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Imaging Comparison of Tubular and Colloid Pancreatic Adenocarcinoma arising from Intraductal Papillary Mucinous Neoplasm on Multidetector CT

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Abstract

Purpose—To compare tubular and colloid subtype pancreatic ductal adenocarcinomas (PDAC) associated with intraductal papillary mucinous neoplasms (IPMN) on CT.

Methods—An IRB approved retrospective study included patients with either IPMN tPDAC or cPDAC. Enhancing mural nodules (MN), solid component (SC), main pancreatic duct diameter (MPD), abrupt change in MPD caliber were evaluated.

Results—22 patients with cPDAC, 17 with tPDAC showed no significant difference in MPD size. MN and SC were seen in cPDAC/tPDAC in 55%/18% and 9%/53% respectively. Abrupt change in MPD caliber was seen in cPDAC/tPDAC at 18%/59%.

Conclusion—Colloid and tubular PDAC differ in the frequency of MN, SC and changes in MPD caliber.

1. INTRODUCTION

Pancreatic cystic lesions are increasingly found incidentally on cross-sectional imaging.[1,2] The management of pancreatic cysts, particularly branch duct intraductal papillary mucinous neoplasms (IPMN)[3], has received great attention with a number of guidelines now available.[4,5] Clinical management relies on clinical evaluation and non-invasive cross-sectional imaging with multidetector computed tomography (MDCT) and magnetic resonance cholangiopancreatography (MRCP) to characterize pancreatic cystic lesions and to identify imaging features that may prompt further interventions.[6,7]

For patients with IPMN, the assessment of “high-risk stigmata” or “worrisome features” on MDCT and MRCP is based on measuring cyst size and pancreatic duct diameter as well as

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identifying abrupt changes in pancreatic duct caliber, thickened cyst walls, mural nodules and solid enhancing components.[4] Despite the use of published guidelines to inform surgical intervention, the ability to preoperatively predict high-grade dysplasia and invasive carcinoma in patients with IPMN remains variable.[8,9] This limitation may be related to our current inability to detect small invasive cancers, which can be challenging with MRCP and especially MDCT.[10] Another possibility is that current imaging-based guidelines do not take into account the differences between subtypes of invasive carcinomas in IPMN.

Two distinct subtypes of invasive pancreatic carcinoma in IPMN have been described: colloid and tubular carcinoma.[11,12] Tubular carcinoma histologically resembles classic pancreatic adenocarcinoma with conventional ductal morphology, invasion, and a strong desmoplastic stromal response. Colloid carcinoma is microscopically distinct and characterized by extensive pools of extracellular mucin with a small number of floating neoplastic cells. In patients with IPMN, colloid carcinoma demonstrates a relatively good prognosis compared to tubular carcinoma (5-year survival rates of 87% and 55%, respectively) [13]; however, their imaging features in the setting of IPMN have not been compared. In only a few, small case series have investigators attempted to describe the radiographic features on MR and CT of colloid cancers [14,15], which arise almost only in the setting of IPMN.[16,17]

Given the divergent clinical outcomes between colloid and tubular invasive carcinomas, an ability to preoperatively identify these subtypes in patients with IPMN may potentially influence their clinical management. Thus, the purpose of our study was to retrospectively compare the imaging characteristics on MDCT of invasive and tubular adenocarcinomas in pathologically confirmed IPMNs.

2. MATERIAL AND METHODS

2.1 Study Population

A retrospective study was performed after obtaining a Health Insurance Portability and Accountability Act-compliant institutional review board-approved waiver of informed consent. Three hundred seventy-three pancreatic resections for IPMN-associated disease between 1996 and 2013 were identified from a search of our prospectively maintained pancreatic database. Invasive disease was initially identified in 97 cases. Of these, 64 patients had images available for review on a Picture Archiving and Computer System (PACS, Centricity 2.0, GE Healthcare, Wisconsin). For two patients who had surgical resections on two separate dates, the second resected tumor was excluded from this study (n=2). Patients' pathology records were reviewed to confirm the diagnosis of IPMN-associated invasive tumor. Patients with the following disease characteristics were excluded: lack of invasive carcinoma (n=4), invasive tumors with no underlying IPMN (n=3), tumors with mixed histology (n=4), and tumors with post chemotherapy changes (n=2). Radiographic exclusion criteria included the following: more than 90 days between CT and surgery (n=2), presence of a diffusely abnormal pancreas (n=3), presence of a pancreatic stent (n=2), and fistulous communication with the stomach or duodenum (n=5). Thus, the final study group included 39 patients with pathologically confirmed invasive tumors, 17 with tubular and 22 with colloid adenocarcinomas. Clinicopathologic patient characteristics

were extracted including age, sex, pathologic tumor size, histologic subtype (tubular, colloid), tumor stage, and survival. Of these 39 patients, 16 have previously been published [18], including 10 with colloid and 6 with tubular invasive tumors.

2.2 Imaging Parameters

MDCT images were obtained from studies performed at our own institution (n=21) and elsewhere (n=18) between 1998 and 2013. Of those performed at our institution, 19 were performed according to a dedicated pancreas protocol as previously published,¹⁸ and an additional 10 were performed with a similar multiphasic pancreas protocol outside of our institution. For the remaining 10 patients, 6 scans were performed with portal venous phase (PV) CT only, one with arterial phase CT, one with arterial and PV CT, one with non-contrast and PV CT, and one scan performed post contrast only in the delayed phase.

2.3 Imaging Analysis

Three radiologists (one in residency training; and two attendings, each with over 5 years' post-training abdominal radiology experience) who were aware of the diagnosis of IPMN with invasive carcinoma, but were blinded to the colloid or tubular pathologic subtype, reviewed the images. The following variables were assessed by the resident and one of the attendings in consensus: diameter of largest cyst present (D), main pancreatic duct (MPD) diameter, presence or absence of abrupt change in MPD caliber, presence or absence of common bile duct (CBD) dilatation and CBD diameter, and presence or absence of CBD stent. Change in MPD caliber was deemed present if the duct abruptly changed from large caliber to a mass lesion, which was assessed qualitatively. No size threshold for pancreatic duct caliber change was given. The two attending radiologists evaluated the following in consensus: the presence (and size when applicable) of enhancing soft tissue either in the form of mural nodules (MN) or solid components (SC). MN were distinguished from SC by the presence of surrounding cyst fluid.[19] Specifically, MN were deemed present when an enhancing soft tissue nodule was surrounded by low attenuation fluid. When pre- and post-contrast PV CT images were available, the enhancement of MN and SC was measured in Hounsfield units (HU), by placing the largest possible region of interest over the enhancing component.

2.4 Statistical Analysis

Statistical analysis was performed using SPSS software version 22.0 for Mac (Chicago, IL). Categorical variables were compared using the Chi-squared test. Continuous variables were reported as means and compared using the two-tailed t-test. Comparisons were made between clinicopathologic variables and radiographic appearance to assess for correlations.

3. RESULTS

Patient demographics and clinicopathologic variables are outlined in Table 1. No significant differences were found between patients' age or sex, or the time between preoperative CT and surgical resection for patients with tubular versus colloid invasive adenocarcinomas. Pancreaticoduodenectomy (Whipple procedure) was the most common operation performed

for both histologic subtypes (n=34, 87%), with the remainder consisting of distal pancreatectomy (n=5, 13%).

Imaging features of IPMN with colloid and tubular invasive carcinoma are summarized in Table 2. Although cyst size (40 vs 29 mm) was larger on average for colloid versus tubular subtype invasive IPMN, the difference was not statistically significant. An abrupt change in MPD caliber was seen more frequently in tubular than colloid subtypes (59% vs 18%, $p=0.009$) (Figure 1). A CBD stent was present in two patients with tubular pathology. The CBD was larger on average for tubular (10.5 mm) than colloid (7.7 mm) subtypes, a difference that nearly reached statistical significance ($p=0.06$).

There was a significant difference in the proportion of colloid and tubular invasive tumors with MN, SC, or neither ($p=0.007$) (Figure 2). MN were more commonly found in the colloid subtype than in the tubular subtype (55% vs 18%, Table 2). In contrast, SC were more commonly found in tubular than in colloid subtypes (53% vs 9%). When either a MN or SC was present, their enhancement on PV phase compared to non-contrast CT was similar between colloid and tubular adenocarcinomas. Mean enhancement of MN and SC was 53 HU for colloid carcinoma and 56 HU for tubular carcinoma ($p=0.78$). Mean enhancement of all 15 MN was 43 HU, while mean enhancement of all 11 SC was 62 HU.

A MN or SC was identified in 8 of 9 colloid (89%) and 7 of 8 (88%) tubular subtype IPMN when the invasive component on pathology was greater than 2 cm. However, when the invasive carcinoma was less than 2 cm, a MN or SC was identified in only 6 of 13 (46%) colloid and 5 of 9 (56%) tubular subtype carcinomas. No significant differences were found in the location of invasive tumors, with the majority occurring in the pancreatic head or uncinate process (Table 2).

4. DISCUSSION

The disease-specific rates of survival outcome in patients with invasive colloid and tubular carcinomas have been found to be quite different. In a matched analysis of invasive IPMN and conventional pancreatic adenocarcinoma patients, colloid carcinoma demonstrated a relatively good prognosis (5-year survival rate of 87%), in comparison with tubular carcinoma and conventional adenocarcinoma (5-year survival rates of 55% and 23%, respectively).[13] Although a few studies have suggested a somewhat more favorable prognosis for tubular carcinoma associated with IPMN than conventional adenocarcinomas, the data are difficult to interpret due to small sample sizes and variations in methods to quantify the invasive component.[11] The present study is the first to directly compare the imaging features of invasive colloid and tubular IPMN. Given the differences in outcome, preoperative determination of histopathologic subtype may result in different treatment recommendations. Although some imaging differences were found between invasive colloid and tubular subtype IPMN on MDCT, sufficient overlap still exists to prevent a definitive distinction between the two groups. Our study did find, however, that an abrupt MPD caliber change was more often seen with tubular (59%) than colloid (18%) subtype carcinomas ($p=0.009$), perhaps because of the greater desmoplastic response associated with tubular carcinomas.[20]

In the 2012 international consensus guidelines for the management of IPMN by Tanaka et al, imaging findings associated with IPMNs are divided into “high-risk stigmata” and “worrisome features.” The former generally prompt operative intervention, and include such findings as an enhancing SC/MN or a MPD greater than or equal to 10 mm. The latter, described as “worrisome features,” generally guide follow-up or further tests and include such findings as MPD cut off and cyst size greater than or equal to 3 cm. [4] Although abrupt MPD caliber change is classified only as a “worrisome feature” by Tanaka et al, our results raise the question of whether this finding should perhaps be reassigned to “high-risk stigmata” given its association with tubular adenocarcinomas. Further work needs to be performed to validate this proposal.

In our study, a majority of colloid carcinomas had visible enhancing MN (55%), whereas a majority of tubular carcinomas had visible enhancing SC (53%) on MDCT. In colloid subtype invasive IPMNs, a distinct MN that is partially outlined by a large cyst or dilated MPD is consistent with the previously reported appearance of colloid carcinomas [15] and probably reflects the extensive pools of extracellular mucin associated with this tumor. Additionally, there is support for our observation that tubular tumors do not produce as much mucin and therefore have the SC appearance more often than colloid tumors.[21] A MN or SC was visible in nearly all (15 of 17) carcinomas greater than 2 cm, but was seen in only half (11 of 22) of the carcinomas smaller than 2 cm. This result is not entirely surprising, given the challenge in identifying small pancreatic adenocarcinomas less than 2 cm in general.

MN and SC detected in our study enhanced by over 50 HU on average. Although the recent guidelines by Tanaka et al refer to non-enhancing versus enhancing MN, all of our MN enhanced by a mean of 43 HU when comparing PV phase CT to non-contrast CT.[4] Also, the Tanaka guidelines do not distinguish between enhancing “mural nodules” and enhancing “solid components” as we and others have previously reported.[19] Our findings suggest that although both MN and SC may be indicative of invasive lesions, their distinction could be an important one to report as it may help to discriminate between colloid and tubular type carcinomas. Additionally, confirming enhancement is crucial for assessment of suspected MN/SC. If non-contrast MR imaging is used to follow up patients with IPMN [22,23], further evaluation with contrast-enhanced CT or MRI may be valuable when the presence of MN or SC is suspected.

Our study has a number of limitations, including its retrospective nature and the small sample size. The sample size reflects the small proportion of IPMNs that are taken to surgery, given changes in the management of this entity over the last decade favoring more observation. The trend in larger cyst size associated with colloid (mean 40 mm) versus tubular (29 mm) invasive IPMNs did not reach statistically significant difference ($p=0.10$), but this may also be due to our small sample size. Similarly, the difference in CBD diameters nearly reached statistical significance, ($p=0.06$). A larger study may confirm these trends and support the idea that colloid subtype IPMN can grow to a larger size because of their indolent nature, while tubular subtypes are more likely to obstruct the CBD because of the associated desmoplastic reaction. Another limitation is that the imaging available for review was not performed uniformly, with a lack of complete pancreatic protocol CT

technique for all patients, which could have influenced our ability to detect smaller invasive tumors. The imaging review was also performed by radiologists in consensus; interobserver variability was not assessed for this study. However, our group has previously evaluated interobserver variability for a larger group of patients with IPMN who had either invasive or non-invasive components [18]. In that study, we have found that the interobserver agreement for MN or SC was fair to moderate between readers. Thus, a consensus read methodology was used in this current study. We acknowledge that the distinction between MN and SC for distinguishing between IPMNs with tubular and colloid invasive cancers will remain a challenge until a better consensus is reached in their definitions.

5. CONCLUSION

In conclusion, colloid and tubular carcinomas in association with IPMN show distinct imaging appearances on MDCT that may result from their underlying histologic differences. Colloid IPMN carcinomas are often observed with enhancing MN, possibly due to their abundant extracellular mucin, whereas tubular IPMN carcinomas often demonstrate enhancing SC with abrupt changes in MPD caliber, presumably from the desmoplastic reaction associated with this subtype. Further prospective studies are needed to confirm these findings. An increased ability to distinguish between these two subtypes of invasive IPMNs may alter the long term management of this patient population.

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Highlights

1. Colloid and tubular pancreatic adenocarcinomas (cPDAC, tPDAC) vary in prognoses.
2. IPMN with cPDAC are more likely to have mural nodules on CT.
3. IPMN with tPDAC are more likely to have soft tissue components.
4. IPMN with tPDAC are more likely to show changes in main pancreatic duct caliber.

Figure 1.

Contrast enhanced CT images of IPMNs with colloid subtype adenocarcinoma (A) and tubular subtype adenocarcinoma (B), both with dilatation of the main pancreatic duct (arrows). In (A), the main pancreatic duct merges with a cystic lesion that contains a mural nodule. In (B), the main pancreatic duct abruptly cuts off to the level of a solid enhancing lesion which is off the plane of this image.

Figure 2. Representative IPMNs with colloid subtype adenocarcinoma (A, B) and tubular subtype adenocarcinoma (C, D) on MDCT before (A, C) and after intravenous contrast during the portal venous phase (B, D). The colloid subtype has a mural nodule in the pancreatic head, defined as enhancing soft tissue surrounded by fluid (B: arrow) while the tubular subtype has a solid component defined as enhancing soft tissue without surrounding fluid (D: arrow).

Table 1

Demographics and Clinical Variables of IPMN-Associated Colloid and Tubular Invasive Adenocarcinoma

	Colloid (n=22)	Tubular (n=17)	P values
Age (mean)	70	67	P = 0.50 *
Sex	12 M, 10 F	10 M, 7 F	P = 0.79 †
Days between CT and surgery (mean)	27	17	P = 0.07 *
Procedure			
Whipple	n = 19 (86%)	n = 15 (88%)	P = 0.86 †
Distal Pancreatectomy	n = 3 (14%)	n = 2 (12%)	
T1 stage invasive cancer	n = 13 (59%)	n = 9 (53%)	P = 0.70 †

P value determined by

* independent samples 2 tailed t-test

† Pearson chi-square tests.

Table 2

Imaging Features of IPMN-Associated Colloid and Tubular Invasive Adenocarcinoma

	Colloid (n=22)	Tubular (n=17)	P values
Cyst size (mm)	39.8	28.8	P = 0.10 [*]
MPD ^a size (mm)	10.8	11.8	P = 0.79 [*]
Abrupt change in MPD caliber	n = 4 (18%)	n = 10 (59%)	P = 0.009 [†]
CBD ^b size (mm)	7.7	10.5	P = 0.06 [*]
Enhancing component			
Mural Nodule	n = 12 (55%)	n = 3 (18%)	P = 0.007 [†]
Solid Component	n = 2 (9%)	n = 9 (53%)	
None	n = 8 (36%)	n = 5 (29%)	
Size of enhancing component (mm)	25.1	30.0	P = 0.30 [*]
Enhancement (HU) ^c	53	56	P = 0.78 [*]
Location of Invasive Tumors ^d			
Head/Uncinate	17	13	P = 0.32 [†]
Body	2	2	
Tail	3	0	

P value determined by

^aMPD, main pancreatic duct^bCBD, common bile duct^cEnhancement was assessed for patients in which non-contrast and portal venous phase imaging was performed (n=10 for colloid, n=11 for tubular).^dThe locations of 2 tubular invasive tumors were too diffuse to assign to a single location.^{*}independent samples 2 tailed t-test[†]Pearson chi-square tests.