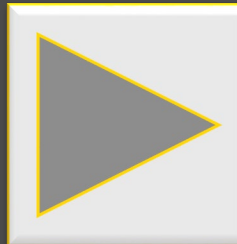


The Pancreas as a Site of Metastasis or Second Primary in Patients with Small Bowel Neuroendocrine Tumors

Aaron T. Scott, MD¹, Daniel Pelletier, MD², Jessica E. Maxwell, MD¹, Scott K. Sherman, MD³, Kendall J. Keck, MD¹, Guiying Li, MD¹, Joseph S. Dillon, MD⁴, Thomas M. O’Dorisio, MD⁴, Andrew M. Bellizzi, MD², and James R. Howe, MD¹

University of Iowa Carver College of Medicine, Departments of ¹Surgery, ²Pathology and ⁴Internal Medicine, ³University of Chicago, Department of Surgery

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INTRODUCTION

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) also present with pancreatic NETs (PNETs), and it is unclear whether these are separate primaries or metastases from one site to the other. We examined this question using gene expression and immunohistochemistry (IHC) in patients with NETs at both sites.

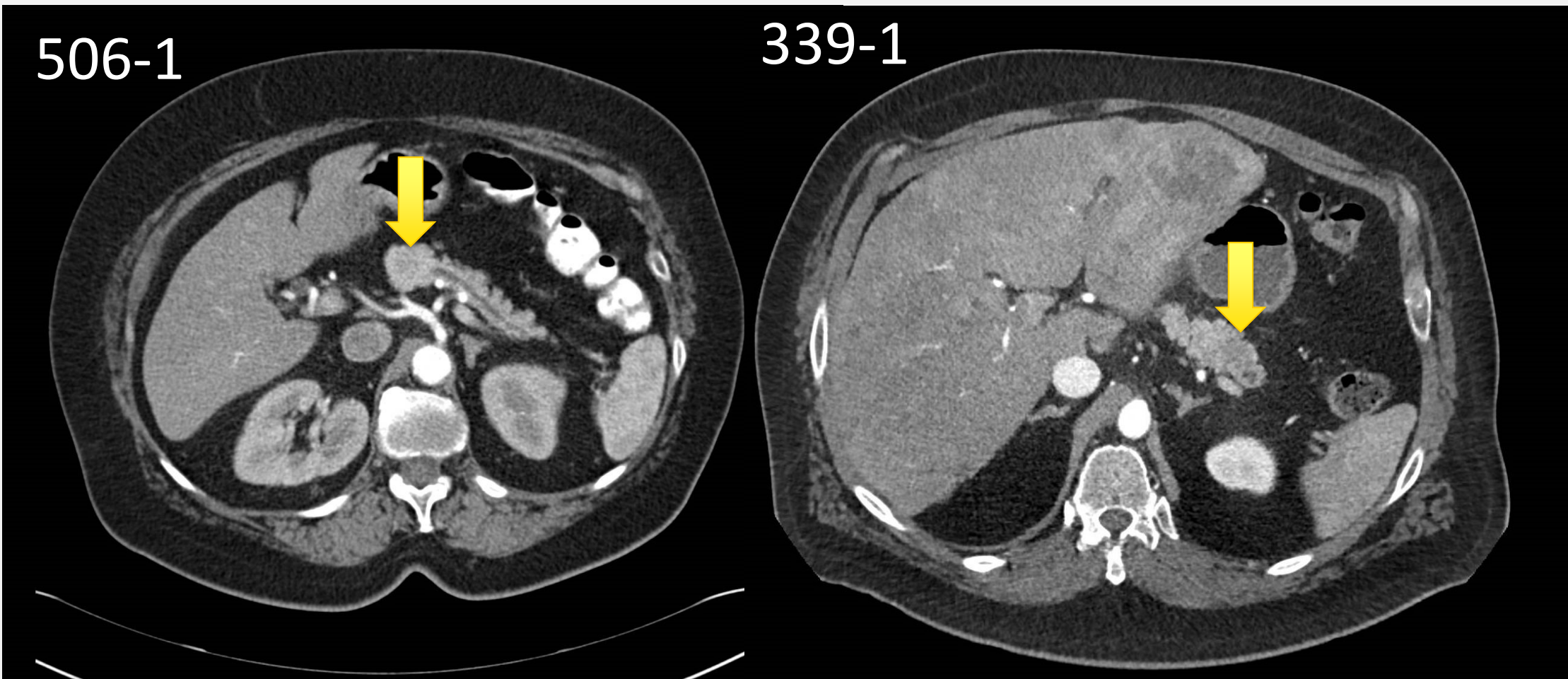


Figure 1: SBNET metastases to the pancreas may present as a hyperenhancing mass as in patient 506-1, or an indistinct, hypoenhancing mass as in patient 339-1.

METHODS

A surgical NET database including patients undergoing operations for SBNETs or PNETs was reviewed. Patients with both tumors at exploration or on follow-up imaging were identified, and available tissues from primary tumors and metastases were examined qPCR and immunohistochemistry (IHC). The site of origin for each tissue was predicted using qPCR expression data (Eq. 1, Fig. 2)¹ and an immunohistochemistry (IHC) panel which included CDX2, serotonin, Islet 1, PAX6 and clusterin (Fig. 3).^{2,3}

$$Pred = \frac{e^{(229.31 - (42.61 \times dCT_{BRS3}) + (20.55 \times dCT_{OPRK1}))}}{1 + e^{(229.31 - (42.61 \times dCT_{BRS3}) + (20.55 \times dCT_{OPRK1}))}}$$

Equation 1: Prediction using dCTs obtained from qPCR. A value ≤ 0.5 indicates small bowel primary while > 0.5 indicates a pancreatic primary.

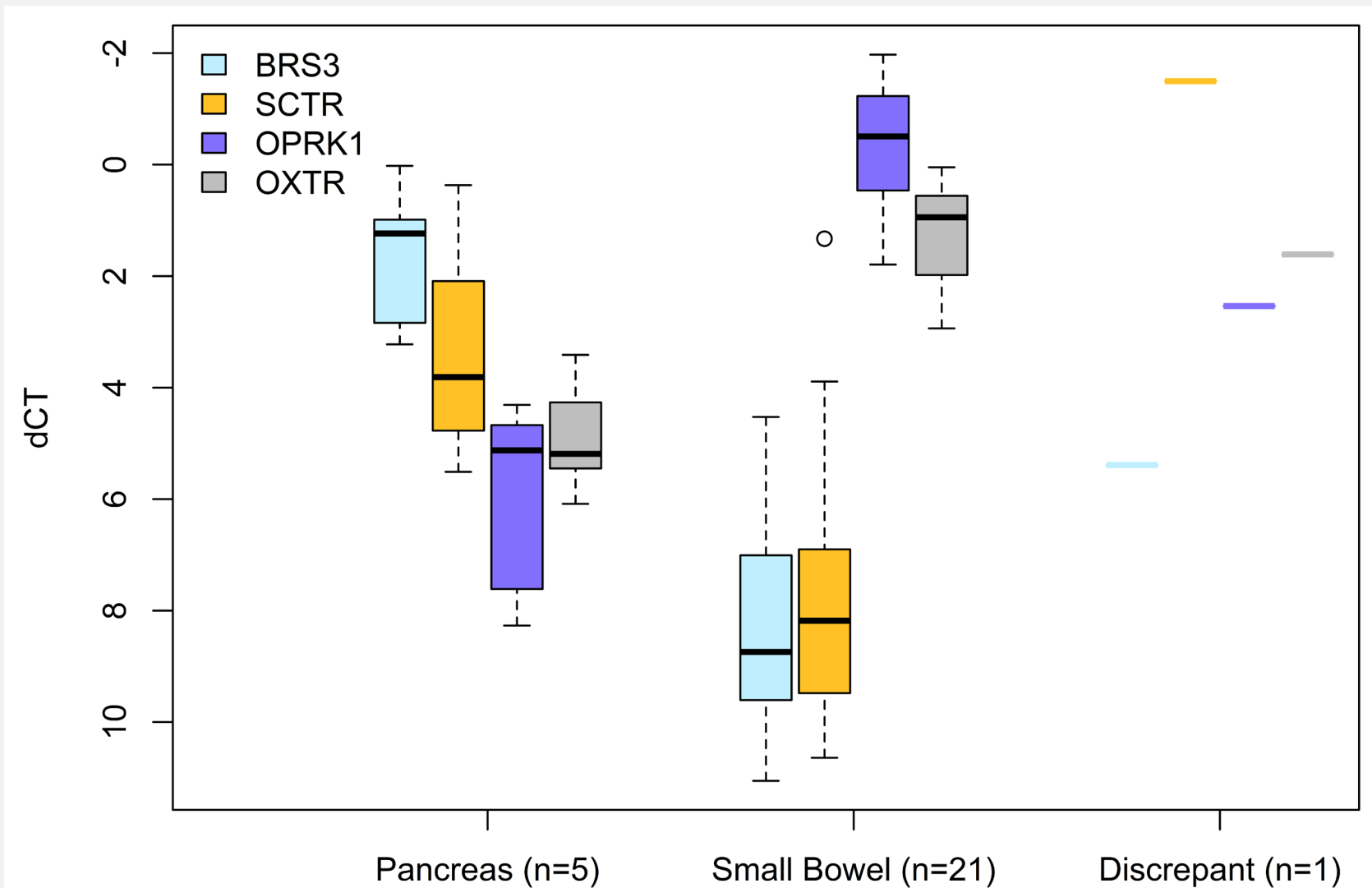


Figure 2: Gene expression profiles in all tissue samples grouped by predicted primary site as determined by qPCR and IHC. A smaller dCT indicates increased expression.

RESULTS

Pt. ID	Presentation	SB Tumor	Pa Tumor	Met	PaT Size	Classification
517-1	Synchronous	na/SB	na/Pa	Pa/Pa	10	Separate
133-1	Synchronous	SB/SB	Pa/Pa	Pa/na	3.2	Separate
256-1	Metachronous (83 mo)	SB/SB	SB/SB	SB/SB	1.2	SBMet
137-1	Metachronous (96 mo)	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	Pa/SB	SB/na	2.5	Discrepant
220-1	Metachronous (27 mo)	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

Table 1: Assignment of primary site by qPCR/IHC. na=not available; SB=small bowel; Pa=Pancreas; mos=months to PNET appearance after SBNET diagnosis; PNET size = largest dimension in cm

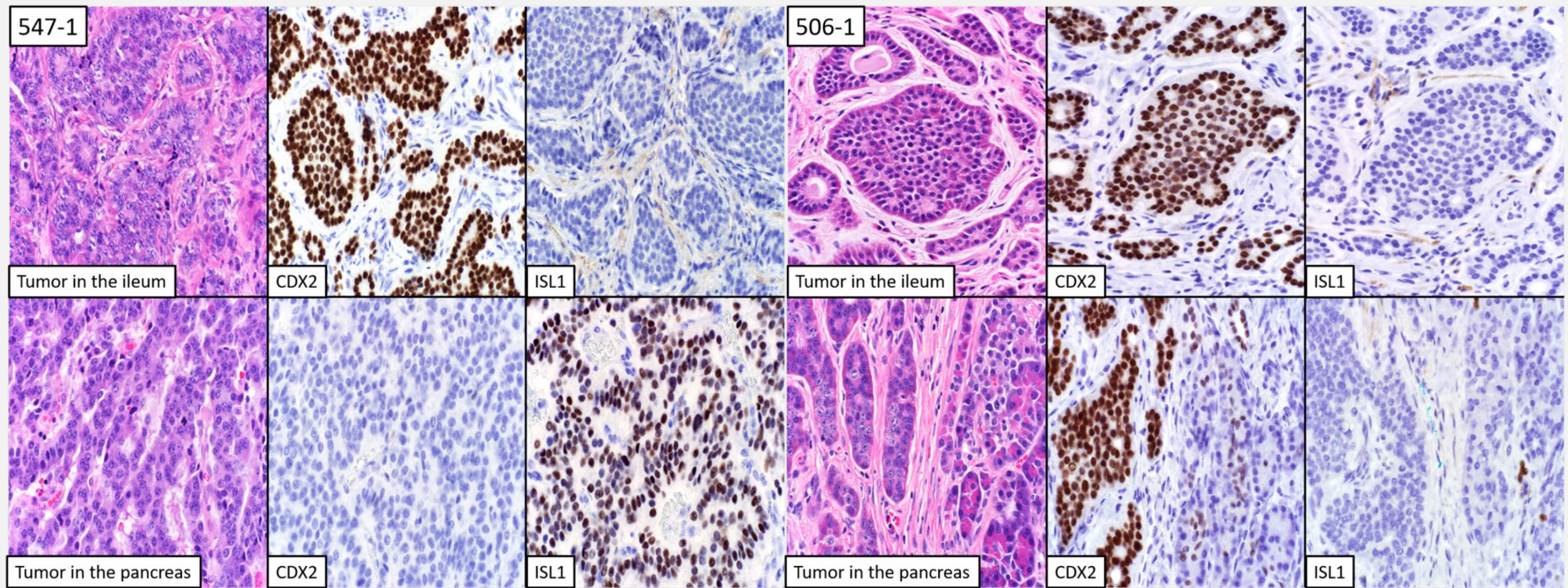


Figure 3: Immunohistochemical stains from the small bowel and pancreatic tumors in patients 547-1 and 506-1. CDX2 positivity indicates small bowel origin while ISL1 positivity indicates pancreatic origin.

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RESULTS

Of 338 patients undergoing exploration, eleven had NETs in both the small bowel and pancreas. Synchronous lesions were found in eight, while three presented initially with a small bowel tumor followed by the pancreatic lesion. Eight patients presented with pancreatic tail or body tumors and underwent distal or central pancreatectomy, while three had pancreatic head masses which were observed. Of these three patients, two developed biliary or pancreatic duct obstruction, and one remains asymptomatic from their pancreatic mass currently four years from their operation. Tissues from eleven small bowel tumors, nine pancreatic tumors and ten metastases were analyzed, revealing that three patients had separate primaries, and five patients had SBNETs which metastasized to the pancreas. Pancreatic tissue was unavailable in two patients, and qPCR and IHC gave discrepant results in one. Separate primary PNETs all presented synchronously and tended to be larger, but this difference was not significant (6.1 vs 2.5 cm, p=0.2).

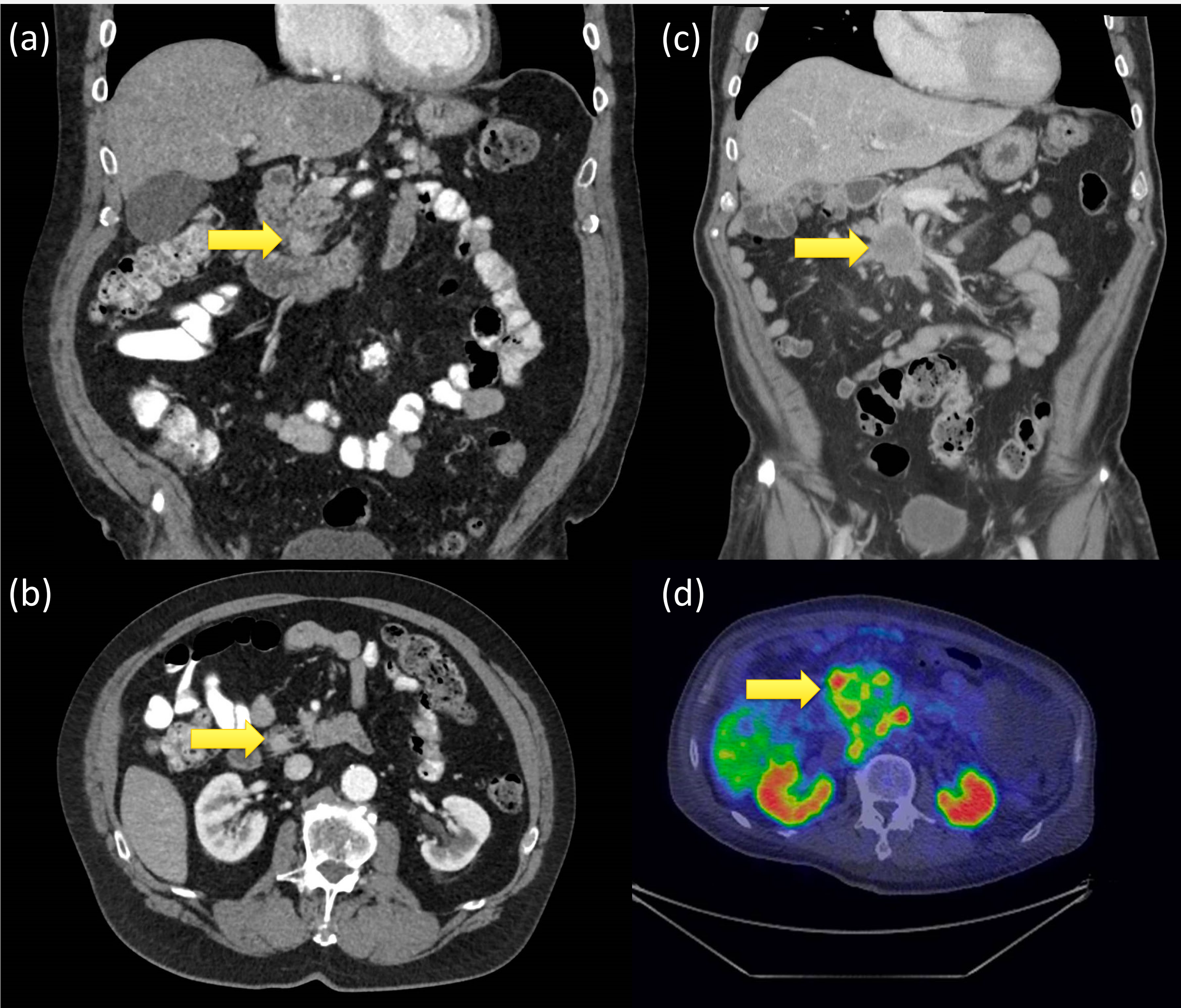


Figure 4: Imaging findings in both patients for whom pancreatic tissue was unavailable. Patient 408-1's enhancing pancreatic mass is shown on arterial phase CT in coronal (a) and axial (b) sections. This mass was confirmed by intraoperative ultrasound and palpation to be contained within the pancreatic parenchyma, in proximity to the duct. Patient 137-1's pancreatic mass is shown on coronal CT (c) and on the axial section from a Gallium-PET scan (d).

CONCLUSIONS

The coincidence of NETs in the small bowel and pancreas is rare^{4,5} occurring in roughly 3% of surgical NET patients treated at the University of Iowa had NETs at both sites, none of whom had MEN1 or VHL. In nearly two thirds of evaluable patients the pancreatic tumor was a metastasis from the SBNET primary, while in the other third of patients it represented a separate primary. Accurate determination of the site of origin can have important implications for prognosis⁶ and treatment⁷.

Determining the origin of the pancreatic NET can help guide the use of systemic therapy, as many agents have only conclusively been shown to be effective in PNETs. In patients with metastases to the pancreas, the risks of biliary obstruction from an unresected tumor must be weighed carefully against the risks of pancreatic resection.

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