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ORIGINAL ARTICLE – ENDOCRINE TUMORS

The Pancreas as a Site of Metastasis or Second Primary in Patients with Small Bowel Neuroendocrine Tumors

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ABSTRACT

Background. The small bowel and pancreas are the most common primary sites of neuroendocrine tumors (NETs) giving rise to metastatic disease. Some patients with small bowel NETs (SBNETs) present with synchronous or metachronous pancreatic NETs (PNETs), and it is unclear whether these are separate primaries or metastases from one site to the other.

Methods. A surgical NET database including patients undergoing operations for SBNETs or PNETs was reviewed. Patients with synchronous or metachronous tumors in both the small bowel and pancreas were identified, and available tissues from primary tumors and metastases were examined using a 4-gene quantitative polymerase chain reaction (qPCR) and immunohistochemistry (IHC) panel developed for evaluating NETs of unknown primary.

Results. Of 338 patients undergoing exploration, 11 had NETs in both the small bowel and pancreas. Tissues from 11 small bowel tumors, 9 pancreatic tumors, and 10 metastases were analyzed. qPCR and IHC data revealed that three patients had separate SBNET and PNET primaries, and five patients had SBNETs that metastasized to the pancreas. Pancreatic tissue was unavailable in two patients, and qPCR and IHC gave discrepant results in one patient.

Conclusions. NETs in both the small bowel and pancreas were found in 3% of our patients. In nearly two-thirds of evaluable patients, the pancreatic tumor was a metastasis from the SBNET primary, while in the remaining one-third of patients it represented a separate primary. Determining the origin of these tumors can help guide the choice of systemic therapy and surgical management.

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have an annual incidence of 3.56/100,000 persons, with approximately 1.2/100,000 arising in the small bowel and 0.8/100,000 in the pancreas.[1] These tumors frequently present with metastases, and approximately 60% of patients will eventually develop metastatic disease.[2] The metastatic patterns of neuroendocrine tumors (NETs) have been characterized using both population-based[3] and radiographic[4] approaches. The overwhelmingly favored site for NET metastases, accounting for approximately 80% of lesions, is the liver, but distant nodal and bone metastases are also frequently seen, and peritoneal spread is not uncommon. Most NET metastases arise from tumors originating either in the small bowel (SBNET) or the pancreas (PNET).[3,4]

Some patients present with NETs located in both the small bowel and the pancreas, and it is not clear if they have two separate primary tumors, or metastasis from one site to the other. Separate primary NETs of the small bowel and pancreas have been reported in association with familial syndromes such as MEN1,[5] but due to the rarity of these tumors, the sporadic occurrence of both in a single patient is unusual. Previous studies of NET metastases have not noted the propensity of these tumors to metastasize to either the pancreas or the small bowel.[2–4]

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For patients with NETs in both the small bowel and pancreas, determining the primary site may have important implications for prognosis and treatment. Survival is shorter in patients with metastatic PNETs when compared with those with metastatic small bowel NETS (SBNETs),[1] and the predicted response to systemic therapy also varies depending on the primary site.[6,7] Resection of the primary tumor has also been shown to improve overall survival, even in patients with metastatic NETs,[8–10] and surgical decision making could be influenced by whether one of these lesions is a metastasis rather than a separate primary.

Pathologists routinely employ immunohistochemical examination to predict the primary site in patients with NET liver metastases and an unknown primary.[11] Previous studies have demonstrated the utility of combining immunohistochemistry (IHC) with quantitative polymerase chain reaction (qPCR) gene expression profiling for identifying the primary site from metastatic NETs of unknown origin.[12,13] Our objective was to identify patients with NETs in both the small bowel and pancreas, and to use a previously validated qPCR gene expression and IHC panel to predict the site of origin for tissue obtained from the small bowel tumor, the pancreatic tumor, and liver or nodal metastases.

METHODS

A prospectively maintained NET database from the University of Iowa that contains clinicopathologic data for patients operated on for GEPNETs between March 1999 and October 2017 was reviewed, and patients with NETs found within both the small bowel and the pancreas were identified. Informed consent was provided by all patients in the database in accordance with a protocol approved by the University of Iowa Institutional Review Board. Patients were included if a histologic diagnosis of NET was made for tumors at both sites, or if the NET diagnosis was made for a tumor at either site, and a lesion consistent with NET was seen at the other site on initial or follow-up imaging. Patients with SBNETs and peripancreatic nodal disease were excluded in order to include only pancreatic tumors contained within the parenchyma of the organ. All available tissues from these patients were examined using qPCR and IHC to determine the primary site.

Quantitative Polymerase Chain Reaction Gene Expression Panel

Tissue samples were obtained from the small bowel, pancreas, nodal metastases, and liver metastases at the time of surgery and stored at − 20 °C in RNALater (Thermo Fisher Scientific, Waltham, MA, USA). Total RNA was extracted using the TRIzol method (Thermo Fisher Scientific) and reverse transcribed to complementary DNA (cDNA). qPCR was performed using Taqman probes and primers and the 7900HT Fast Real-Time PCR system (Thermo Fisher Scientific). Expression levels were calculated from reactions performed in triplicate for four genes (*BRS3*, bombesin-like receptor-3; *OPRK1*, opioid receptor kappa-1; *OXTR*, oxytocin receptor; and *SCTR*, secretin receptor), which are significantly differentially expressed in SBNETs and PNETs.[13,14] Two internal control genes, polymerase (RNA) II polypeptide A (*POLR2A*) and glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) were used to calculate the delta cycle threshold (dCT) for each gene for each tissue sample. These dCT values were then used to predict the site of origin using a previously validated algorithm for NET metastases.[13]

Immunohistochemistry

Immunohistochemical staining was performed for all available tissues, either on tumor in tissue microarrays (TMAs) or whole section slides, on 4-μm tissue sections using antibodies against caudal type homeobox 2 (CDX2; clone DAK-CDX2; dilution 1:25; Agilent Dako, Santa Clara, CA, USA), serotonin (clone 5HT-H209; dilution 1:50; Agilent Dako), paired box gene 6 (PAX6; clone PAX6; dilution 1:25; Developmental Studies Hybridoma Bank, Iowa City, IA, USA), insulin gene enhancer binding protein ISL-1 (Islet 1; clone 40.3A4; dilution 1:200; Developmental Studies Hybridoma Bank), and clusterin (clone 41D; dilution 1:7500; MilliporeSigma, Burlington, MA, USA). Tissue sections were deparaffinized, rehydrated, and subjected to heat-induced epitope retrieval in Dako Target Retrieval Solution pH 6 (serotonin) or pH 9 (all others). Endogenous peroxidase activity was blocked with 3% hydrogen peroxide. After primary antibody incubation (15 min for CDX2 and clusterin; 30 min for PAX6, ISL-1, and serotonin), the Dako EnVision FLEX + kit was used for primary antibody detection (15 min for CDX2, ISL-1, and clusterin; 30 min for serotonin and PAX6).

Immunohistochemical staining was assessed as absent, weak (1+), moderate (2+), or strong (3+), and evaluated in a blinded fashion. Assignment of the small bowel primary was based on moderate or strong CDX2 and/or serotonin expression in the absence of PAX6, ISL-1, or clusterin expression. The designation of pancreatic origin was made by the presence of any PAX6 or ISL-1 expression.[11,15]

Analysis

Patients with both tumors predicted to arise from the small bowel were classified as SBNET metastasis (SBMet),

while those with both tumors predicted to arise from the pancreas were classified as PNET metastasis (PMet). When tissue from one primary site was unavailable, patients were classified as 'Unknown'. When tumors of the small bowel and pancreas were both predicted to have originated independently at each site, patients were classified as 'Separate Primaries' (Separate). Finally, if there was disagreement between the predictions made by qPCR and IHC, the patient was classified as 'Discrepant'. Overall survival was calculated using the Kaplan–Meier method. All statistical analyses were performed in R version 3.4.1 (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Overall, 338 patients undergoing surgery for NETs were identified in the database, and 11 of these had NETs in both the small bowel and pancreas (Table 1). None of these patients had a hereditary cancer syndrome associated with NETs. Eight patients presented with synchronous lesions at both sites, while three patients presented initially with small bowel tumors and later developed pancreatic lesions. All patients with lesions in the body or tail of the pancreas underwent distal pancreatectomy, or, in one case, central pancreatectomy (Table 2). The three patients who were observed had pancreatic head masses; one patient developed a common bile duct obstruction while under observation, requiring endoscopic stenting; one patient developed pancreatic ductal obstruction; and the last patient has remained asymptomatic from their pancreatic head lesion now 4 years post-operation. Additional surgical and systemic treatments received are shown in Table 2. Six patients are alive following surgery, and the median overall survival calculated from the date of diagnosis for all 11 patients was 10.6 years.

Tissues that were predicted to originate in the small bowel showed strong CDX2 and serotonin positivity and were negative for ISL-1 and/or PAX6, while tissues predicted to originate in the pancreas showed the opposite pattern (Fig. 1), with three exceptions: one ileal tumor was only weakly CDX2-positive but was strongly serotonin-positive; one ileal tumor was only weakly serotonin-positive but was strongly CDX2-positive; and one pancreatic tumor was weakly CDX2-positive but also expressed both PAX6 and ISL-1. By design, the qPCR gene expression prediction algorithm will never return an 'uncertain' value—a primary site prediction is always made.[12] In tissues evaluated by qPCR and IHC, both techniques made consistent predictions for the primary site in all but one case—the pancreatic tumor of patient 494-1. This tumor was predicted to originate in the small bowel by IHC, while the qPCR gene expression algorithm predicted a PNET primary (Table 1, Fig. 2).

In five patients, both the tumors in the small bowel and the pancreas were predicted to originate from the small bowel, indicating a primary SBNET that had metastasized to the pancreas (Table 1). Three patients were found to have separate primary NETs of both the pancreas and the small bowel. In two patients, no pancreatic resection or biopsy was performed, and thus no conclusion regarding the origin of the pancreatic tumor could be drawn; the imaging findings from these two patients are shown in Fig. 3. In one patient, the pancreatic tumor was predicted to originate in the pancreas by qPCR, while IHC predicted a small bowel metastasis. In all three patients with separate

TABLE 1 Assignment of primary site based on the prediction made by qPCR/IHC

Patient ID	Presentation	SB tumor	Pa tumor	Metastasis	PaT size	Classification
517-1	Synchronous	NA/SB	NA/Pa	Pa/Pa	10	Separate
133-1	Synchronous	SB/SB	Pa/Pa[a]	Pa/NA	3.2	Separate
256-1	Metachronous (83 mos)	SB/SB	SB/SB	SB/SB	1.2	SBMet
137-1	Metachronous (96 mos)	SB/SB	NA/NA	SB/SB	3.1	Unknown
339-1	Synchronous	SB/SB	SB/SB	SB/SB	3	SBMet
494-1	Synchronous	SB/SB[a]	Pa/SB	SB/NA	2.5	Discrepant
220-1	Metachronous (27 mos)	SB/SB	NA/SB	SB/SB	1.8	SBMet
506-1	Synchronous	SB/SB	SB/SB	NA/NA	2.7	SBMet
518-1	Synchronous	SB/SB	SB/SB	SB/NA	3.8	SBMet
547-1	Synchronous	SB/SB	Pa/Pa	Pa/NA	5.1	Separate
408-1	Synchronous	SB/NA	NA/NA	SB/NA	1.6	Unknown

qPCR quantitative polymerase chain reaction, *IHC* immunohistochemistry, *NA* not available, *Pa* pancreas, *SB* small bowel, *mos* months to pancreatic tumor appearance after NET diagnosis, *PaT size* largest dimension of pancreatic tumor, in centimeters, *NET* neuroendocrine tumor, *SBMet* small bowel NET metastasis

[a]IHC was not performed on two samples; the primary site was assigned by morphology

primaries, the available liver metastases were predicted to arise from the PNET, while in patients with SBNET primaries, the evaluable liver metastases were predicted to be of small bowel origin. Separate primary PNETs tended to be larger than pancreatic SBNET metastases, however this difference did not reach statistical significance (mean 6.1 vs. 2.5 cm, $p = 0.2$).

DISCUSSION

The coincidence of NETs in the small bowel and pancreas is rare, occurring in only 11 of 338 patients (approximately 3%) in our database. Five of 11 evaluable patients in this study were predicted to have SBNETs that had metastasized to the pancreas, while three had separate primary SBNETs and PNETs. We did not observe any patients predicted to have a primary PNET that had metastasized to the small bowel. There is a paucity of literature describing any of these clinical scenarios. A single case report describes a patient with synchronous SBNET and PNET, which were determined to be separate primary tumors based on IHC and morphology.[16] Another case report described a patient with a primary rectal NET with metastasis to the pancreas and liver.[17] Finally, a larger series reported on pancreatic involvement in five patients with primary SBNETs or duodenal NETs.[18] In a study of 3827 autopsies examining the metastatic patterns of cancers from a variety of primary sites, the pancreas was a relatively uncommon site for metastases, and none of these arose from a small bowel primary tumor.[19] This study did not describe the histology of tumors, but another paper investigating 103 patients with secondary tumors of the pancreas reported five cases of neuroendocrine carcinoma that had metastasized to the pancreas, although none of

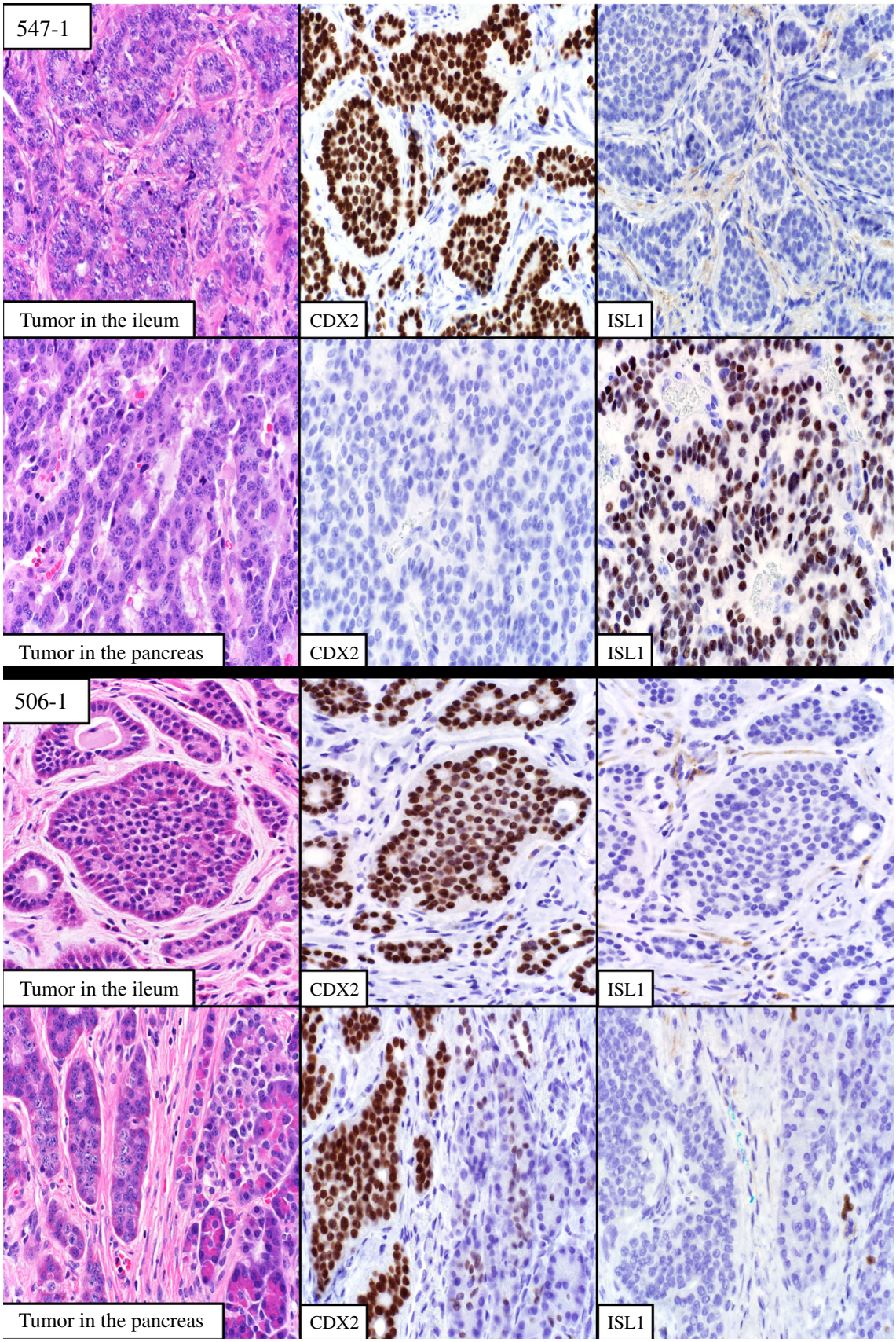
◀**FIG. 1** Immunohistochemical staining from the small bowel and pancreatic tumors in patients 547-1 and 506-1. *CDX2* positivity indicates small bowel origin, while *ISL1* positivity indicates pancreatic origin

TABLE 2 Clinical characteristics of the patient cohort

Patient ID	FU time	Died	SSA	Surgical treatment	Other treatment	PNET location
517-1	12.65	No	Yes	Synchronous distal pancreatectomy and small bowel resection, cholecystectomy, subsequent liver debulking	Percutaneous liver ablation	Body
133-1	4.98	Yes	Yes	Synchronous distal pancreatectomy and ileocolectomy, cholecystectomy liver debulking, para-aortic lymphadenectomy	CAPTEM, everolimus, bland HAE, PTK787 trial	Tail
256-1	13.21	Yes	Yes	Ileocolectomy and cholecystectomy followed by distal pancreatectomy and liver debulking	Pre-op PRRT, post op PRRT, TACE, CAPTEM	Body
137-1	10.56	Yes	Yes	Ileocolectomy, cholecystectomy and liver debulking, observation of pancreatic tumor	FOLFOX, bland HAE, everolimus, CAPTEM	Head
339-1	2.59	Yes	Yes	Synchronous ileocolectomy and distal pancreatectomy, cholecystectomy	Y90 HAE, TKM-PLK1 trial, everolimus	Tail
494-1	2.11	No	Yes	Synchronous ileocolectomy and distal pancreatectomy with liver debulking	None	Body
220-1	6.07	Yes	Yes	Small bowel resection, cholecystectomy, endoscopic pancreatic mass biopsy	None	Head
506-1	1.71	No	No	Synchronous small bowel resection and central pancreatectomy, cholecystectomy	None	Body
518-1	1.51	No	Yes	Synchronous small bowel resection and distal pancreatectomy, cholecystectomy, liver debulking	Pre-op sunitinib	Tail
547-1	1.21	No	Yes	Synchronous small bowel resection and distal pancreatectomy, cholecystectomy, liver debulking, para-aortic lymphadenectomy	None	Tail
408-1	4.18	No	Yes	Small bowel resection, cholecystectomy and liver debulking	None	Head

All bowel resections include regional lymphadenectomy to the base of the mesenteric vessels; liver debulking includes intraoperative ablation, enucleation wedge resection, and/or formal hepatectomy

FU time time in years to death or last follow-up, *SSA* somatostatin analog treatment, *CAPTEM* capecitabine/temozolomide, *FOLFOX* folinic acid, fluorouracil and oxaliplatin, *PRRT* peptide receptor radionuclide therapy, *HAE* hepatic artery embolization, *TACE* transarterial chemoembolization, *pre-op* preoperatively, *post-op* postoperatively, *PNET* pancreatic neuroendocrine tumors


547-1
Tumor in the ileum
CDX2
ISL1
Tumor in the pancreas
CDX2
ISL1
506-1
Tumor in the ileum
CDX2
ISL1
Tumor in the pancreas
CDX2
ISL1

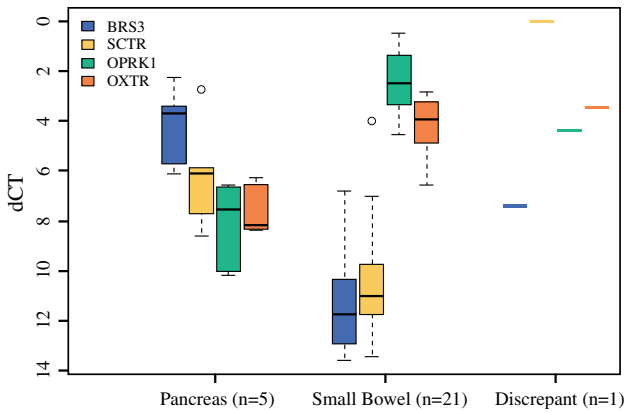


FIG. 2 Gene expression profiles of tumors from the small bowel, pancreas, and liver, grouped according to the predicted primary tissue according to IHC and the qPCR panel. Five tumors (2 pancreatic tumors, 3 metastases) were assigned a pancreatic origin based on IHC and qPCR, 21 were assigned a small bowel origin (11 small bowel tumors, 5 pancreatic tumors, 5 liver metastases), and the discrepant tumor was assigned small bowel by IHC and pancreas by qPCR. The y-axis is inverted, with a lower dCT indicating higher expression. *IHC* immunohistochemistry, *qPCR* quantitative polymerase chain reaction, *dCT* delta cycle threshold, *BRS3* bombesin-like receptor-3, *OPRK1* opioid receptor kappa-1, *OXTR* oxytocin receptor, and *SCTR* secretin receptor

these were from SBNETs.[20] Another review of 109 secondary pancreatic tumors in autopsies and surgical specimens further supports the rarity of metastases from the small bowel to the pancreas, with only two pancreatic tumors originating from small bowel gastrointestinal stromal tumors.[21]

Due to the limited literature describing dual primary SBNETs and PNETs, or SBNETs metastasizing to the pancreas, there is no standardized approach to the treatment of these two clinical situations. Evidence supporting the benefits of several systemic therapies, including various chemotherapies, is stronger in PNETs than SBNETs, and thus identifying the origin of the pancreatic tumor and the liver metastases may help guide the use of systemic therapy.[6,7,22,23] Additionally, there is substantial evidence that patients with metastatic PNETs tend to have shorter overall survival than those with metastatic SBNETs,[1,24,25] and if survival in patients with both of these tumors is largely defined by the more aggressive of the two, determining that the pancreatic tumor originated in the pancreas may aid prognostication. In patients with separate primary tumors in our series, the liver metastases invariably arose from the PNET, lending further support to this idea since liver failure is the leading cause of death in these patients.[8]

The mechanism by which SBNETs spread to the pancreas is unclear. Tumors may reach the pancreas by several routes: direct invasion, lymphatic or hematogenous metastasis, or peritoneal dissemination. The small bowel tumors in this series were not directly adjacent to the pancreas, and no patients had peritoneal metastases evident during surgical exploration or on imaging, leaving lymphatic or vascular spread as the possible mechanisms. Circulating tumor cells are detectable in blood samples from approximately half of the patients with metastatic NETs, and have been found to correlate with tumor burden and survival.[26] That these tumor cells give rise to metastases preferentially in certain organs, such as the liver and bone, argues for a favorable tumor microenvironment in these tissues. Although NET metastases to the pancreas are significantly rarer, it is possible that a similarly favorable tumor microenvironment may account for the establishment of these lesions.

The optimal surgical management for PNETs in patients with NETs in the small bowel and pancreas remains to be defined. If the pancreatic mass can be resected with a distal pancreatectomy, it has been our practice to perform this operation, which is generally associated with a 15–20% overall complication rate.[27,28] In contrast, resection of tumors in the pancreatic head usually requires pancreaticoduodenectomy, which is associated with a 45–50% overall complication rate.[28,29] All three patients whose pancreatic tumors were observed in this series had masses in the head of the pancreas. Two of these patients developed obstructive symptoms associated with the pancreatic metastases. In patients with head lesions, the benefits of pancreaticoduodenectomy to prevent obstruction and possibly improve survival must be carefully balanced against the potential for complications and the extent of disease, for these patients commonly also have multiple liver metastases.

CONCLUSIONS

NETs located in both the small bowel and pancreas were present in 3% of patients undergoing surgery for GEPNETs at a large referral center. Approximately two-thirds of these patients were found to have primary SBNETs that had metastasized to the pancreas, while one-third had separate primary SBNETs and PNETs. Patients with dual primaries tended to have larger pancreatic tumors, and in these patients, the liver metastases were invariably found to represent metastases from the PNET. Systemic therapy in patients with tumors at both sites should be informed by the identity of the pancreatic tumor. Optimal therapy for patients with NET metastases to the pancreas is not clear, but the potential complications of resection must be weighed carefully against the potential for obstruction from an enlarging, unresected lesion. Preoperative biopsy of the PNET, along with specific immunohistochemical stains to determine the site of origin, may aid in this clinical decision making.

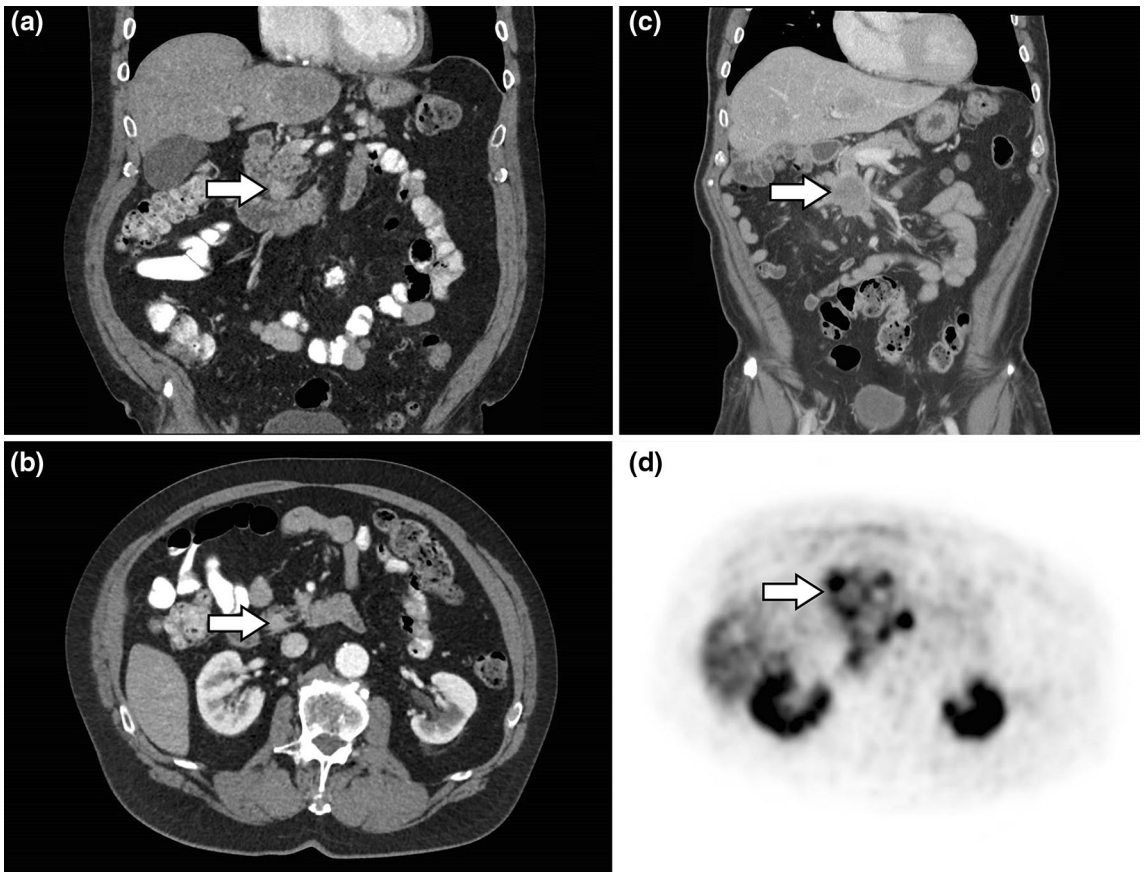


FIG. 3 Imaging findings in both patients for whom pancreatic tissue was unavailable. Patient 408-1 had an enhancing pancreatic mass on arterial phase CT in the (**a**) axial and (**b**) coronal sections. This mass was confirmed by intraoperative ultrasound and palpation to be contained within the pancreatic parenchyma, in proximity to the duct. Pancreatic mass in patient 137-1 is shown on (**c**) coronal CT and (**d**) on the axial section from a DOTA-PET scan. *CT* computed tomography

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