European Radiology (2019) 29:3132–3140
https://doi.org/10.1007/s00330-018-5841-0

HEPATOBILIARY-PANCREAS

CT imaging comparison between intraductal papillary neoplasms of the bile duct and papillary cholangiocarcinomas

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Received: 7 August 2018 / Revised: 26 September 2018 / Accepted: 19 October 2018 / Published online: 5 December 2018

Abstract

Objectives To identify imaging features that assist in discriminating intraductal papillary neoplasms of the bile duct (IPNBs) from papillary cholangiocarcinomas (PCCs).

Methods This study was approved by the institutional review board. Using the recently proposed histological diagnostic criteria for biliary papillary neoplasms, IPNBs and PCCs were selected from 537 biliary neoplasms consecutively resected in a 12.5-year period. Clinical and imaging features were compared between the two groups.

Results The histology review identified 19 IPNBs and 48 PCCs, representing an estimated prevalence of IPNBs among biliary neoplasms of 4%. Approximately one half of IPNBs were incidentally found on imaging conducted for other purposes. In terms of tumor location, 15/19 IPNBs (79%) developed in intrahepatic bile ducts, and 41/48 PCCs (85%) in the distal bile duct. Cystic appearance was highly suggestive for IPNBs ($p < 0.001$). Using these two parameters, 78% of papillary bile duct neoplasms could be classified into IPNBs or PCCs. Other imaging findings favoring IPNBs included frond-like mural nodule, downstream bile duct dilatation, and the lack of abnormal enhancement in the adjacent bile duct. Interestingly, two patients with non-invasive or microinvasive IPNB had undergone abdominal imaging studies > 3 years before, and a retrospective review of the previous images identified small nodular or cystic lesions, suggesting a less progressive nature of IPNBs than currently thought.

Conclusions Imaging findings useful for discriminating IPNBs from PCCs appear to be tumor location, shape of tumor, appearance of mural nodules, duct dilatation at unaffected duct, and abnormal enhancement of the adjacent bile duct.

Key Points

- *Intrahepatic location and cystic dilatation of the affected bile duct are the strong discriminators between IPNBs and PCCs.*
- *The shape of the mural nodule and appearance of the neighboring bile duct are helpful for distinguishing IPNBs and PCCs.*
- *The less aggressive behavior of IPNBs compared with PCCs may facilitate less invasive management in patients with IPNB.*

Keywords Bile ducts · Tomography, X-ray computed · Cholangiocarcinoma

Abbreviations

CT	Computed tomography
DP	Delayed phase
EP	Early phase
HU	Hounsfield unit
IPMN	Intraductal papillary mucinous neoplasm
IPNB	Intraductal papillary neoplasm of the bile duct
MRI	Magnetic resonance imaging
ROI	Region of interest

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Introduction

Intraductal papillary neoplasm of the bile duct (IPNB) was first described by Chen et al in 2001 as a biliary papillary tumor associated with hepatolithiasis [1]. Thereafter, this diagnostic category was expanded to include similar cases not associated with intrahepatic stones [2]. In 2010, the World

Health Organization classification defined IPNBs as "non-invasive papillary or villous biliary neoplasms covering delicate fibrovascular stalks." [3] Given that IPNBs typically present with duct dilatation, intraductal papillary tumor, and occasional mucin overproduction, they are often regarded as the biliary counterpart of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas [2, 4–8].

Cholangiocarcinomas, representing 3% of all gastrointestinal malignancies [9], also sometimes exhibit predominantly intraductal growth, and these cases have been called papillary cholangiocarcinomas (PCCs). Discrimination between IPNBs and PCCs has been unclear with some pathologists regarding all papillary tumors as IPNBs, while others used the diagnostic term of IPNBs in selected typical cases [10]. Recently, a histological separation scheme was proposed [11]. Based on that standard, IPNBs appeared to be distinct from PCCs in many aspects including the microscopic growth pattern, immunophenotype of neoplastic cells, and degree of invasiveness. Most importantly, patients with IPNB showed a significantly better prognosis than those with PCCs. Therefore, although the differential diagnosis of IPNBs and PCCs largely depended on pathologists' preference, the histologic distinction between IPNBs and PCCs appeared to be crucial for the clinical management of patients with biliary papillary neoplasm. Although several prior studies examined radiological features of IPNBs, imaging findings that assist in the discrimination between IPNBs and PCCs have not been established yet [12–16].

The present study compared clinical and imaging features between IPNBs and PCCs that were diagnosed based on the recently proposed histological criteria, in order to identify imaging features that assist in discriminating IPNBs from PCCs.

Materials and methods

Case selection

This study was approved by the institutional review board at Kanazawa University Hospital and acquisition of written informed consent was waived because of its retrospective nature. A total of 537 patients with primary biliary neoplasm who underwent surgical resection were found in the radiology and pathology database at Kanazawa University Hospital and affiliated hospitals between January 2004 and July 2016. After cases that showed predominantly intraductal growth were selected, their histology was reviewed by a single hepatobiliary pathologist with 19 years' experience (Y. Z.). Eventually, 67 cases (12%) that met the diagnostic criteria (see below) of either IPNB or PCC remained for this study. Electronically stored clinical records of the selected patients were reviewed, in terms of age, gender, symptoms at the initial presentation, tumor markers (e.g., CEA, CA19-9), and history of chronic hepatobiliary diseases (e.g., viral hepatitis).

Diagnostic criteria

The diagnosis of IPNB and PCC was made based on the recently proposed histological scheme. Briefly, IPNBs were defined as non-invasive papillary neoplasms consisting of a neoplastic epithelium and thin fibrovascular stalks with an overall uniform papillary architecture throughout the tumor. Mucin overproduction was not essential for the diagnosis. Infiltrative cancers with a non-invasive component consistent with IPNB were classified as IPNBs with an associated invasive cancer. Cases with PCCs grossly showed predominantly intraductal growth, and histologically consisted of mainly papillary or papillotubular adenocarcinomas, with an overall architecture that was more complex than would be expected in IPNBs (e.g., irregular papillary branching, conspicuous tubular or solid components, and irregularities in the thickness of papillae).

Protocols of radiological examinations

Preoperative CT images were available for all 67 patients. Four-, 10-, 16-, 64-, 80-detector row CT were performed in six, one, 22, 35, and three patients, respectively. Each examination was performed with a tube voltage of 120 kVp and an automatic exposure control system, which was adjusted for the body build of the patient for 58 patients, and for nine patients, a tube voltage of 135 kVp and 400 mAs was used. Slice thickness for each examination was 2.0–5.0 mm for all but one with a 10.0-mm thickness. Contrast-enhanced multiphase (including early phase [EP] and delayed phase [DP]) dynamic CT images were obtained in 62 cases and the remaining five underwent CT examinations with pre-contrast and DP images. The EP images and DP images were obtained with 35–45- and 150–240-s delays after starting the administration of nonionic contrast medium using a power injector at an injection rate of 3.0–4.0 mL/s, respectively. Because of the multi-institutional retrospective nature of this study, the scanning protocols were inconsistent.

In addition to images that were taken at the time of diagnosis, previous images obtained > 6 months earlier were available for 11 patients. Their imaging features were retrospectively reviewed in terms of whether or not the tumor had already been detectable and, if detectable, how the imaging appearance changed in between. Follow-up images after surgical resection were available for all patients with a median follow-up period of 39.1 months (range 0.5–122.0 months), and they were also analyzed regarding tumor recurrences. Recurrence patterns were classified into local recurrence at the anastomotic site, intrabiliary recurrence at non-anastomotic sites, and remote metastasis.

Image analysis

All CT images were independently reviewed by two radiologists (T. K. and D. I. with 6 and 16 years' clinical experience of abdominal image interpretation, respectively), who were not involved in the data preparation. They were aware that those images had been obtained from patients with IPNB or PCC, but were blinded to the final pathological diagnosis. If interpretations of subjective parameters differed between the two radiologists, consensus was finally reached through discussion with a re-reviewing session.

Imaging features analyzed were the predominant location of tumors (intrahepatic, hilar, or distal bile ducts), tumor shape (cast-like or cyst-forming; their definition is shown in Fig. 1), shape and size of the mural nodules (frond-like or papillary; as defined in Fig. 2), abnormal enhancement of the duct wall adjacent to the nodule, presence or absence of the dilatation of the upper (> 5 mm) and downstream bile duct (> 10 mm), and pancreatic IPMNs. In cyst-forming tumors, the maximum diameter of the cyst, shape (aneurysmal type or diverticulum type; their definition is shown in Fig. 1), appearance (unilocular or multilocular), and margin of the cyst (smooth or lobular) were also examined according to the previous reports [17, 18].

Enhancement patterns of the mural nodule were assessed by placing a region of interest (ROI). The circle-shaped ROI was set on the nodular lesion as large as possible (median 65.8 mm^2; range 12.2–128.4 mm^2). The ROI position was also determined by consensus of the two radiologists. Enhancement patterns of nodules were classified into three groups using the difference of CT values between EP and DP (CT value on DP minus that on EP; > 10 HU, delayed enhancement pattern; between -10 and 10 HU, persistent pattern; and ≤ 10 HU, washout pattern).

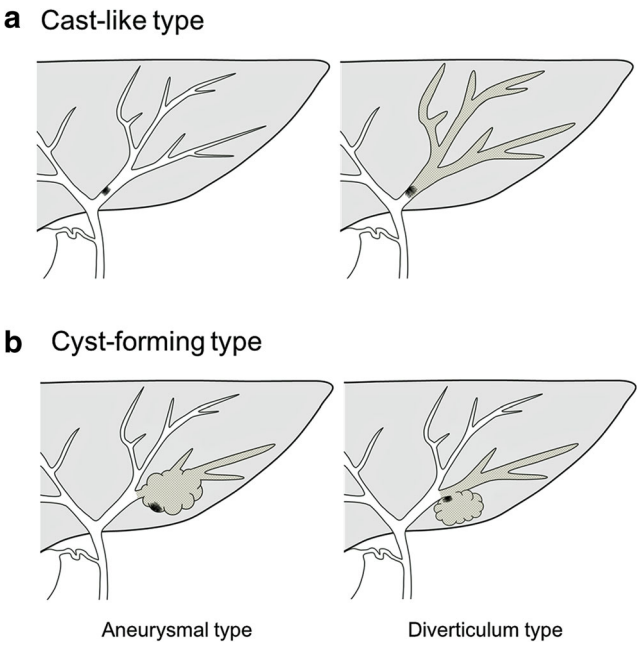

Fig. 1 Classification and definition of tumor shapes. **a** Cast-like tumors represent intraductal nodular lesions without cystic dilatation of the affected bile duct. **b** Cyst-forming tumors correspond to the tumors associated with cystic dilatation of the affected bile duct. Cyst-forming tumor could be further classified into aneurysmal and diverticulum type

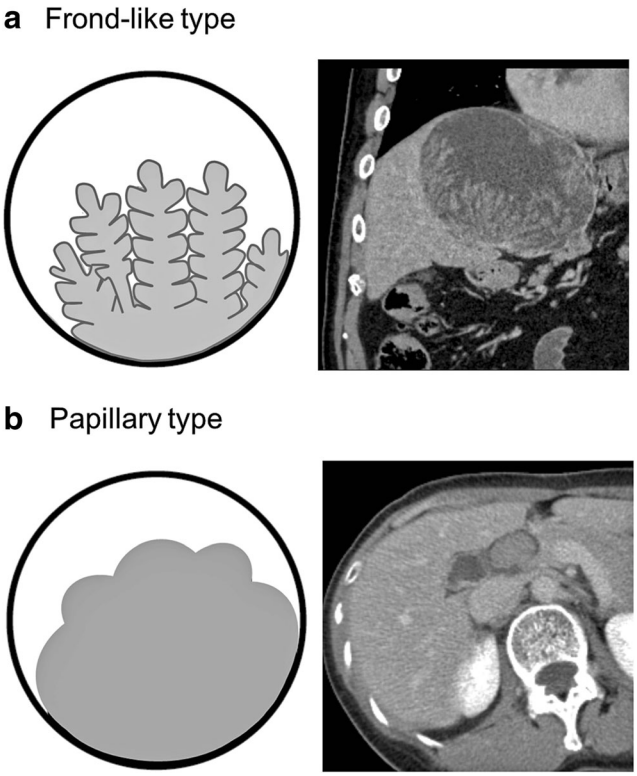

Fig. 2 Classification and definition of the shapes of mural nodules. **a** Nodules with delicate finger-like projections were defined as "frond-like." **b** The papillary type was determined as more solid intraductal nodules

Statistical analysis

Statistical analysis was conducted using SPSS 23.0 software (Statistical Package for the Social Sciences for Windows, version 23.0; IBM Corp). Fisher's exact test was used to compare the imaging findings between IPNBs and PCCs. The Mann-Whitney *U* test was applied to compare age, tumor markers, and size of the nodular lesions between the two groups. A *p* value of less than 0.05 was considered to indicate a significant difference. Inter-reader agreement was assessed by calculating a simple kappa value for the subjective parameters. A kappa value less than 0.20 was interpreted as poor agreement, in the range of 0.21–0.40 as fair agreement, in the range of 0.41–0.60 as moderate agreement, in the range of 0.61–0.80 as good agreement, and more than 0.81 as excellent agreement.

Results

Clinical features

Through pathological re-evaluation, 19 cases were diagnosed with IPNBs, and 48 cases with PCCs. The frequency of IPNBs and PCCs in the entire cohort (537 cases) was 4% and 9%, respectively, with IPNBs comprising 28% of biliary tumors showing predominantly intraductal growth. As shown in Table 1, patients with IPNB were significantly younger than those with PCC ($p = 0.018$). In terms of initial clinical presentation, 9/19 (47%) patients with IPNB were incidentally found to have a biliary neoplasm on imaging taken for surveillance of other diseases or routine medical checkup with the asymptomatic presentation more common in IPNBs than in PCCs ($p = 0.009$). In contrast, most patients (85%) with PCC presented with symptoms such as abdominal pain and jaundice. In terms of tumor markers, PCCs had higher CA19-9 concentrations than IPNBs ($p < 0.001$). No significant difference was identified in terms of history of chronic viral hepatitis. No patients had a history of primary sclerosing cholangitis or hepatolithiasis.

Of 19 IPNBs, 13 were associated with high-grade dysplasia but no invasive cancer, with some of them also having low-grade components. Of the other 6 cases, 3 showed only microinvasion (< 1 mm in depth), while the remaining 3 showed wide invasion. In contrast, PCCs were microinvasive ($n = 4$, 8%) or widely invasive ($n = 39$, 81%).

Table 1 Clinicopathologic characteristics of IPNBs and PCCs examined in the present study

	IPNB ($n = 19$)	PCC ($n = 48$)	p value*
Median age (range)	67 (34–79)	73.5 (43–85)	0.018
Male/female (male ratio)	8/11 (42%)	27/21 (56%)	NS
Symptoms			
Asymptomatic	9 (47%)	7 (15%)	0.009
Symptomatic†	10 (53%)	41 (85%)	
Abdominal pain	8	17	
Jaundice	2	17	
Others	2	18	
Tumor marker			
CEA (ng/mL)‡	2 (0.9–5.4)	2.2 (0.8–33.7)	NS
CA19-9 (U/mL)‡	8 (1.2–5417.5)	16.5 (4.0–587.0)	< 0.001
Chronic viral hepatitis			
HBV	3 (16%)	2 (4%)	NS
HCV	1 (5%)	5 (10%)	NS

NS not significant, *IPNB* intraductal papillary neoplasm of the bile duct, *PCC* papillary cholangiocarcinoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus

*Unless otherwise indicated, p values were calculated with Fisher's exact test or the Mann-Whitney U test

† multiple symptoms, if any, were recorded

‡ data shown as median (range)

Radiological features

Table 2 compares the imaging findings of IPNBs and PCCs. The tumor location appeared to differ markedly between the two conditions with 15/19 IPNBs (79%) found in the intrahepatic bile duct, while 41/48 PCCs (85%) developed in the distal bile duct. Regarding the lesional shape, unlike PCCs, which were all classified as cast-like tumors, 11/19 IPNBs (58%) were cyst-forming neoplasms ($p < 0.001$). Although all cases had mural nodules, the shape of nodules differed between the two groups. Delicate frond-like projections were more commonly seen in IPNBs ($p < 0.001$), while solid papillary nodules were more frequently observed in PCCs ($p < 0.001$). In PCCs, the upstream ducts were more extensively dilated ($p < 0.001$), and abnormal enhancement of the duct wall adjacent to the nodule was more frequently observed ($p < 0.001$). On the other hand, downstream bile duct dilatation was frequently seen in IPNBs ($p = 0.029$). Representative images of cyst-forming IPNB, cast-like IPNB, and PCC are shown in Fig. 3. Regarding inter-reader reproducibility, kappa values for all findings were greater than 0.81, indicating excellent agreement. No significant difference was observed in terms of recurrence patterns, but intrabiliary recurrence at non-anastomotic sites was found only in IPNBs.

Diagnostic performance for differentiating IPNBs from PCCs

As the remarkable tendency was seen in lesional shape and tumor location, 52 of 67 cases (78%) were correctly classified into either IPNB or PCC based on a combination of these two findings (Fig. 4). For the remaining 15 cases (including 8 IPNBs and 7 PCCs), which developed in intrahepatic or hilar bile ducts with cast-like lesion, diagnostic performance of other imaging findings preferable for IPNBs (including frond-like nodule, presence of the downstream bile duct dilatation, lack of the upstream bile duct dilatation, or absence of abnormal duct wall enhancement adjacent to the nodule) was further examined. Of these findings, dilatation of downstream bile duct revealed high specificity (100%) though, sensitivity remained 25%, and accordingly, diagnostic accuracy was 60%. For other findings, sensitivities, specificities, and diagnostic accuracies ranged from 25 to 75%, 57 to 100%, and 53 to 67%, respectively (Table 3).

Characterization of cyst-forming IPNBs

Since 58% of IPNBs were cyst-forming, these 11 cases were further examined. The diameter of the cystic tumors ranged from 26 to 120 mm (median 37 mm) and was less than 60 mm

Table 2 Comparison of imaging features between IPNBs and PCCs

	IPNB ($n = 19$)	PCC ($n = 48$)	p value*	k value
Location†			< 0.001	1
Intrahepatic	15 (79%)	3 (6%)		
Left lateral segment	11	3		
Left medial segment	2	0		
Right lobe	2	0		
Hilar bile duct	4 (21%)	4 (8%)		
Distal bile duct	0	41 (85%)		
Shape of the tumor			< 0.001	1
Cast-like type	8 (42%)	48 (100%)		
Cyst-forming type	11 (58%)	0		
Dilatation of the bile duct				
Upstream (> 5 mm)	11 (58%)	46 (96%)	< 0.001	
Downstream (> 10 mm)	7 (37%)	5 (10%)	0.029	
Nodular lesion				0.836
Shape			< 0.001	
Papillary type	4 (21%)	39 (81%)		
Frond-like type	15 (79%)	9 (19%)		
Size (mm)‡	22.1 (5.1–54.1)	18.6 (6.2–51.2)	NS	
Enhanced pattern of the nodular lesion			NS	
Delayed enhancement	3	11		
Persistent	13	22		
Washout	3	10		
Enhancement in the adjacent duct	3 (11%)	36 (75%)	< 0.001	0.818
IPMN of the pancreas	2 (11%)	12 (25%)	NS	1
Recurrence	6 (32%)	13 (27%)	NS	
Local recurrence	1	10		
Intraductal recurrence	3	0		
Distant metastasis	2	3		

NS not significant, *IPNB* intraductal papillary neoplasm of the bile duct, *PCC* papillary cholangiocarcinoma, *IPMN* intraductal papillary mucinous neoplasm

*Unless otherwise indicated, p values between IPNBs and PCCs were calculated with Fisher's exact test or the Mann-Whitney U test; † the predominant location examined; ‡ data shown as median (range)

in 9 cases (82%). The cyst shape was aneurysmal type ($n = 8$, 73%) or diverticulum type ($n = 3$, 27%). The cystic tumors were unilocular in all but one case that presented with a multilocular cystic mass. Mural nodules were frond-like in all cases. The outline of the cystic tumors was smoothly rounded in 6 cases (55%) or lobulated in 5 (45%). Despite the predominantly cystic appearance, bile duct communication was identified in all cases. In this way, a unilocular aneurysmal cystic tumor of ~ 60 mm in diameter with a frond-like mural nodule was the most typical appearance of cyst-forming IPNBs noted in this study.

Retrospective evaluation of previous images

Previous images that were taken more than 6 months before the diagnosis were available in 2 cases of IPNBs and 9 cases of PCCs. The first case of IPNB already had a 26.9-mm solid mass in previous CT and MR images taken 64 months before, which had been initially interpreted as a hemangioma. Imaging taken at the current presentation revealed a 41.2-mm mass lesion inside the dilated bile duct, suggesting a diagnosis of IPNB. On resected specimen, the nodule was still non-invasive IPNB with high-grade dysplasia. The second case of IPNB with multiple previous images available initially presented with localized bile duct dilatation with a small intraductal nodule (Fig. 5). However, immediate surgical resection was not offered because of the small nodular size (5.4 mm) and indeterminate nature. On images obtained in the following 39 months, the nodule showed a gradual increase in size up to 15.9 mm with the diameter of the cystically dilated bile duct also changed from 12.9 to 22.3 mm. On the resected specimen, the tumor was mainly non-invasive IPNB with only small foci of microinvasion.

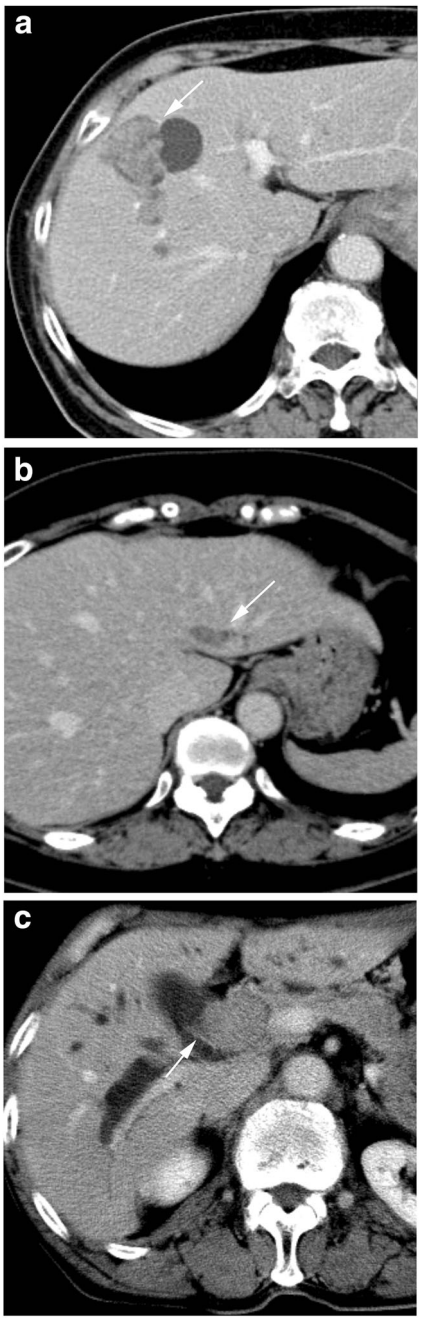

Fig. 3 Representative images of cyst-forming IPNB (**a**), cast-like-type IPNB (**b**), and PCC (**c**). **a** Contrast-enhanced CT image in a 73-year-old woman shows cystic dilatation of the affected duct accompanied with frond-like nodule (arrow). **b** Contrast-enhanced CT image of a 62-year-old woman demonstrates frond-like nodule in the left intrahepatic bile duct without cystic dilatation (arrow). **c** Contrast-enhanced CT image of a 60-year-old man. Abnormal bile duct enhancement is revealed adjacent to the papillary nodule in the distal bile duct (arrow). The upstream bile duct is extremely dilated

In contrast, of 9 patients with PCC who had previous imaging examinations, a single case was found to have hepatobiliary abnormalities. A retrospective review of his images identified a 6.6-mm nodule in the bile duct, which had been overlooked at the initial interpretation. The nodule size increased from 6.6 to 12.9 mm in an 11-month period. In the remaining 8 cases, no tumor was found in previous images taken 9–65 months (median 31 months) earlier.

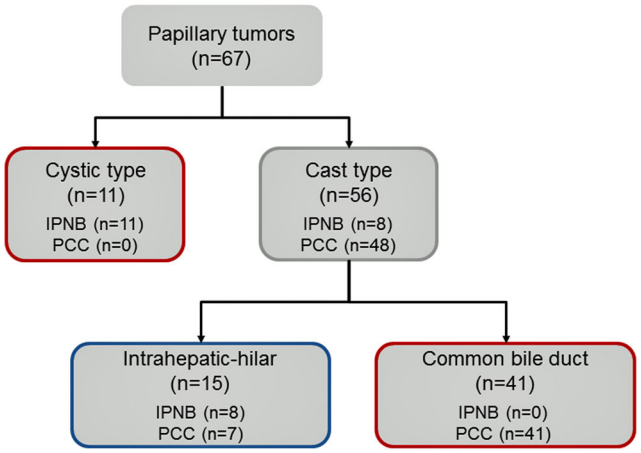

Fig. 4 Classification of IPNBs and PCCs based on the major imaging findings (tumor shape and location). Of all biliary papillary tumors, 11 IPNBs and 41 PCCs can be correctly classified based on the combination of tumor shape and location (red column). Fifteen cases (8 IPNBs and 7 PCCs) remain as unclassifiable cases (blue column)

Discussion

The results of our present study could be summarized as follows: (i) the prevalence of IPNBs and PCCs among surgical cases of biliary neoplasms was 4% and 9%, respectively; (ii) around one half of IPNBs were incidentally found on imaging; (iii) most IPNBs developed in intrahepatic bile ducts, while PCCs most often occurred in the distal bile duct; and (iv) cystic appearance, frond-like mural nodule, downstream bile duct dilatation, less prominent upstream bile duct dilatation, and lack of abnormal enhancement in the adjacent bile duct were determined to be imaging features favoring IPNBs over PCCs.

The reported prevalence of IPNBs ranges from 5 to 15% [8, 11, 19–21]. The present study suggested that IPNBs comprise 4% of surgically resected biliary neoplasms representing an incidence of almost one half of that of PCCs. These figures are nearly identical to those reported in a recent study that proposed stringent histological diagnostic criteria for IPNBs [11]. Except for the study of Fujikura et al, most previous reports suggested an incidence of > 10%, indicating that the diagnostic criteria of IPNBs used were less stringent, and PCCs might have been mis-categorized as IPNBs. The significant differences in not only clinicopathological features but also imaging appearance between the two conditions suggest that they are biologically distinct, and further justify the proposed separation scheme. In addition, a recent exome-sequencing study revealed that IPNBs have distinct molecular features with *APC* and *CTNNB1* mutated in 43% of cases [22].

Table 3 Diagnostic performance of imaging parameters

	CT findings suggestive of IPNB	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Classification for papillary tumors ($n = 67$)	Shape of the tumor (cyst-forming type)	58 (11/19)	100 (48/48)	100	86	88
Classification for cast-like-type tumors ($n = 56$)	Location (intrahepatic or hilar bile duct)	100 (8/8)	85 (41/48)	53	100	88
Classification for the unclassifiable cases ($n = 15$)*	Shape of the nodular lesion (frond-like shape)	50 (4/8)	86 (6/7)	80	60	67
	No dilatation of upstream bile ducts (< 5.0 mm)	25 (7/8)	86 (6/7)	67	50	53
	Dilatation of downstream bile ducts (> 10.0 mm)	25 (2/8)	100 (7/7)	100	54	60
	Absence of abnormal bile duct enhancement adjacent to the nodule	75 (6/8)	57 (4/7)	67	67	67

IPNB intraductal papillary neoplasm of the bile duct, *PPV* positive predictive value, *NPV* negative predictive value

*Diagnostic trial for the challenging cases, we attempted further discrimination by applying other imaging parameters demonstrated a significant difference in the univariate analysis. Unclassifiable cases are the papillary tumors arising in the intrahepatic to hilar bile duct with cast-like nodules.

Of the multiple imaging features examined, location is highly useful for the differential diagnosis. It is worth emphasizing here that IPNB is exceptional in the distal bile duct, while > 80% of PCCs develop at this particular site. Additionally, cystic appearance was also characteristic and only seen in IPNBs. By combining these two findings, 78% of papillary bile duct neoplasms were correctly classified into either IPNBs or PCCs. Four other dominant imaging discriminators favoring in IPNBs appeared to be the appearance of mural nodule (frond-like), downstream bile duct dilatation, less extensive upstream bile duct dilatation, and absence of abnormal duct wall enhancement adjacent to the nodule. These findings were similar to those noted in previous reports on IPNB [13–16, 18]. Applying these parameters for difficult cases enabled us further discrimination of these two conditions. Although these were somewhat subjective findings, the high inter-observer agreement suggests that a reproducible interpretation is possible. However, the differential diagnosis remains difficult in cast-like tumors which develop in the intrahepatic or hilar bile duct. Ying et al suggested that IPNBs with mucin overproduction have different imaging features from those without mucin production [16]. Given that at least some cases of mucin-poor IPNBs in their study supposedly correspond to PCCs based on our criteria, their study and our investigation examined similar aspects of biliary papillary neoplasms.

Considering the pathological differences between IPNBs and PCCs, frond-like mural nodule and downstream bile duct dilatation could be considered reflecting the thin fibrovascular stalks in mural nodules and mucin hypersecretion, respectively. The less extensive upstream bile duct dilatation in IPNBs may be attributable to the fact that the bile duct is not completely obliterated due to the less invasive nature of IPNBs, while all PCCs were invasive cancers causing ductal obstruction. A similar explanation may be applicable to abnormal enhancement in the adjacent bile duct. In PCCs, complete obstruction of the duct purportedly leads to periductal inflammation (obstructive cholangitis), a histological change likely corresponding to the abnormal enhancement.

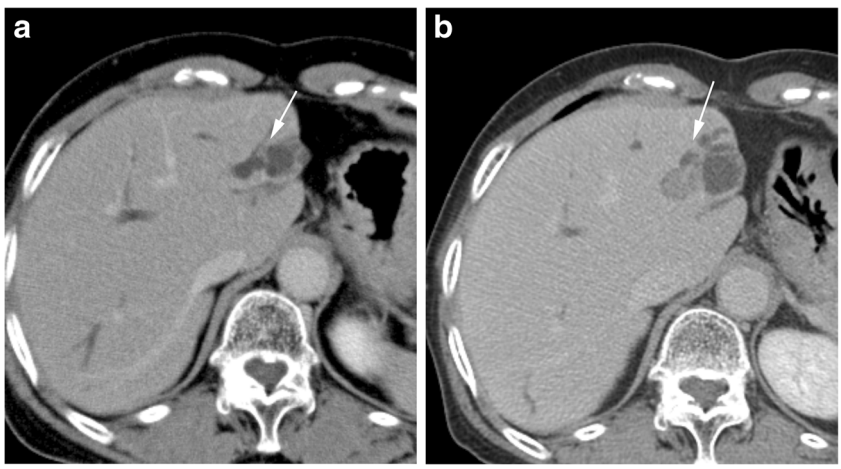

Fig. 5 A 39-month imaging course of a 76-year-old woman with IPNB. Contrast-enhanced CT images at the initial presentation (**a**) and 39 months later (**b**). The cystic lesion gradually increased in size with an intraductal nodule appearing more obvious (arrows). The surgical specimen confirmed the diagnosis of IPNB with minimal invasion

Surgical resection is currently the treatment of choice for IPNBs, the same as for cholangiocarcinomas [1, 7, 8, 11, 19–21, 23–26]. However, a less invasive therapeutic approach may be justified for patients with IPNB in the future. A similar discussion has been made for pancreatic IPMNs. The less invasive pancreatic neoplasms used to require surgical resection [27, 28], but many cases are currently followed up without invasive therapy [29, 30]. In the present study, both patients with IPNB who had previous imaging studies already had abnormalities 3 years earlier. In addition, resected IPNBs were still non-invasive or only minimally invasive. In contrast, all but one patient with PCC did not have detectable lesions in previous imaging examinations. This observation suggests that IPNBs are less progressive than currently suspected.

This study has a few limitations. First, because of its retrospective and multi-institutional nature, imaging protocols were inconsistent; therefore, detailed enhancement patterns could not be examined. Second, MRI comparison may provide imaging features that more accurately discriminate the two conditions. In fact, a recent study suggested that MRI is useful to predict the presence of invasive malignancy in IPNBs [31]. Third, because of the rarity of IPNB, the number of cases examined was relatively small. Last, even using multiple radiological findings, it is still challenging to determine whether IPNB or PCC is the more likely in some cases, particularly PCCs developing in the intrahepatic bile ducts.

In conclusion, papillary tumors comprised ~ 15% of surgically resected biliary neoplasms with one third of them meeting the diagnostic criteria of IPNBs. Imaging findings useful for discriminating IPNBs from PCCs appear to be location of the affected duct, shape of tumor, appearance of mural nodules, upstream or downstream bile duct dilatation, and abnormal enhancement of the adjacent bile duct. Although surgical treatment is currently the treatment of choice for IPNBs, watchful follow-up may become acceptable in selected patients given the less progressive nature than currently supposed.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dai Inoue.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Case-control study
- Multicenter study

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