor	Type of pNET	Additional treatment with curative intent (cycles)	Surgical procedure	Tumor size (cm)	AJCC stage	Margin status	Disease status
Watase et al. (1992)[13]	51/F	None	Body/tail	Non-functioning	Adjuvant 5-fluorouracil (3 years)	DP, splenectomy, distal gastrectomy, left nephrectomy, partial colectomy	NR	NR	NR	NED, alive >60 months
Yamamoto et al. (1995)[14]	49/M	Occasional abdominal pain	Body/tail	Non-functioning	None	TP, distal gastrectomy, partial resection of the transverse colon, resection and reconstruction of PV	8	NR	NR	NED, alive 38 months
Obuz et al. (2001)[11]	61/M	Blunted mental acuity, confusion, LOC	Entire pancreas	Insulinoma	None	Incomplete resection due to extensive adhesions and tumor thrombus	NA	NA	NA	NR
Bedirli et al. (2004)[10]	60/F	Abdominal pain, vomiting, weight loss	Body/tail	Non-functioning	None	DP, splenectomy, segmental resection of PV	7.2	NR	NR	NED, alive 25 months
Kawakami et al. (2007)[3]	68/M	Abdominal pain	Head	Non-functioning	None	Subtotal stomach preserving pancreaticoduodenectomy, segmental resection of PV	2.9	NR	NR	Recurrence 7 months, dead 11 months
Yamato et al. (2009)[15]	33/F	Epigastric pain	Body/tail	Non-functioning	Preoperative chemotherapy (drug and duration unknown), TAE	DP; splenectomy; left nephrectomy; adrenalectomy; partial resection of the stomach, colon, jejunum, and left lobe of the liver; segmental resection of PV	6.8	NR	NR	NED, alive 9 months
Barbier et al. (2010)[9]	56/F	None	Tail	Non-functioning	None	1st step: extended left pancreatectomy with venous thrombectomy and "clearance" of the left hepatic lobe 2nd step: right hepatectomy, RFA	NR	IV	R0	NED, alive 15 months
Rodriguez et al. (2014)[12]	44/F	Subcostal pain radiating to the epigastrium, n/v, diarrhea	Tail	Non-functioning	None	En bloc resection of DP, splenectomy, and thrombus	3.3	IB	NR	NR

F female, *M* male, *n/v* nausea and vomiting, *LOC* loss of consciousness, *TAE* transarterial embolization, *DP* distal pancreatectomy, *TP* total pancreatectomy, *RFA* radio-frequency ablation, *PV* portal vein, *R0* negative margin of resection, *NED* no evidence of disease, *NR* not reported, *NA* not applicable

extension of a primary malignancy into adjacent veins; such thrombi are invulnerable to anticoagulation, and therefore, surgery represents the only treatment option. Both types may develop in association with pNETs, and in this setting, they may often be differentiated using contrast-enhanced cross-sectional imaging studies. Like primary pNET tumors themselves, associated tumor thrombi appear to enhance in the arterial phase following the administration of intravenous contrast, as opposed to bland thrombi, which generally do not. Additionally, tumor thrombi tend to directly extend into the lumen of the adjacent vein and cause an expansion of the vessel, whereas bland thrombi result from external compression of the vessel, leading to narrowing at the site of thrombosis. Finally, tumor thrombi often appear contiguous with the primary tumor mass.[8] Discrimination between a benign and malignant etiology for a thrombus may occasionally be difficult despite these differences and the use of modern imaging modalities.[17]

Tumor thrombi commonly develop in patients with HCC and RCC, and the surgical approaches to management of such thrombi have been well documented.[5, 6, 8] Although less frequently reported, tumor thrombi are also common in patients with pNET. Indeed, we previously analyzed the cross-sectional imaging studies of 88 patients with non-functioning pNETs and found one or more tumor thrombi in either the small or large vessels in 33 % of patients.[2] In such patients, tumor thrombi may be clinically silent or may result in an increase in left-sided venous pressure.[12, 13] Left-sided hypertension may lead to the development of varices and gastrointestinal hemorrhage.[18] Furthermore, bland and tumor thrombosis of the splenic vein has been reported to be associated with higher rates of intraoperative blood loss, complications from surgery, and possibly, a shorter long-term survival following primary tumor resection.[19]

It should be emphasized that although the techniques of thrombectomy we described here may be appropriate in some cases of pNET which involve the portal venous system, these cases must be well selected. Three important considerations are noteworthy in this regard. First, tumor thrombectomy is only appropriate when mobile tumor thrombus exists within the venous system and extends as an appendage from the primary tumor; it is clearly inappropriate in cases in which venous involvement by tumor is characterized by direct encasement and narrowing of the vessel. Second, the need for resection of additional organs and vital structures, in addition to portal thrombectomy and pancreatectomy, should be anticipated in these cases and the operative plan should be rigorously developed prior to entry into the operating room. Finally, a comprehensive treatment strategy should be developed within the context of a multidisciplinary group and preoperative therapy may be considered in many of these locally advanced cases, both to address macro- and micrometastases and in an attempt to reduce the anatomic extent of the primary tumor. Cytotoxic chemotherapy regimens such as 5-fluorouracil, doxorubicin, and streptozocin (FAS), a regimen with a response rate of approximately 39 %, are preferred over targeted agents like everolimus and sunitinib in this scenario.[20, 21] A combination of capecitabine and temozolomide has also been associated with an exceptionally high and durable response rate, particularly in the setting of metastatic pNET.[22]

In summary, we have described a technique for portal venous thrombectomy that may be used to safely extract tumor thrombi that may develop in association with pNET. This strategy may be used to effectively resect locally advanced primary tumors without the need for segmental venous resection and reconstruction in selected cases.

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