Published in final edited form as:

J Comput Assist Tomogr. 2018 ; 42(3): 405–411. doi:10.1097/RCT.0000000000000698.

Does CT have the ability to differentiate aggressive from non-aggressive solid-pseudopapillary neoplasm?

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Abstract

Purpose—To assess the ability of contrast-enhanced computed-tomography (CECT) to differentiate aggressive from non-aggressive solid-pseudopapillary neoplasms (SPNs).

Materials and Methods—Forty treatment-naïve patients with pathologically proven pancreatic SPNs were included. Imaging characteristics were determined by consensus of three radiologists blinded to histopathologic aggressiveness. All patients underwent four-phase CECT using a pancreatic-protocol. The ROIs of the tumor and the normal pancreas were documented on all phases. Lymph nodes were considered metastatic if >1.0 cm in short-axis diameter.

Fisher exact and Wilcoxon rank-sum tests were used to compare between aggressive and non-aggressive tumors.

Results—No significant difference was noted between imaging covariates, such as internal hemorrhage, calcification, wall thickness perceptibility, vascular invasion, margins, cystic component and pancreatic and biliary ductal dilation. Tumors with > 62.5HU and progressive-enhancement during the delayed phase had aggressive characteristics (p=0.03).

Conclusion—On delayed phase CECT pathologically aggressive SPNs may show greater enhancement than non-aggressive SPNs.

Keywords

Solid-pseudopapillary neoplasm; Contrast enhanced CT; delayed phase; aggressive; non-aggressive; pancreas

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None of the authors have conflicts of interest.

Introduction

Solid pseudopapillary neoplasms (SPNs) account for 1%–2% [1, 2] of pancreatic neoplasms and approximately 50% of SPNs are detected incidentally. Since the late 1950s, SPN of the pancreas has been recognized as a separate entity among pancreatic neoplasms [1, 3]. SPNs are most commonly seen in young females often in their 20s, but can also be seen in patients ranging in age of 2–85 years [2].

SPNs are generally thought to be low-grade neoplasms with an indolent growth pattern regardless of the presence of metastatic disease. The originating cell of these tumors in the pancreas is unclear. Theories include origination from acinar and endocrine cells, centroacinar cells, or possibly genital ridge-related cells [4–8]. Most SPNs activate the Wnt signaling pathway [9] and have somatic point mutations in exon 3 of *CTNNB1*. This mutation results in focal abnormal nuclear localization of the β -catenin protein, which can be visualized on immunohistochemical analysis. Typically, the neoplastic cells in SPN are uniform polyhedral cells with grooved nuclei, loosely arranged around delicate fibrovascular cores. This pattern is fairly uniform despite heterogeneity in morphologic patterns, with solid, pseudopapillary, or microcystic pattern [10]. In 1990, Matsunou et al reported invasion of surrounding pancreatic parenchyma on microscopy along with cellular atypia in case reports of SPNs [11]. They also found a higher degree of malignant change in long-standing tumors.

SPNs have an abnormal nuclear position of β -catenin, detected by immunohistochemical analysis [4]. These tumors express vimentin, CD10, and neuron-specific enolase as well as demonstrate a loss of E-cadherin from the cytoplasmic membrane [12]. However, no specific pathologic marker has been linked to the malignant potential of this tumor [13]. Characteristics associated with malignant potential or “aggressive behavior” (metastatic disease or recurrence) on histologic analysis include extra-pancreatic invasion, pancreatic parenchymal invasion, perineural [14] or vascular (especially muscular vessels) wall invasion [15, 16]. Nuclear pleomorphism alone has not been found to be related to aggressiveness in these tumors [10, 17]; however, the presence of undifferentiated carcinoma in rare cases have a particularly aggressive course. High Ki-67 immunoreactivity has been suggested to be related to poor outcomes in SPNs [18, 19]. SPNs have a different etiology and pathogenesis from pancreatic ductal cancer and neuroendocrine tumors and may require their own markers for determining prognosis [20].

Radiologic features that have been suggested to predict SPN aggressiveness on imaging include tumor size, soft tissue component within the tumor [21], focal discontinuity or invasion of the capsule [21], and lobulated margins [22–24]. The aim of our study was to retrospectively evaluate the utility of contrast-enhanced computed tomography (CECT) in differentiation of aggressive from non-aggressive SPNs.

Materials and Methods

This retrospective, single-institution, institutional review board–approved study included patients with pathologically proven pancreatic SPNs. Patients with SPNs were identified by

a search of the radiology database. Patients who had surgical resection prior to assessment at our institution were excluded. A total of 40 treatment-naïve patients with pathologically proven SPNs were included in the study. Patients without arterial and portal venous phase CECT imaging as well as patients who did not have a pancreatic protocol with a non-contrast study were excluded from the final analysis. 35 patients had non contrast, arterial and portal venous phase exams. 4 patients did not have pre-contrast and arterial phase imaging performed. Only 30 of these patients had delayed phase imaging. Imaging characteristics were determined by the consensus of three radiologists who were blinded to the final histopathologic status with respect to tumor aggressiveness and whose experience in radiology totaled 4 years (V.S.), 15 years (P.B.), and 17 years (K.E.).

Imaging protocol

The CECT examinations were performed on a 64-detector computed tomography scanner (LightSpeed VCT; GE Healthcare, Milwaukee, WI). The pancreatic parenchymal scanning was performed at a 2.5-mm slice thickness (revolution time 0.5 sec, pitch 0.5:1, table feed/rotation 20.625mm, 120kVp and mA was automated based on dFOV) using smart prep (GE Healthcare, Milwaukee, WI) with a monitoring delay of 10 seconds, an aortic enhancement threshold of 100 Hounsfield units (HU), and a diagnostic delay of 20 seconds following administration of 125 cc of intravenous contrast (Omnipaque 300; GE Healthcare, Cork, Ireland) at 4 cc/sec, and was preceded by noncontrast study through the abdomen. The portal venous phase scan was performed 20 seconds after the arterial phase scan, and the delayed phase scan was performed 15 seconds after the portal-venous phase scan. Multiplanar reconstructions were performed in the sagittal and coronal planes.

Qualitative analysis

The SPNs were analyzed for imaging features of size, location, wall thickness (imperceptible vs perceptible), shape (irregular, lobulated, or round), margins (well-circumscribed vs poorly circumscribed), gross vascular invasion, and associated pancreatic or common bile duct dilation. The largest size of the tumor was recorded in the axial, coronal or the sagittal plane (Supplemental Fig 1, 2 and 3). Patients' symptoms were recorded. The tumor wall was considered perceptible if it was >3 mm thick. Vascular invasion was suggested if there was a contiguous filling defect in the vessel extending from the tumor and showed contrast enhancement and similar imaging features to the primary tumor. The pancreatic duct was considered dilated if it was >5 mm in size. The tumors were categorized as homogeneous or heterogeneous and as predominantly cystic, predominantly solid, or mixed in internal architecture. Internal hemorrhage was defined by high-attenuation material present within the tumor at >45 HU. Calcifications were categorized by location within the tumor: central punctate, eccentric, or peripheral punctate.

Quantitative analysis

The regions of interest (ROIs) in the tumor and the normal pancreas were documented. The ROIs included the entire solid portion of the tumor and were drawn manually on the non-contrast, arterial, portal-venous, and delayed phases of contrast enhancement. A 2cm² ROI was also placed on normal pancreas upstream from the tumor during all three contrast

phases. Lymph nodes in the peripancreatic region, and in the portahepatis were considered suspicious for metastatic disease if they were >1.0 cm in the short-axis diameter [25].

Pathologic analysis

Pathologically aggressive tumor features were defined as a diameter of >5 cm, tumor necrosis, invasion into peripancreatic soft tissue, extension into the adjacent fat and lymphovascular/perineural invasion (Fig1) [26]. Tumors which had these pathologic features were considered aggressive and tumors which did not have these features were considered non-aggressive.

Statistical analysis

Qualitative features were analyzed using contingency tables with Fisher's exact test. HU values between tumor groups were compared using Wilcoxon rank-sum test. The tumors were classified as aggressive vs nonaggressive based on pathological analysis. Recursive partitioning analysis (RPA) was performed to identify a cutoff value for predicting invasiveness. Kaplan–Meier analysis was used to assess overall survival. P values less than 0.05 were considered statistically significant. The RPA analysis and data plotting were carried out using R version 3.1.1 (R Foundation, Vienna, Austria). Other statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Forty patients were included in our analysis. Based on pathology fifteen (37.5%) patients had aggressive tumors and 25 (62.5%) patients did not. The mean patient age was 30.7 years (standard deviation, 14.3 years). The mean tumor size was 5.3 cm (standard deviation, 3.6 cm). There were 35 female and five male patients. Three of the five male patients had pathologically aggressive tumors. Twelve of the 35 female patients had aggressive tumors based on pathology. Patients were generally symptomatic, presenting with vague abdominal pain, nausea, vomiting, and bloating. Two patients presented with jaundice. None of the patients had elevated cancer antigen 19-9 at presentation. Two patients presented with aggressive features on pathology had metastatic disease to the liver.

Qualitative analysis

Location (head, body, or tail) did not significantly differ between aggressive and nonaggressive tumors ($p=0.32$). Nine of the 19 tumors presenting in the head of the pancreas had aggressive features (Fig 2 and 3). The following morphologic CECT features of the tumors also did not significantly differ between aggressive and nonaggressive tumors, including internal hemorrhage ($p=0.67$), calcification ($p=0.71$), wall thickness perceptibility ($p=0.67$), homogeneity on enhancement ($p=0.67$), calcification ($p=0.87$), vascular invasion ($p=0.42$), margins ($p>0.99$), capsule irregularity ($p=0.44$), pancreatic ductal dilation ($p>0.99$), biliary ductal dilation ($p=0.06$), and lymphadenopathy ($p=0.13$). The amount of cystic component within the tumor did not significantly differ between aggressiveness groups ($p=0.64$). All tumors had low attenuation relative to the pancreatic parenchyma on all phases of contrast enhancement.

Lymphadenopathy was seen in 11/40 patients on imaging; however, none of the lymph nodes contained metastases by pathology.

Quantitative analysis

The HU values of the tumor did not significantly differ between aggressive and nonaggressive tumors when correlated with pathologic diagnosis in the pancreatic parenchymal phase ($p=0.36$) or portal-venous phase ($p=0.45$). However, greater enhancement in the delayed phase of contrast was associated with aggressiveness ($p=0.03$; Table 1). Based on RPA of $HU > 62.5$, the accuracy was 73%, sensitivity was 90%, specificity was 65%, PPV was 56%, and NPV was 93%. The prediction of aggressive vs non aggressive tumors using $> 62.5HU$ had a $p=0.0026$ Table 2, Fig4. The tumors which had aggressive features had progressive enhancement, whereas the non-aggressive tumors demonstrated wash out of contrast (Fig 5). Two Patients who had aggressive features on pathology and liver metastases had tumors that showed progressive enhancement. On last follow-up, three patients had died, and the rest were still alive. The survival time of the three patients was 6, 13 and 15 months. The Kaplan Myer curve showed the 10 year survival of SPNs was $>90\%$ (Fig 6).

Discussion

Our study suggests $HU > 62.5$ on delayed phase of SPNs correlated with aggressive pathologic features. Also, SPNs that showed a progressive increase in enhancement had aggressive pathologic features, whereas non aggressive tumors showed washout of contrast. This imaging finding has not been described in the literature. All SPNs however were lower in attenuation to the pancreatic parenchyma similar to a recently published study [27].

Most of the tumors we encountered were solid with a low incidence of mixed solid-cystic and purely cystic lesions. Prior studies reported mixed cystic tumors and solid-appearing tumors to be more common among SPNs than those with a mostly solid or mostly cystic composition [28]. Also, studies have suggested that solid tumors have an aggressive pathology than cystic or mixed cystic tumors [21]. However, we found aggressive and non-aggressive pathologic features occurring with nearly equal frequency in solid and cystic lesions. We also found that aggressive and nonaggressive tumors could not be differentiated by the qualitative enhancement characteristics (low, equal, or high in attenuation compared with the pancreatic parenchyma) of their solid component.

Most of the lesions in our study had well-circumscribed margins with imperceptible walls, and these features did not significantly differ between aggressive and nonaggressive disease. Most of the tumors were round or lobulated irrespective of pathologic features. Two aggressive tumors demonstrated capsular irregularity, i.e., focal discontinuity of the capsule, which has been suggested as a feature that can be used to diagnose tumor aggressiveness [29]. Yin et al showed a difference in capsular morphologic features such that aggressive tumors had discontinuity of the capsule ($p=0.05$) or size >6 cm ($p=0.02$) [30]; however, such differences in association with aggression did not reach statistical significance in our study.

Calcification (16/40) and hemorrhage (9/40) within the lesions were not frequently observed in our study. Yin et al stated that presence of amorphous or scattered calcifications and solid composition favor a benign pathology [30]. Another study suggested that the presence of calcification is a behavior of malignancy [31]. Although we also found calcifications and hemorrhage to be more prevalent in benign tumors, the divergence in these features was not significantly associated with aggression.

A study has suggested that SPNs <3 cm in diameter are more likely to be completely solid with a well-circumscribed margin and to have other different imaging characteristics, compared with tumors that are >3 cm [32]. In our study, seven tumors were ≤ 3 cm; one of these was completely cystic, and one had mixed cystic and solid components. Three of these tumors did not have a well-circumscribed margin. None of the tumors that were ≤ 3 cm had internal hemorrhage, which is in accordance with the findings of Chae et al [32, 33]. No pancreatic ductal dilation was seen in patients who had tumors ≤ 3 cm (0/7); however, eight of the 32 tumors >3 cm did show pancreatic ductal dilation. Ductal dilation has been correlated with recurrence and metastases in SPNs, but we did not see this link in our study [34]. SPNs are low in attenuation relative to the pancreatic parenchyma, an imaging finding similar to pancreatic ductal cancer; even though SPNs may present with ductal dilation, they should not be mistaken for pancreatic cancer.

As shown in the literature, SPNs in our study were more commonly seen in females than in males (88% vs 13%) [2, 33]. Two female patients with aggressive pathology in our cohort had liver metastases. This finding is in accordance with a study suggesting that patients with aggressive tumor features on pathologic analysis may present with metastatic disease [35, 36], and these histopathologic findings may warrant close follow-up of patients [35]. One of the female patients with hepatic metastases demonstrating growth into the superior mesenteric and portal vein is alive, and this finding is in concordance with one series that suggested that venous invasion/ extension based on imaging findings does not adversely affect the long term outcome [37].

Our results are similar to those published in the literature [30, 38–42] showing that the malignant potential (potential to metastasize) of SPNs cannot be determined on the basis of factors such as sex [43]; age; cystic, solid, or mixed appearance on cross-sectional imaging; or location. The overall prognosis of SPN is good for both aggressive and nonaggressive tumors [44]. In the presence of extra-pancreatic extension, the tumors are resected en bloc, including resection of the portal/superior mesenteric venous confluence if necessary [45, 46]. Even in SPNs with metastases, surgical removal of tumor and metastases is the standard approach owing to the favorable biologic features of these tumors [10, 47]. We did not observe recurrence in our cohort; however, studies have suggested that SPNs with aggressive histopathologic features may recur [16, 36]. Follow-up imaging may be necessary in these patients to detect early recurrence.

In our cohort, despite the presence of large lymph nodes on imaging, patients did not have metastatic adenopathy, as also seen in a study by Tipton et al [26, 35]. Other studies have also alluded that a formal lymphadenectomy, despite the presence of enlarged lymph nodes, may not be necessary [35, 40, 48, 49]. Given the excellent prognosis and difficulty to predict

the outcomes of patients with pathologically aggressive tumors surveillance following surgical resection of the tumor is crucial [44]. There are several limitations to our study. First, it was a retrospective analysis in a single institution and had the limitations inherent to that design. Only patients who has baseline imaging prior to surgical resection were included in the study. Second, the images were interpreted in consensus; hence, we could not assess the kappa statistic. Third, all the images were not obtained on the same 64-detector General Electric scanner, and inter-scanner variability was not taken into account. Fourth, on enhancement using the ROIs; only the HU values of the solid portion of the tumor were assessed, and the HU values of the cystic areas were not recorded.

Conclusion

Our study suggests that pathologically aggressive SPNs may have HU values of 62.6 of the solid component of the tumor on the delayed phase of contrast and show progressive enhancement. SPNs with these aggressive-associated features should be followed up closely, as they may develop metastases or have recurrence based on literature. Further prospective studies would be helpful in confirming our findings of progressive enhancement and correlation with aggressive features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant P30CA016672.

We thank DR Preeta Ramalingam MD for assisting with the pathology images. Dr. Santosh Shah MD and Dr. Vineet Shah for data mining.

This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center.

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Fig. 1.

Of solid area of the tumor shows tumor arranged in sheets and is composed of round to ovoid neoplastic cells with homogenous to finely stippled chromatin and occasional small nucleoli. Grooves, a characteristic feature of SPN nuclei, are seen (arrow). The cytoplasm is eosinophilic with occasional vacuolization (hematoxylin and eosin, 9400) (a) Hemotshows a partial pseudocapsule (arrow) around the tumor adjacent to the normal pancreas. (b) shows a tumor ble cells surrounding the nerve (light pink ovoid structure) representing perineural invasion (c) shows the tumor (arrow) extending into the addjacent pericolonic fat. (d) Blue cells representing the tumor extend into the a small vascular space containing tumor (arrow) representing lymphovascular invasion

Fig. 2. 17-year-old female with epigastric pain and solid pseudopapillary neoplasm in the head of the pancreas. The noncontrast axial (a) arterial (b) portal venous (c) and delayed phase of contrast images show a pathologically non aggressive well circumscribed mass (arrow) in the pancreatic head.

Fig. 3.

58-year-old male with an incidental pancreatic solid pseudopapillary neoplasm. The noncontrast axial {29HU} (a) arterial {59HU} (b) portal venous {72HU} (c) and delayed phase {85 HU} of contrast images show a pathologically aggressive mass (arrow) in the pancreatic head. The tumor has a central area of low attenuation and has eccentric calcifications as seen on the non contrast image (a).

Fig. 4.

Shows a Box plot of the Hounsfield values on delayed phase of contrast plotted against aggressive vs nonaggressive pathology. The boxplots were overlaid with the actual data points (blue). To avoid overlap of data points with same value, the data points were scattered horizontally (jittered). In the Box-and-whisker plot, the ends of the box represent the 25th and 75th quantiles. The line within the box represents the median sample value. The red diamond shape represents the mean. The difference between the 25th and 75th quantiles is called the interquartile range (IQR). The lower whisker extend from the lower end of the box to the minimum value that is greater than or equal to the 25th quartile minus 1.5 time the IQR, and the upper whisker extend from the upper end of the box to the maximum value that is less than or equal to the 75th quartile plus 1.5 times the IQR.

Figure 5. Enhancement patterns of pathologically aggressive and nonaggressive solid pseudo papillary tumors (SPN) of the pancreas

Fig. 6. Kaplan Myer survival curves shows survival in all patients with solid pseudopapillary tumors. Number of death = 3 and number of censored = 40. Survival time for the three patients who died were 6, 13, and 15 months.

HU values of pathologically aggressive and nonaggressive solid-pseudopapillary tumors on different phases of contrast enhancement

Table 1

Phase of contrast	Aggressiveness	N	Mean	SD	P value
Non contrast	N	22	33.3	12.4	0.26
	Y	13	37.5	6	
	All	35	34.9	10.6	
Arterial	N	22	66.1	31.4	0.36
	Y	13	70.2	22.6	
	All	35	67.6	28.2	
Portal-venous	N	22	63.7	28.2	0.45
	Y	14	70.8	24.7	
	All	36	66.4	26.8	
Delayed	N	20	58.8	27.2	0.03
	Y	10	76.9	15.1	
	All	30	64.8	25.1	

Shows prediction of pathological aggressiveness based on delayed imaging using recursive partitioning using > 62.5 Hounsfield unit as a cutoff value on the delayed phase of contrast.

Table 2

	Aggressive		Non-aggressive		All		P-value
	N	%	N	%	N	Total %	
Aggressive	9	56%	7	44%	16	53%	0.0026
Non-aggressive	1	7%	13	93%	14	47%	