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Clinical and immunohistochemical features of 34 solid pseudopapillary tumors of the pancreas

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Abstract

Background and Aim: Clinicopathological data regarding pancreatic solid pseudopapillary tumors (SPT) in a multiethnic country are limited. The aim of the present study was to characterize pancreatic SPT in Australia.

Methods: Clinicopathological features, treatment, immunohistochemical findings and outcome data of 34 patients (79% Caucasian, 12% Asian, 6% South Pacific Islander and 3% African) with pancreatic SPT were reviewed.

Results: The most presenting complaint was abdominal pain. Median diameter of tumors was 60 mm (range: 20–220); predominantly located in the pancreatic tail (tail : body : head = 23:3:8). All tumors were resected and patients underwent surgery, including a liver resection for metastasis, all patients were alive after a median follow up of 70 months (IQR: 48–178). Two patients underwent repeated surgery for local recurrences with liver metastases after 8 and 18 months, which were successfully managed by surgical resection. Completeness of excision, perineural spread, vascular space invasion, mitotic rate and cellular atypia did not predict recurrence. In all cases, there was aberrant nuclear staining of beta-catenin and a loss of membranous expression of E-cadherin with aberrant nuclear localization of the cytoplasmic domain. Most pancreatic SPT were also strongly positive for CD10 (96%), progesterone receptor (79%), cytokeratin (28%), synapthophysin (26%) and chromogranin (15%).

Conclusions: Pancreatic SPT occur in all races and are uniformly indolent. Given complete resection of a pancreatic SPT is usually curative and recurrences can be treated with re-operation, correct diagnosis is important.

Introduction

Solid pseudopapillary tumors (SPT), also known as Frantz's tumors,[1–3] are rare pancreatic neoplasms of uncertain lineage[4–7] and account for 1–2% of all exocrine pancreatic neoplasms.[1,2,8,9] These tumors are most prevalent in young women and are thought to have a distinct indolent clinical course.[9–12] Surgical resection is the treatment of choice, with a good prognosis[9–12] even with distant metastasis or recurrence.[13–15] Therefore, accurate diagnosis of these tumors is paramount in providing optimal care for these often very young patients. Given its rarity, clinical data regarding these tumors are mostly limited to case reports or small case series, particularly from Asian populations.[9,16] The only Caucasian cohort of significant size characterizing the clinicopathological features and outcomes for SPT is a recent Italian series of 31 patients.[9–12] The aims of the present study were to examine the clinicopathological features, treatment and outcome of SPT in an ethnically diverse population, and to characterize the immunohistochemical features that distinguish them from other pancreatic neoplasms.

Methods

Subjects and data collection

Detailed clinicopathological, treatment and outcome data of all patients with a diagnosis of pancreatic SPT who underwent pancreatic resection from January 1981 to December 2007 were obtained from teaching hospitals associated with the NSW Pancreatic Cancer Network (NSWPCN; http://www.pancreaticcancer.net.au) in Sydney, Australia (Table 1). Ethical approval for the study was obtained from the Human Research Ethics Committee at each participating institution.

Table 1 Demographics, clinical features, treatment details and outcomes of 34 patients with pancreatic solid pseudopapillary tumors

	Total $n = 34$ (%)
Female : male	30:4
Median age (years)	33.3 (IQR: 19.6–42.3)
Presentation	
Abdominal pain or discomfort	27 (79)
Abdominal mass	3 (9)
Jaundice	1 (3)
Fever	1 (3)
Vomiting	2 (6)
Weight loss	4 (13)
Nausea	6 (19)
Indigestion	2 (6)
Incidental finding	7 (22)
Risk factors	
Cigarette smoking	9 (28)
Alcohol	4 (13)
Diabetes	3 (9)
Pancreatitis	1 (3)
Hepatitis B or C	3 (9)
Treatment	
Left-sided pancreatectomy	24 (67)
Whipple's resection	9 (26)
Subtotal pancreatectomy	1 (7)
Complications	
Wound Infection	3 (10)
Abdominal pain	1 (3)
Pancreatic collection	2 (7)
Pancreatitis	1 (3)
Type 2 diabetes	1 (3)
Recurrence (liver)	2 (7)
Survival† *n*	32

†Loss of long-term follow up in two patients.

Histology and immunohistochemistry

All cases were centrally reviewed by an experienced panel of observers (AJG, ALJ, JGK) to confirm the diagnosis. Independent assessments were also made of the resection margin status, mitotic count, lymphovascular space invasion, perineural spread and cellular atypia whilst blinded to all clinical data. Where archival tissue were available, tissue microarrays were constructed and immunohistochemical staining for the following markers were carried out: chromogranin, synaptophysin, progesterone receptor, cytokeratin (AE1/AE3), CD56, beta-catenin, E-cadherin membranous domain, e-cadherin cytoplasmic domain, CD10, Ki-67 and vimentin. Immunohistochemistry for all antibodies was carried out using tissue microarrays sectioned at 4 μm onto positively charged slides (Superfrost plus; Menzel-Glaser, Braunschweig, Germany) and stained using the Vision Biosystems BondmaX automated staining system (Vision Biosystems, Melbourne, Victoria, Australia) according to the manufacturer's instructions. The specific antibodies and concentrations used were: Ki-67 1/50 (MIB-1, M7240; Dako, Carpenteria, CA, USA), beta-catenin 1/100 (17C2, NCL-B-Cat; Novocastra, Newcastle-upon-Tyne, UK), E-Cadherin cytoplasmic domain 1/25 (36B5, NCL-E-Cad, Novocastra), E-Cadherin membranous domain 1/1000 (36E, 610182, BD Transduction labs, Lexington, KY, USA), CD10 1/50 (56C6, NCL-L-CD10-270; Novocastra), Vimentin 1/20 (V9, NCL-L-Vim-V9; Novocastra), CD56 1/50 (1B6, NCL-L-CD56-1B6; Novocastra), chromogranin 1/200 (A0430; Dako) Synaptophysin 1/100 (27912, NCL-L-Synap-299; Novocastra) and progesterone receptor (PgR636 M3569; Dako). Antigen retrieval was carried out using the manufacturer's acidic retrieval solution (ER1: VBS part no: AR9961) for 30 min for E-Cadherin, Vimentin, CD56, AE1/AE3 and synaptophysin, and in the manufacturer's alkaline retrieval solution (ER2: VBS part no: AR9640) for 30 min for Ki-67, beta-catenin, CD10 and progesterone receptor. Chromogranin enzyme-based antigen retrieval was carried out for 10 min in the manufacturer's solution (VNS part no: AR9551). A biotin-free detection system was used (VBS part no: DS 9713). With the exception of beta catenin and Ki-67, the tumors were scored as positive, negative or weak using the following criteria: (i) positive (more than 95% of cells staining); (ii) weakly positive (less than 5% of cells staining); or (iii) negative (no cells staining). Positive nuclear staining for both beta-catenin and E-cadherin refers to both nuclear and cytoplasmic accumulation with absent membrane staining. Ki-67 was expressed as a proliferative index (percentage of epithelial cells staining positively). Immunohistochemical scoring was carried out by the review panel (AJG, ALJ, JGK) blinded as to other data.

Statistical analysis

Categorical data were compared using the χ^2-test with Yates' correction, and continuous variables were compared using the Mann–Whitney *U*-test. All analyses were carried out using GraphPad Prism 4 (v 4.02, San Diego, CA, USA) statistical software. A *P*-value of < 0.05 was considered significant.

Results

Between January 1981 and December 2007, 872 patients that underwent pancreatic resection for pancreatic neoplasms were identified in the NSW Pancreatic Cancer Network database. These consisted of 452 pancreatic adenocarcinomas (51.9%), 83 neuroendocrine tumors (9.5%), 82 ampullary neoplasms (9.4%), 77 intraductal papillary mucinous neoplasms (8.8%), 66 mucinous cystic neoplasms (7.6%), 61 serous cystadenomas (7.0%), 34 solid pseudopapillary tumors (3.9%) and 17 other miscellaneous neoplasms (1.9%; metastatic [$n = 13$], lymphoma [$n = 1$], lymphagioma [$n = 1$], sarcomatoid carcinoma [$n = 1$]). The demographics and clinical features of the patients diagnosed with SPT are summarized in Table 1. The majority of the patients were female (30/34; 88%). The most common presenting complaint was abdominal pain or discomfort (79%). Although there was no family history of pancreatic neoplasm or pancreatitis in the cohort, three patients had a positive family history of esophageal, colonic or breast cancer. The ethnic origin of patients included Caucasian (79%), Asian (12%), South Pacific Islander (6%) and African (3%). There has been no significant change in the incidence of SPT over three decades, including the periods 1981–1990, 1991–2000, and 2001–2007 ($P > 0.5$). All patients had preoperative imaging with computed tomography (CT) scanning, showing a mixed solid-cystic component in the majority of cases. Seven tumors (23%) had radiographic evidence of necrosis and/or hemorrhage,

and two had calcification. Endoscopic ultrasound examination was carried out in two patients preoperatively and the tumors appeared as a large heterogeneous mass with both hyper- and hypo-echoic areas. Doppler examination showed that the tumors were highly vascular. Sonographic-guided fine-needle aspiration was carried out preoperatively in seven patients (5 percutaneous ultrasound [US], 2 endoscopic US) for cytology. A definitive cytological diagnosis of SPT was made in just two (29%). One case was signed out as a neuroendocrine tumor on fine needle aspiration and four cases were signed out as non-diagnostic.

Pathological and immunohistochemical features of SPT

The majority of tumors were located in the body/tail of the pancreas (76%) and the median maximal diameter was 60 mm (range: 45–90; Table 2). The tumors were well encapsulated (41%), with areas of necrosis/hemorrhage present in 32% (Fig. 1). Tumors located in the head were larger (80 [50–100] *vs* 50 mm [38–80 mm]), were more often symptomatic (88 *vs* 76%) and occurred in a younger age group (24.9 [17.4–29.3] *vs* 32.0 years [26.2–48.0 years]) than those in the body/tail of the pancreas. A total of 27 patients (79%) had resection margins free of tumor (R0), and of these, vascular and perineural involvement was present in three and one patient, respectively. Seven patients (21%) had microscopic involvement of the resection margin (R1). Of these patients, two had both perineural and vascular involvement, and one had vascular invasion (Table 2). One patient had a synchronous liver metastasis that was resected at the time of pancreatectomy. The immunohistochemical features of the tumors were characterized in 28 patients and are summarized in Table 3 and shown in Figure 2. All 28 tumors showed negative membrane, but positive nuclear staining for beta-catenin. The progesterone receptor was diffusely positive in 22 cases, weakly positive in five cases and completely negative in one case. A total of 26 (96%) cases were CD10 positive, sometimes with perinuclear dot-like accentuation. Just 18 (64%) of cases were completely synapthophysin negative with four (14%) being weakly positive and five (22%) being strongly positive. Six cases (21%) showed positive staining for cytokeratin and four cases (15%) showed focal weak staining for chromogranin. A total of 20 cases showed a ki-67 proliferative index of less than 0.5%, one case was 0.5%, four cases were 1%, one case was 2% and one case was 3%. Using the antibody directed at its membranous domain (Clone 36B5), all tumors were negative for E-cadherin. However, aberrant nuclear staining of varying intensity was found with E-cadherin antibody directed against the cytoplasmic domain (Clone 36E). In the non-neoplastic pancreas, the cytoplasmic membrane was stained positively for E-cadherin with both membranous and cytoplasmic domain antibodies (Fig. 3d,e).

Although the proportion of non-Caucasians was small, there were no differences between SPT from Caucasians versus non-Caucasians in term of: (i) age of presentation; (ii) sex; (iii) tumor location and size; (iv) tumor cystic-solid ratio; (v) Ki-67 proliferative index; (vi) positivity for CD56, Vimentin, progesterone receptor, beta-catenin and CD10; and (vi) median survival duration (Table 4).

Table 2 Macroscopic and microscopic features of 34 patients with pancreatic solid pseudopapillary tumors

	Total $n = 34$ (%)
Tumor location	
Head/neck : body : tail	9:2:23
Median maximum tumor diameter (mm)	60 (45–90)
Well demarcated	30 (84)
Ill defined	4 (12.5)
Mixed solid-cystic lesion	17 (50)
Margin of resection	
Clear	27 (79)
Involved	7 (21)
Vascular Invasion	4 (12.5)
Pattern of growth	
Infiltrative	6 (19)
Expansive	16 (50)
Confined	8 (25)
Extrapancreatic involvement	9 (28)
Perineural invasion	3 (9)
Microscopic features	
Nuclear atypia	7 (22)
Mitosis	7 (22)
< 1/50 hpf	6 (19)
1/50 hpf	3 (9)

Treatment details and outcomes

All patients underwent surgical resection, which included left-sided pancreatectomy (24), Whipple's procedure (9) and total pancreatectomy (1). All but three patients had an uncomplicated postoperative recovery, with a median length of stay in hospital of 10 days (9–16 days). The length of hospital stay of patients who had a Whipple resection was longer than that of patients who had a left sided pancreatectomy (17 [11–20] *vs* 9 days [9–13 days]). Three patients (10%) had postoperative intra-abdominal collections that were managed with percutaneous drainage. Adjuvant chemotherapy or radiotherapy was not given to any of the patients. Long-term follow up was available for 32 patients, with a median follow up of 70 month (IQR: 48–178 months). All patients lived. Two patients (6%) developed local recurrence and/or liver metastases that were treated surgically. The first patient was known to have a liver metastasis preoperatively, and both the pancreatic and hepatic lesions were resected at the initial surgery. Histological examination showed cellular atypia and a positive resection margin (R1), but no mitoses, a Ki-67 index of less than 0.05% and no evidence of lymphovascular invasion or perineural spread. Local recurrence with further liver metastasis developed 8 months after the initial surgery. The second patient was found to have a liver metastasis 18 months after a negative margin resection (R0). There was no cellular atypia. Again, there were no mitoses, no lymphovascular invasion or perineural spread and the Ki-67 index was less than 0.05%. In both patients, the local recurrence and liver metastases were managed successfully with surgical resection and both patients were disease-free after 24 months of follow up. None of the other six patients with a R1 resection developed either

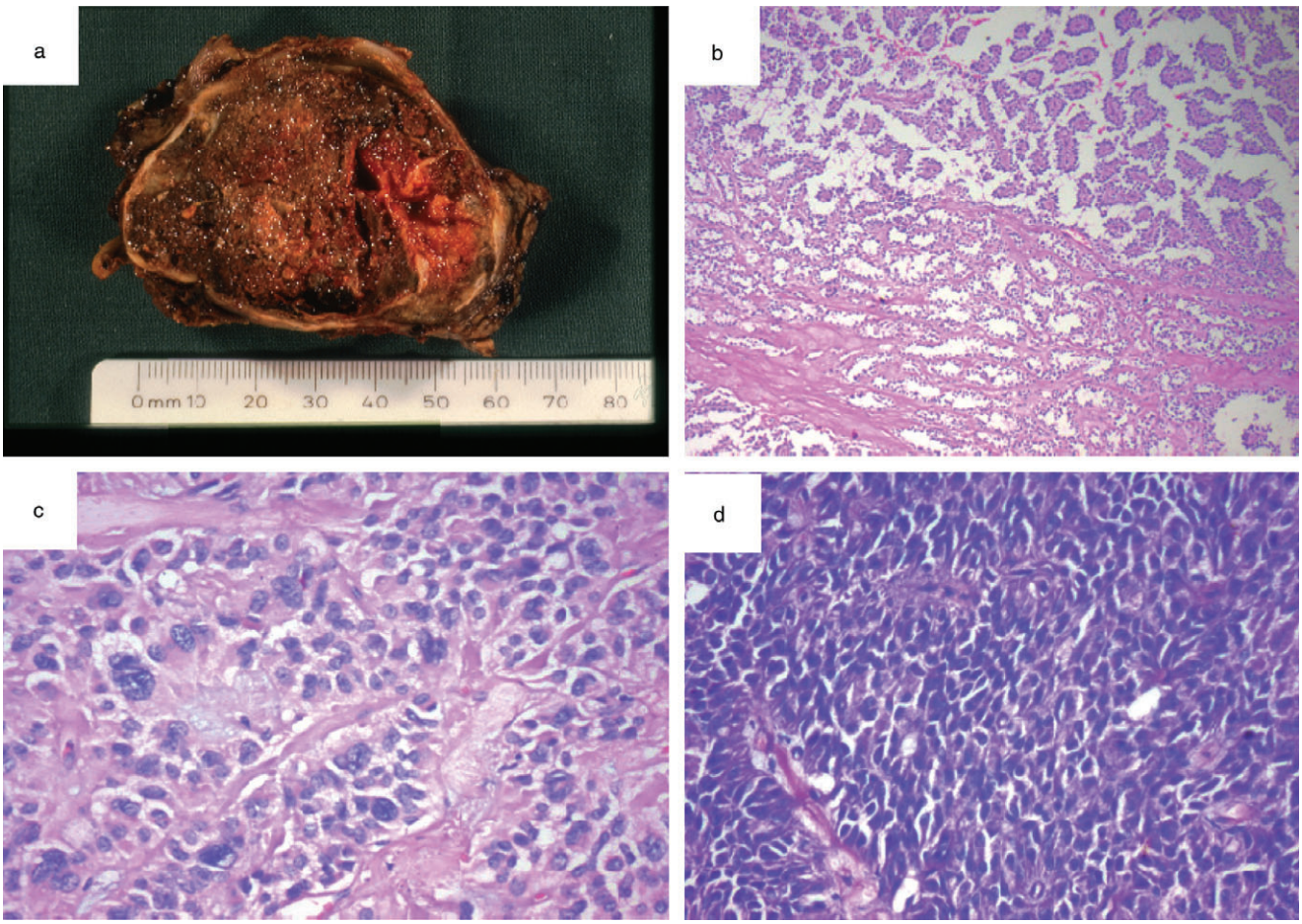

Figure 1 Macroscopic and histological features of solid pseudopapillary tumors (SPT). (a) These tumors are frequently well encapsulated and contain hemorrhagic and cystic areas. (b) Histological features of SPT include a pseudopapillary architecture with fibrovascular stalks and small uniform tumor cells with round nuclei and (c) eosinophilic or vacuolated cytoplasm. (d) Cellular atypia, although unusual, may be present.

Table 3 Immunohistochemical profiles of pancreatic solid pseudopapillary tumors in 28 patients

Antigen	Total number	Negative (%)	Weak (%)	Strongly positive (%)	Total positive (%)
Cytokeratin (AE1/AE3)	28	20 (71)	6 (21)	2 (7%)	8 (29)
CD-56	28	1 (4)	6 (21)	21 (75)	27 (96)
Vimentin	28	0	0	28 (100)	28 (100)
Progesterone Receptor	28	1 (4)	5 (18)	22 (79)	27 (96)
Beta-Catenin Nuclear stain	27	0	0	27 (100)	27 (100)
Chromogranin A	27	23 (85)	4 (15)	0	0
CD-10	27	1 (4)	0	26 (96)	26 (96)
Synaptophysin	28	18 (64)	4 (14)	6 (22)	10 (36)
E-Cadherin (mem domain)	28	28 (100)	0	0	0
E-cadherin (cyt domain)†	28			28 (nuclear only)	100

†The E-cadherin cytoplasmic domain antibody showed negative cytoplasmic membrane staining. Cyt, cytoplasmic; mem, membranous.

recurrence or metastatic disease during the period of follow up. The only long-term complication was new-onset diabetes mellitus, which occurred in one patient (3%), 2 years after a left-sided pancreatectomy.

Discussion

The characteristics of this relatively large cohort of patients treated for SPT in a heterogeneous population show that these tumors are:

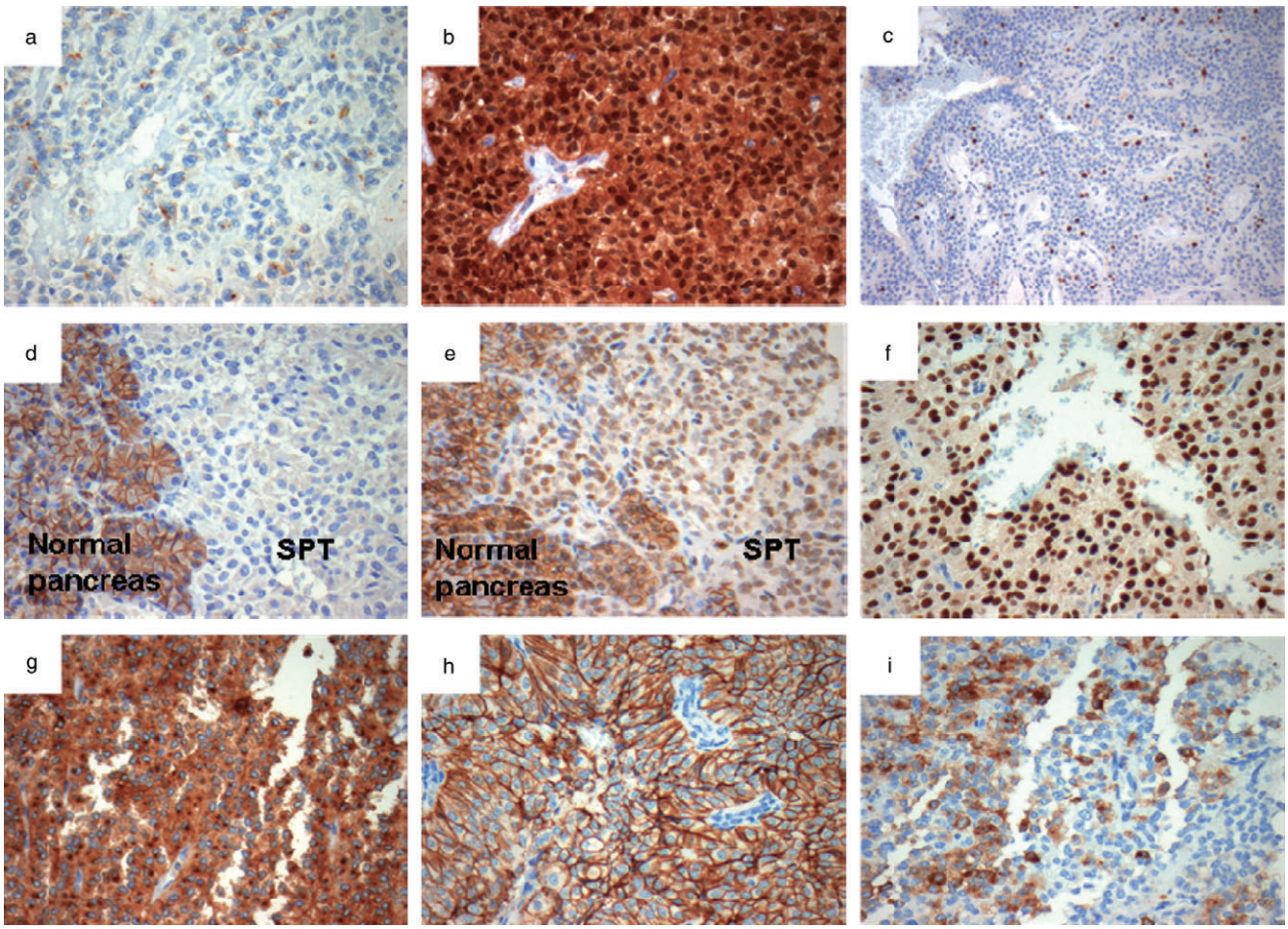

Figure 2 Immunohistochemical characteristics of solid pseudopapillary tumors (SPT); (a) chromogranin, (b) beta-catenin, (c) Ki-67, (d) E-cadherin membrane domain, (e) E-cadherin cytoplasmic domain, (f) progesterone receptor, (g) CD10, (h) CD56 and (i) synaptophysin. The tumors are characterized by the absence of staining for (a) chromogranin and (d) the E-cadherin membrane domain, but positive nuclear staining for (b) beta-catenin, (c) Ki-67, (f) progesterone receptor, (g) CD10, (h) CD56 and (i) synaptophysin. (d,e) Immunohistochemistry was carried out on the junction between the normal pancreas and SPT using an antibody directed against (d) the membranous domain and (e) an antibody directed against the cytoplasmic domain of E-cadherin. (d) Although the SPT is completely negative for the membranous domain, (e) there is nuclear staining for the E-cadherin cytoplasmic domain. In this context, nuclear staining refers to both nuclear and cytoplasmic accumulation similar to that seen for beta-catenin.

(i) relatively indolent; (ii) occur predominantly in young females; (iii) have an excellent prognosis with surgical resection; (iv) recurrence is uncommon even with a positive resection margin; and (v) metastasis and recurrence can be treated surgically with good outcomes. In addition to consolidating the current understanding of the clinicopathological features of SPT,[12,17–21] our findings also suggest that there are no dramatic differences in the tumor's presentation and behavior between Caucasians and non-Caucasians, although it is difficult to draw firm conclusions based on the number of non-Caucasians in the present cohort. The study also shows that the incidence of SPT has not changed significantly over the past three decades, and the apparent increasing number of SPT reported in the current literature is potentially related to "publication bias" or "diagnostic bias", as pathologists have become more aware of this unique tumor type. Preoperatively, the CT imaging characteristics of SPT are those of a large, well-circumscribed and highly vascularized tumor with solid and cystic areas, and a necrotic/hemorrhagic component.[17–19,21] Although intratumor calcifications and septa are characteristic features of SPT, they are not pathognomonic and are only present in a small proportion of tumors (7% in the current study).[17–19,21] Endoscopic sonographic features of SPT include a well-defined echo-poor mass (86%), a mixed echoic lesion with solid and cystic areas (39 %), and rarely a uniform hypoechoic mass consistent with a pure cystic lesion (11%).[22–26] The current study further shows that SPT are indolent tumors with an excellent prognosis, and that surgical resection is the mainstay of treatment, even in the presence of local invasion and extrapancreatic involvement.[12,27,28] In the present series, there was no correlation between histological features, such as vascular and perineural invasion, infiltrative growth pattern, solid versus

Table 4 Comparison of demographics, clinicopathological and immunohistochemical features between pancreatic solid pseudo-papillary tumors of Caucasian and non-Caucasian patients

	Caucasian patients ($n = 27$)	Non-caucasian patients ($n = 7$)
Female : male	24:3	7:0
Age (years)	31.9 ± 2.7	30.0 ± 3.3
Tumor location		
Head/neck : body : tail	6:2:19	3:0:4
Maximum tumor diameter (mm)	65.2 ± 6.6	62.9 ± 5.7
Tumor cystic-solid ratio	40:60	40:60
Margin of resection (*n* (%))		
Involved	5 (19)	2 (29)
Clear	22 (81)	5 (71)
Invasion (*n* (%))		
Vascular	5 (19)	2 (29)
Perineural	2 (7)	1 (14)
Pattern of growth (*n* (%))		
Infiltrative	3 (11)	3 (42)
Expansive	13 (48)	3 (42)
Confined	7 (26)	1 (14)
Extrapancreatic involvement	5 (19)	4 (57)
Ki-67 proliferative index	1.2 ± 0.1%	1.5 ± 0.4%
Positive IHC staining (*n* (%))	($n = 21$)	($n = 7$)
CD-56	17 (81)	5 (71)
Vimentin	21 (100)	7 (100)
Progesterone Receptor	17 (81)	6 (86)
Beta-Catenin Nuclear	21 (100)	6 (86)
Chromogranin A	0 (0)	0 (0)
CD-10	21 (100)	6 (86)
Synaptophysin	7 (33)	3 (43)
E-Cadherin (mem domain)	0 (0)	0 (0)
E-cadherin (cyt domain)	21 (100)	7 (100)
Treatment (*n* (%))		
Left sided pancreatectomy	20 (74)	4 (57)
Whipple's resection	6 (22)	3 (43)
Subtotal pancreatectomy	1 (4)	0 (0)
Survival† (*n* (%))	25 (100)	7 (100)

†Loss of long-term follow up in two patients. Cyt, cytoplasmic; IHC, immunohistochemical; mem, membranous.

cystic architecture, nuclear atypia or mitotic activity and recurrence risk. Similarly. surgical margin involvement (R1) does not appear to be associated with a poor outcome. Up to 20% of cases in reported series have had liver metastases at the time of resection, but the overall 5-year survival rate is still over 95%.[28] In view of these good long-term results and similarly good results after re-resection for local recurrences and metastatic disease, close follow up with regular CT scanning is warranted. Long-term complications appear to be limited to the development of diabetes mellitus in 3–5% of patients.[27,28] The present study suggests that SPT can develop in patients from all ethnic backgrounds, with no dramatic predilection for a particular race. In contrast to previous reports,[12,29] a majority of our patients were symptomatic from the mass-effect of the tumor, with abdominal pain or discomfort as the most common presenting complaint. As the tumors are located mostly in the body/tail of the pancreas, jaundice is an uncommon presentation. Furthermore, the current study did not support previous reports that tumors in the head of the pancreas are smaller.[12] We found that SPT in the head of the pancreas were larger and were more symptomatic than those located in the body/tail of pancreas. The younger age of patients with tumors in the head, however, is consistent with previous reports.[12]

The primary morphological differential diagnosis of SPT is pancreatic endocrine tumor. Traditionally, negative staining for neuroendocrine markers, particularly chromogranin, has been considered the key to this distinction.[2,7,12,29,30] However, the present study shows that synapthophysin staining is present in 36% of morphologically and clinically typical SPT and therefore has little role in this differential diagnosis. Chromogranin staining, albeit focal and weak, was present in four (15%) cases. Therefore, whilst negative staining can be used to support the diagnosis of SPT, positive chromogranin staining, particularly if it is focal and weak, cannot be used to exclude this diagnosis. Given that all our SPT are beta-catenin positive, our findings support others who have suggested that nuclear staining for beta-catenin, which is found in less than 3.5% of pancreatic endocrine tumors, is the most sensitive and specific marker of SPT.[16,31] Whilst positive staining for CD10 is characteristic of SPT, it is less useful in differential diagnosis, as it occurs in approximately 10% of both pancreatic ductal adenocarcinomas and neuroendocrine tumors.[31] Until recently, E-cadherin staining in SPT has not been well characterized. All studies have reported loss of the normal membranous pattern of staining. However, two separate groups recently reported aberrant nuclear accumulation of E-cadherin,[32–34] which had not been reported by others.[16,35] The present study supports the hypothesis of Chetty *et al*.[32,36] that this apparent discrepancy is a result of the different specificities of the antibodies being used with loss of membrane staining being found with all antibodies, but aberrant nuclear accumulation only being found with an antibody directed against the cytoplasmic domain of E-cadherin. Whilst intriguing, this finding has little role in histopathological differential diagnosis, given that absent cytoplasmic membrane staining is found in 60% and aberrant nuclear staining of E-cadherin in 32% of pancreatic endocrine tumors.[37] However, it does shed light on the pathogenesis of SPT, as the combined aberrations in the expression and accumulation of nuclear beta-catenin,[31,38,39] and E-cadherin[32,36] support data from *in vivo* models of SPT, which shows that Wnt signaling plays a role in SPT pathogenesis.[31,38]

In conclusion, SPT of the pancreas is a low-grade and indolent neoplasm predominantly occurring in young women. Resection, even with microscopic residual disease, is usually curative and recurrences can be treated with re-resection. Accurate diagnosis is fundamental in deciding the appropriate therapeutic strategy in these patients, particularly in distinguishing them from neuroendocrine tumors. There are several characteristic immunohistochemical features of SPT of which nuclear accumulation of beta-catenin appears to be the most specific and sensitive. However no immunohistochemical stains are definitive and accurate diagnosis depends on awareness of the combined morphological and clinical features.

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