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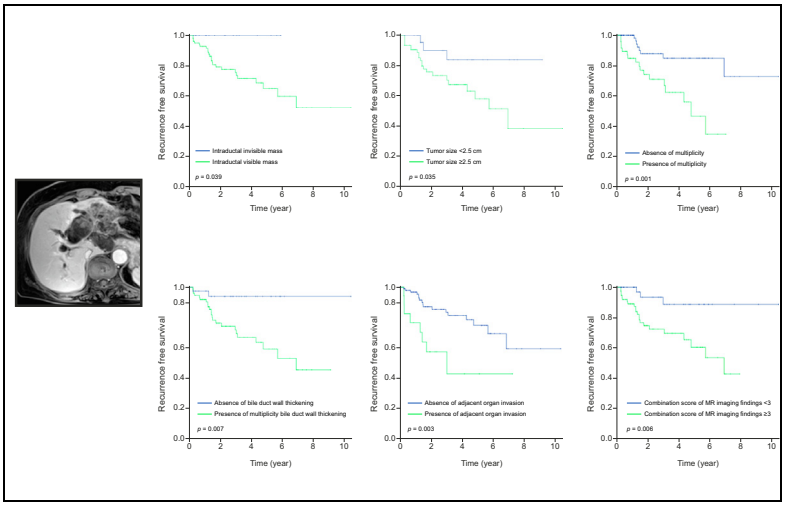
Graphical abstract



Highlights

- MRI findings were able to discriminate IPNB with an invasive carcinoma from IPNB with intraepithelial neoplasia.
- MRI findings of IPNB with an invasive carcinoma were linked to worse clinical outcome.
- Tumor multiplicity on MRI was an independent factor for RFS of IPNB after surgery.

Authors

Sunyoung Lee, Myeong-Jin Kim, Sohee Kim, Dongil Choi, Kee-Taek Jang, Young Nyun Park

Correspondence

kimnex@yuhs.ac
(M.-J. Kim)

Lay summary

Significant magnetic resonance imaging findings that differentiated between an intraductal papillary neoplasm of the bile duct (IPNB) with an associated invasive carcinoma and an IPNB with intraepithelial neoplasia were intraductal visible mass, tumor size ≥2.5 cm, multiplicity of the tumor, bile duct wall thickening, and adjacent organ invasion. Significant magnetic resonance imaging findings of invasive IPNB have a negative impact on recurrence-free survival.

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Intraductal papillary neoplasm of the bile duct: Assessment of invasive carcinoma and long-term outcomes using MRI

Sunyoung Lee[1], Myeong-Jin Kim[1,*], Sohee Kim[2], Dongil Choi[2], Kee-Taek Jang[3], Young Nyun Park[4]

[1]*Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea;* [2]*Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;* [3]*Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;* [4]*Department of Pathology, BK21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Republic of Korea*

Background & Aims: Imaging characteristics for discriminating the malignant potential of intraductal papillary neoplasm of the bile duct (IPNB) still remain unclear. This study aimed to define the magnetic resonance (MR) imaging findings that help to differentiate IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia and to investigate their significance with respect to long-term outcomes in patients with surgically resected IPNB.

Methods: This retrospective study included 120 patients with surgically resected IPNB who underwent preoperative MR imaging with MR cholangiography before surgery from January 2008 and December 2017 in two tertiary referral centers. Clinical and MR imaging features of IPNB with intraepithelial neoplasia (n = 34) and IPNB with an associated invasive carcinoma (n = 86) were compared. Regarding significant features for discriminating IPNB with or without an associated invasive carcinoma, recurrence-free survival (RFS) rates were evaluated.

Results: Significant MR imaging findings for differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia were intraductal visible mass, tumor size ≥2.5 cm, multiplicity of the tumor, bile duct wall thickening, and adjacent organ invasion (all $p \leq 0.002$). The 1-, 3-, and 5-year RFS rates for surgically resected IPNB were 93.8%, 79.1%, and 70.0%, respectively. RFS rates were significantly lower in patients with each significant MR imaging finding of IPNB with an associated invasive carcinoma than in those without significant MR imaging findings (all $p \leq 0.039$).

Conclusions: MR imaging with MR cholangiography may be helpful in differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia. Significant MR imaging findings of IPNB with an associated invasive carcinoma have a negative impact on RFS.

Lay summary: Significant magnetic resonance imaging findings that differentiated between an intraductal papillary neoplasm of the bile duct (IPNB) with an associated invasive carcinoma and an IPNB with intraepithelial neoplasia were intraductal visible mass, tumor size ≥2.5 cm, multiplicity of the tumor, bile duct wall thickening, and adjacent organ invasion. Significant magnetic resonance imaging findings of invasive IPNB have a negative impact on recurrence-free survival.

Introduction

Intraductal papillary neoplasm of the bile duct (IPNB) is characterized by a papillary or villous biliary neoplasm covering delicate fibrovascular stalks and a histological spectrum ranging from benign disease to invasive malignancy.[1,2] According to the 2010 World Health Organization classification, IPNB can be classified into the following 3 histologic grades: IPNB with low- or intermediate-grade intraepithelial neoplasia, IPNB with high-grade intraepithelial neoplasia, and IPNB with an associated invasive carcinoma. IPNB with low- or intermediate- and high-grade intraepithelial neoplasia are regarded as premalignant and non-invasive IPNB, whereas IPNB with an associated invasive carcinoma is considered malignant and invasive IPNB.

IPNB presents as an intraductal mass within the dilated intrahepatic or extrahepatic bile ducts on imaging studies.[3–5] However, small-sized papillary lesions may be hard to detect by conventional imaging studies, such as ultrasonography (US) or computed tomography (CT). Currently, magnetic resonance (MR) imaging with MR cholangiography is being commonly used as the imaging modality of choice for evaluating various biliary disorders. Given the superior contrast resolution, MR imaging with MR cholangiography has advantages in the detection and evaluation of small intraductal tumor and tumor multiplicity of IPNB.[6,7]

IPNB has been considered a biliary counterpart of intraductal papillary mucinous neoplasms (IPMN) of the pancreas.[8] In IPMN of the pancreas, morphologic criteria based on imaging findings that indicate the presence of a malignant neoplasm, that is, "high-risk stigmata" or "worrisome features", are well established by international consensus guidelines of 2012 and 2017.[9,10] Contrary to well-documented IPMN of the pancreas, imaging characteristics of IPNB for discriminating malignant potential are poorly understood. It may be helpful to know the imaging findings suggestive of the presence of malignancy and invasive carcinoma in IPNB, since early diagnosis and preoperative evaluation of tumor invasiveness is crucial for determining proper therapy and for better prognosis. To our

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* Corresponding author. Address: Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. Tel.: +82-2-2228-7400, fax: +82-2-395-3035.
E-mail address: kimnex@yuhs.ac (M.-J. Kim).

knowledge, there is only one previous study regarding the MR imaging features of non-invasive and invasive IPNBs.[11] However, this study only reviewed 23 cases in a single institution; moreover, it did not evaluate the relation between MR imaging findings and long-term outcomes.

Thus, the purpose of this study was to define the MR imaging findings that help to differentiate IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia and to investigate their significance with respect to long-term outcomes in a large number of patients with surgically resected IPNB from 2 institutions.

Materials and methods

Study population

This multicenter study was conducted as a retrospective analysis at 2 tertiary academic centers (Severance Hospital and Samsung Medical Center, Seoul, Korea). The institutional review board of both hospitals approved the study and the requirements for informed consent were waived (Severance 2018-1768-001 and SMC 2018-08-103). We searched 2 academic referral institutions' surgical database between January 2008 and December 2017 using the terms 'intraductal papillary neoplasm' or 'biliary papilloma(tosis)' and identified 256 patients. Our study inclusion criteria were as follows: (a) patients with pathologically confirmed IPNB after surgery; (b) patients who underwent preoperative enhanced MR imaging with MR cholangiography within 3 months prior to surgery; and (c) patients who had more than 3 months of follow-up after surgery. Finally, 120 patients (mean age, 66.2 years; range, 44–83 years) consisting of 72 men (mean age, 66.3 years; range, 44–83 years) and 48 women (mean age, 66.0 years; range, 48–83 years), were included in our study. Types of operation included hemihepatectomy (n = 104, 86.6%), sectionectomy (n = 11, 9.2%), and bile duct resection (n = 5, 4.2%). The mean interval between the MR imaging and surgery was 24.9 days (range, 2–90 days).

MR imaging examination

All MR imaging studies were performed with a 1.5- or 3-T scanner. The required sequences were T1-weighted spoiled gradient-recalled-echo out-of-phase and in-phase sequences, breath-hold or respiratory triggered T2-weighted sequences, T2-weighted MR cholangiographies, and diffusion-weighted images with 3 or 4 *b* values. Dynamic T1-weighted imaging was obtained after administering one of the 2 contrast materials (Primovist, Bayer Healthcare, Berlin, Germany; Dotarem, Guerbet, France): a bolus injection of 0.1 ml/kg gadoxetic acid (n = 89) at a rate of 1.0 ml/second or 0.2 ml/kg gadoteric acid (n = 31) at a rate of 2.0 ml/second, followed by a 20 ml saline flush using a power injector. A 3-dimensional spoiled gradient-recalled-echo sequence with chemical selective fat suppression was performed before injecting the intravenous contrast agent. Contrast-enhanced images were obtained at arterial phase (AP, 20–35 s), portal venous phase (PVP, 60 s), and delayed phase (DP, 3 min). The detailed parameters of the MR imaging sequences are shown in Table S1.

Image analysis

Gastrointestinal radiologists (S.L. and M-J.K. with 7 and 26 years' experience in abdominal MR imaging, respectively, at Severance Hospital, and S.K. and D.C. with 5 and 24 years' experience in abdominal MR imaging, respectively, at Samsung Medical Center) retrospectively reviewed the images on a Picture Archiving and Communication System (PACS, Centricity, General Electric Medical Systems, Milwaukee, WI) monitor with the ability to adjust the optimal window setting for each patient. They were blinded to clinical, laboratory, pathologic, and follow-up results but knew that the study population had IPNB. The 2 reviewers at each institution independently evaluated the following imaging features: (a) the presence or absence of intraductal visible mass; (b) multiplicity of the tumor, defined as more than 2 discontinuous visible tumors;[12] (c) mucin hypersecretion, defined as aneurysmal dilatation of the bile duct with or without visible intraductal mucin-secreting tumors or dilation of the downstream duct;[7,13] (d) bile duct wall thickening, defined as a wall thicker than 3 mm; (e) adjacent organ invasion, such as hepatic parenchyma, vascular structure, or peritoneum; and (f) imaging patterns based on the morphologic appearances, classified into the following 5 subtypes:[3,14,15] type 1, diffuse duct dilation with a grossly visible intraductal mass; type 2, diffuse duct dilation without a visible mass; type 3, intraductal polypoid mass within localized duct dilatation; type 4, mild ductal dilation filled with intraductal cast-like lesions; and type 5, a focal stricture-like lesion with mild proximal duct dilation. For the cases in which an intraductal mass was depicted on MR imaging, tumor location was evaluated and categorized as intrahepatic duct, hilar bile duct, and common bile duct according to the location of the largest portion of the tumor. Tumor signal intensity on each unenhanced T1-weighted and T2-weighted image, dynamic-enhanced AP, PVP, and DP images, diffusion-weighted (DW) image (b = 800 sec/mm^2), and apparent diffusion coefficient (ADC) map was assessed relative to the surrounding liver parenchyma and classified as hypointensity, isointensity, and hyperintensity. After an independent image review, interobserver agreement was evaluated, and discordant results between the radiologists were adjusted by consensus.

One radiologist (S.L. with 7 years' experience in abdominal MR imaging) measured the maximum tumor size in the longitudinal length of intraductal mass on contrast-enhanced T1-weighted images.{Hong, 2016 #18} Invisible tumor on MR imaging was excluded from the size assessment. ADC values for intraductal visible mass were measured in patients with DW images. The b values of 0 and 800 s/mm^2 were used to generate the ADC map. A region of interest (ROI) was drawn around the solid tumor components and the mean ADC values were calculated.

Pathologic analysis

Pathologic findings were evaluated by 2 pathologists (Y.N.P. with 25 years' experience in biliary pathology at Severance Hospital and K-T.J. with 20 years' experience in biliary pathology at Samsung Medical Center). IPNB with intraepithelial neoplasia was classified into low- or intermediate-grade intraepithelial neoplasia and high-grade intraepithelial neoplasia according to degree of cellular and nuclear atypia. IPNB with an associated invasive carcinoma was defined as IPNB with evident invasion of carcinoma cells to the bile duct wall and/or adjacent organ.[16] Resection margin status was categorized as negative, dysplasia, and invasive carcinoma according to the malignant potential. Lymph node metastasis was also assessed.

Evaluation of recurrence-free survival

For follow-up, patients underwent contrast-enhanced CT or MR imaging and laboratory tests including serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA), every 3–6 months during the first 2 years and every 6–12 months after that. The mean follow-up period was 52.8 months (range, 3–125 months). Median follow-up durations for IPNB with intraepithelial neoplasia and IPNB with an associated invasive carcinoma were 50.5 months (interquartile range, 29.3–67.5) and 49.0 (interquartile range, 22.8–82.5) months, respectively. There was no significant difference between the 2 groups ($p = 0.688$). Recurrence-free survival (RFS) was defined as the interval between the date of surgery and that of tumor recurrence or the latest follow-up visit, with final evaluation on June 30, 2018.

Statistical analysis

Categorical variables were compared by using Fisher's exact test. Continuous variables were evaluated using the 2-sample *t* test or Mann-Whitney *U* test. A receiver operating characteristic (ROC) curve analysis was used to determine cut-off values for significant continuous values. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), accuracy, positive likelihood ratio (+LR), and negative likelihood ratio (−LR) of each significant MR imaging finding and their combinations for differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia were also calculated. The cumulative RFS rates were estimated using the Kaplan-Meier method, and differences between curves were evaluated using the log-rank test. To explore the preoperative MRI features associated with RFS, we used the Cox proportional hazards regression model with Firth's penalized partial likelihood approach. All variables with *p* values <0.05 on the univariate analysis were selected for the multivariate analysis. SPSS version 23.0 (IBM, Armonk, New York), MedCalc version 16.2.1 (MedCalc Software, Ostend, Belgium), and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses. A *p* value of <0.05 was considered statistically significant.

Results

MR imaging findings for IPNB with intraepithelial neoplasia and IPNB with an associated invasive carcinoma

A comparison of the characteristics between IPNB with intraepithelial neoplasia and IPNB with an associated invasive carcinoma is presented in Table 1. The proportion of intraductal visible mass was significantly higher in IPNB with an associated invasive carcinoma than in IPNB with intraepithelial neoplasia (p <0.001). The mean tumor size was significantly larger in IPNB with an associated invasive carcinoma than in IPNB with intraepithelial neoplasia (3.6 *vs.* 2.2 cm; p <0.001). To calculate the cut-off value of tumor size for identifying IPNB with an associated invasive carcinoma, ROC analysis was conducted. The area under the ROC curves of tumor size was 0.82 (95% CI 0.73–0.89). With a cut-off value of 2.5 cm, tumor size provided a sensitivity of 82.9% and a specificity of 80.0%. Tumor multiplicity was also more commonly seen in IPNB with an associated

Table 1. Comparisons of clinical, radiologic, and pathologic features of IPNB.

	Total (n = 120)	IPNB with low- or intermediate-/high-grade intraepithelial neoplasia (n = 34)	IPNB with an associated invasive carcinoma (n = 86)	*p* value
Age* (yr)	66.2 ± 8.0	64.5 ± 8.3	66.9 ± 7.8	0.106
Sex (Male)	72 (60.0)	21 (61.8)	51 (59.3)	0.839
Associated diseases				
Hepatolithiasis	25 (20.8)	8 (23.5)	17 (19.8)	0.627
Clonorchiasis	34 (28.3)	11 (32.4)	23 (26.7)	0.653
Tumor markers				
CA19-9† (U/ml)	16.0 (7.4–45.1)	14.1 (6.8–37.2)	16.4 (7.7–51.0)	0.473
CEA† (U/ml)	1.8 (1.0–2.8)	1.6 (1.0–2.4)	1.8 (1.0–3.0)	0.274
MR imaging findings				
Intraductal visible mass	102 (85.0)	20 (58.8)	82 (95.3)	<0.001
Tumor size*,§ (cm)	3.3 ± 1.3	2.2 ± 1.0	3.6 ± 1.3	<0.001
Multiplicity of the tumor	49 (40.8)	6 (17.6)	43 (50.0)	0.001
Mucin hypersecretion	42 (35.0)	10 (29.4)	32 (37.2)	0.525
Bile duct wall thickening	81 (67.5)	5 (14.7)	76 (88.4)	<0.001
Adjacent organ invasion	18 (15.0)	0 (0)	18 (20.9)	0.002
Imaging pattern				<0.001
Type 1	26 (21.7)	4 (11.8)	22 (25.6)	
Type 2	7 (5.8)	5 (14.7)	2 (2.3)	
Type 3	43 (35.8)	11 (32.3)	32 (37.2)	
Type 4	33 (27.5)	5 (14.7)	28 (32.6)	
Type 5	11 (9.2)	9 (26.5)	2 (2.3)	
Pathologic findings				
Resection margin status				0.697
Negative	111 (92.5)	33 (97.1)	78 (90.7)	
Dysplasia	7 (5.8)	1 (2.9)	6 (7.0)	
Invasive carcinoma	2 (1.7)	0 (0)	2 (2.3)	
Lymph node metastasis	4 (3.3)	0 (0)	4 (4.7)	0.576

CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; IPNB, intraductal papillary neoplasm of the bile duct; MR, magnetic resonance.
Unless otherwise indicated, data represent number of patients, with percentage in parentheses. Categorical variables were compared using Fisher's exact test.
*Data are mean ± standard deviation and compared by using the two-sample *t* test.
†Data are median with interquartile ranges in parentheses and compared by using the Mann-Whitney *U* test.
§Tumor size assessment was excluded in case of intraductal invisible mass on MR imaging (n = 18).

invasive carcinoma than in IPNB with intraepithelial neoplasia (50.0% *vs.* 17.6%; $p = 0.001$). Bile duct wall thickening was present in 14.7% and 88.4% of IPNB with intraepithelial neoplasia and an associated invasive carcinoma, respectively, and this difference was statistically significant ($p < 0.001$). Adjacent organ invasion was not observed in any of IPNB with intraepithelial neoplasia, whereas 18 (20.9%) of the 86 patients with an associated invasive carcinoma had adjacent organ invasion ($p = 0.002$) (Figs. 1 and 2). With a combination of these significant MR imaging findings to determine IPNB with an associated invasive carcinoma, the score was calculated by adding the individual numbers for each of 5 factors, which ranged from 0 for those with none of the factors to 5 for those with all 5 factors. The area under the ROC of combination score was 0.92 (95% CI 0.85–0.96) (Fig. 3). The optimal cut-off score for determining IPNB with an associated invasive carcinoma was 3, with its sensitivity and specificity were 84.9% and 85.4%, respectively.

The diagnostic performance of each significant MR imaging finding and their combinations for differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia was analyzed. Intraductal visible mass had high sensitivity (95.4%), but relatively low specificity (41.2%). The presence of adjacent organ invasion had high specificity (100%) but low sensitivity (20.9%). Bile duct wall thickening showed sensitivity of 88.4% and specificity of 85.3% (Table 2).

The characteristics of intraductal visible mass on MR images for IPNB with intraepithelial neoplasia and IPNB with an associated invasive carcinoma are summarized (Table 3). There was no statistically significant difference between the groups in tumor location ($p = 0.813$). Compared with the normal hepatic parenchyma, most of the intraductal masses of IPNB showed hypointensity on T1-weighted image and hyperintensity on T2-weighted image, equivalent or greater enhancement on AP, and hypointensity on PVP and DP, but no significant differences were observed between the groups (all, $p > 0.05$).

DW images were acquired in 77 patients. Hyperintensity on DW imaging was observed in all patients. The intraductal masses on ADC map showed hypointensity or isointensity in 11 (73.3%) of IPNB with intraepithelial neoplasia and 60 (96.8%) of IPNB with an associated invasive carcinoma

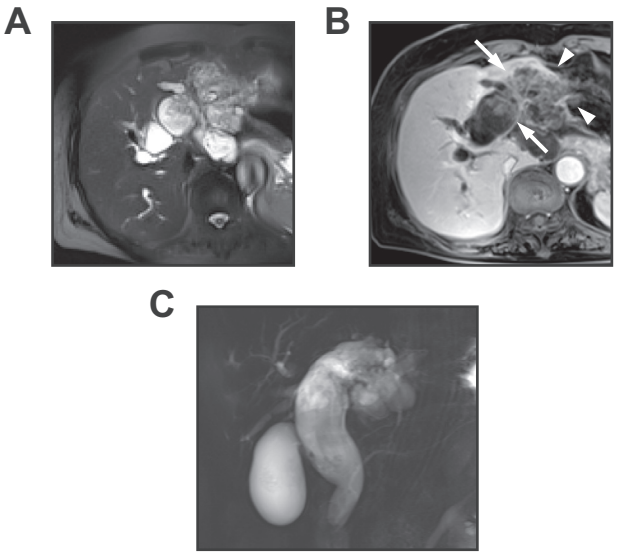

Fig. 1. Images in a 65-year old-woman with surgically confirmed intraductal papillary neoplasm of the bile duct with an associated carcinoma. (A) T2-weighted image shows dilatation of the bile duct with multiple intraductal papillary masses. The largest tumor size is 3.6 cm. (B) Portal phase contrast-enhanced MR image shows bile duct wall thickening (arrows) and adjacent organ invasion (arrowheads). (C) MR cholangiography image shows diffuse dilatation of intra-and extrahepatic bile ducts with papillary intraductal masses. MR, magnetic resonance.

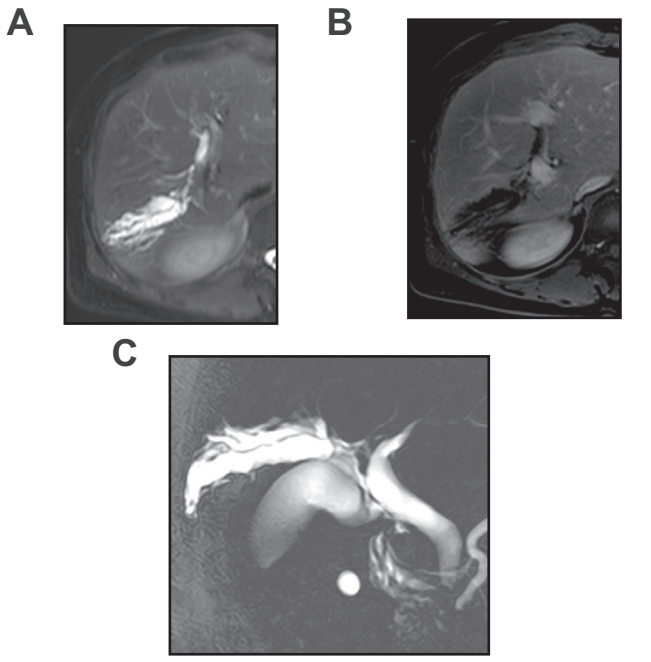

Fig. 2. Images in a 57-year old-woman with surgically confirmed intraductal papillary neoplasm of the bile duct with low- or intermediate-grade intraepithelial neoplasia. (A) T2-weighted image shows a focal stricture-like lesion with proximal duct dilation. No intraductal visible mass is identified. (B) Portal phase contrast-enhanced MR image does not show bile duct wall thickening or adjacent organ invasion. (C) MR cholangiography image shows bile duct dilatation with a focal stricture-like lesion. MR, magnetic resonance.

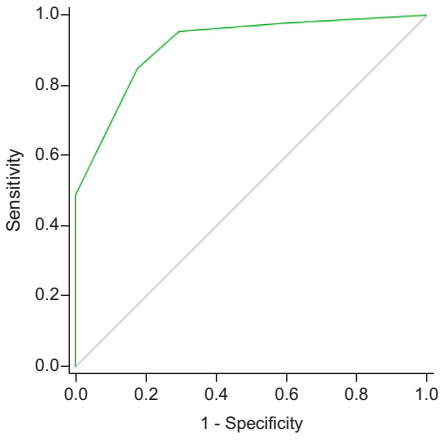

Fig. 3. Receiver operating characteristic curves for combination score of 5 significant MR imaging findings for determining IPNB with an associated invasive carcinoma. The area under the receiver operating characteristic analysis of the combination score of 5 significant MR imaging findings for determining IPNB with an associated invasive carcinoma was 0.92 (95% CI 0.85–0.96). IPNB, intraductal papillary neoplasm of the bile duct; MR, magnetic resonance. (This figure appears in colour on the web.)

Table 2. Diagnostic performance of MR findings in the differentiation of IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy	+LR (95% CI)	−LR (95% CI)
Intraductal visible mass	95.4 (88.5–98.7)	41.2 (24.7–59.3)	80.4 (71.4–87.6)	77.8 (52.4–93.6)	80.0	1.6 (1.2–2.2)	0.1 (0.0–0.3)
Tumor size ≥2.5 cm*	86.6 (77.3–93.1)	75.0 (50.9–91.3)	93.4 (85.3–97.8)	57.7 (36.9–76.7)	84.3	3.5 (1.6–7.4)	0.2 (0.1–0.3)
Multiplicity of the tumor	50.0 (39.0–61.0)	82.4 (65.5–93.2)	87.8 (75.2–95.4)	39.4 (28.0–51.8)	59.2	2.8 (1.3–6.0)	0.6 (0.5–0.8)
Bile duct wall thickening	88.4 (79.7–94.3)	85.3 (68.9–95.1)	93.8 (86.2–98.0)	74.4 (57.9–87.0)	87.5	6.0 (2.7–13.6)	0.1 (0.1–0.3)
Adjacent organ invasion	20.9 (12.9–31.1)	100.0 (89.7–100.0)	100 (81.5–100.0)	33.3 (24.3–43.4)	43.3	Not applicable	0.8 (0.7–0.9)
Combination score of MR findings ≥3	84.9 (75.5–91.7)	82.4 (65.5–93.2)	92.4 (84.2–97.2)	68.3 (51.9–81.9)	84.2	4.8 (2.3–10.0)	0.2 (0.1–0.3)

CI, confidence interval; IPNB, intraductal papillary neoplasm of the bile duct; +LR, positive likelihood ratio; –LR, negative likelihood ratio; MR, magnetic resonance; NPV, negative predictive value; PPV, positive predictive value.
Data are presented as percentages.
*Data (n = 102) were calculated after excluding non-assessable cases (invisible tumor on MR imaging).

Table 3. Characteristics of intraductal visible mass on MR images.

	IPNB with low- or intermediate-/high-grade intraepithelial neoplasia (n = 20)	IPNB with an associated invasive carcinoma (n = 82)	*p* value
Tumor location			0.813
Intrahepatic duct	15 (75.0)	58 (70.7)	
Hilar bile duct	5 (25.0)	19 (23.2)	
Common bile duct	0 (0)	5 (6.1)	
Unenhanced T1-weighted			0.279
Hypointensity	15 (75.0)	71 (86.6)	
Isointensity	4 (20.0)	10 (12.2)	
Hyperintensity	1 (5.0)	1 (1.2)	
T2-weighted			0.583
Hypointensity	0 (0)	0 (0)	
Isointensity	0 (0)	4 (4.9)	
Hyperintensity	20 (100)	78 (95.1)	
Arterial phase			0.228
Hypointensity	2 (10.0)	23 (28.0)	
Isointensity	6 (30.0)	17 (20.7)	
Hyperintensity	12 (60.0)	42 (51.2)	
Portal venous phase			0.914
Hypointensity	14 (70.0)	58 (70.7)	
Isointensity	5 (25.0)	18 (22.0)	
Hyperintensity	1 (5.0)	6 (7.3)	
Delayed phase			0.836
Hypointensity	19 (95.0)	71 (86.6)	
Isointensity	1 (5.0)	8 (9.8)	
Hyperintensity	0 (0)	3 (3.7)	

IPNB, intraductal papillary neoplasm of the bile duct; MR, magnetic resonance.
Data represent number of patients, with percentage in parentheses.
For the cases (n = 102) in which an intraductal mass was depicted on MR imaging, the following characteristics of intraductal visible mass was compared by using Fisher's exact test.

($p = 0.012$). The ADC value was significantly lower for IPNB with an associated invasive carcinoma than for IPNB with intraepithelial neoplasia (mean ± SD, 1.21 ± 0.45 *vs.* $1.50 \pm 0.49 \times 10^{-3}$ mm^2/sec; $p = 0.034$).

RFS of patients with IPNB according to significant MR imaging findings

During follow-up, 25 (20.8%) patients developed tumor recurrence. The 1-, 3-, and 5-year cumulative RFS rates for surgically resected IPNB were 93.8%, 79.1%, and 70.0%, respectively. Compared to IPNB with intraepithelial neoplasia, IPNB with an associated invasive carcinoma showed significantly higher recurrence rates (5.9% *vs.* 26.7%; $p = 0.012$). Fourteen patients had local tumor recurrence and 11 patients had distant metastasis. The sites of distant metastasis were peritoneal seeding (n = 5), lymph node (n = 4), and lung (n = 2).

Patients with intraductal visible mass had a significantly lower RFS than those with invisible mass (5-year RFS rate, 65.5% *vs.* 100 %; $p = 0.039$) (Fig. 4A). RFS of patients with tumor size <2.5 cm was superior to that of patients with tumor size ≥2.5 cm (84.0% *vs.* 58.7% at 5 years; $p = 0.035$) (Fig. 4B). Multiplicity of the tumor was found to be associated with significantly lower RFS than the single tumor (46.9% *vs.* 85.1% at 5 years; $p = 0.001$) (Fig. 4C). Patients with bile duct wall thickening demonstrated significantly worse RFS compared with those without bile duct wall thickening (5-year RFS rate, 59.7% *vs.* 94.0%; $p = 0.007$) (Fig. 4D). The 5-year RFS for IPNB with adjacent organ invasion was significantly lower than that for IPNB without adjacent organ invasion (43.2% *vs.* 74.9%; $p = 0.003$) (Fig. 4E). Patients with a combination score of significant MR imaging findings of ≥3 had significantly lower RFS compared to those with a combination score of significant MR imaging findings of <3 (5-year RFS rate, 60.6% *vs.* 88.7%; $p = 0.006$) (Fig. 4F).

Cox survival analysis of MR imaging predictors of RFS is presented in Table 4. In the multivariate analysis, multiplicity of the tumor (hazard ratio 2.60; 95% CI 1.14–6.42; $p = 0.022$) was a significant independent predictor of RFS.

Discussion

In the present study, intraductal visible mass, tumor size ≥2.5 cm, multiplicity of the tumor, bile duct wall thickening, and adjacent organ invasion were significant MR imaging findings for differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia. RFS rates were significantly lower in patients with each significant MR imaging finding of IPNB with an associated invasive carcinoma than in those without significant MR imaging findings.

Previous studies reported that US and CT detected intraductal masses in less than 50% of patients with IPNB.[17,18] In our study using MR imaging with MR cholangiography, intraductal mass was observed in 85% of patients with IPNB. This discrep-

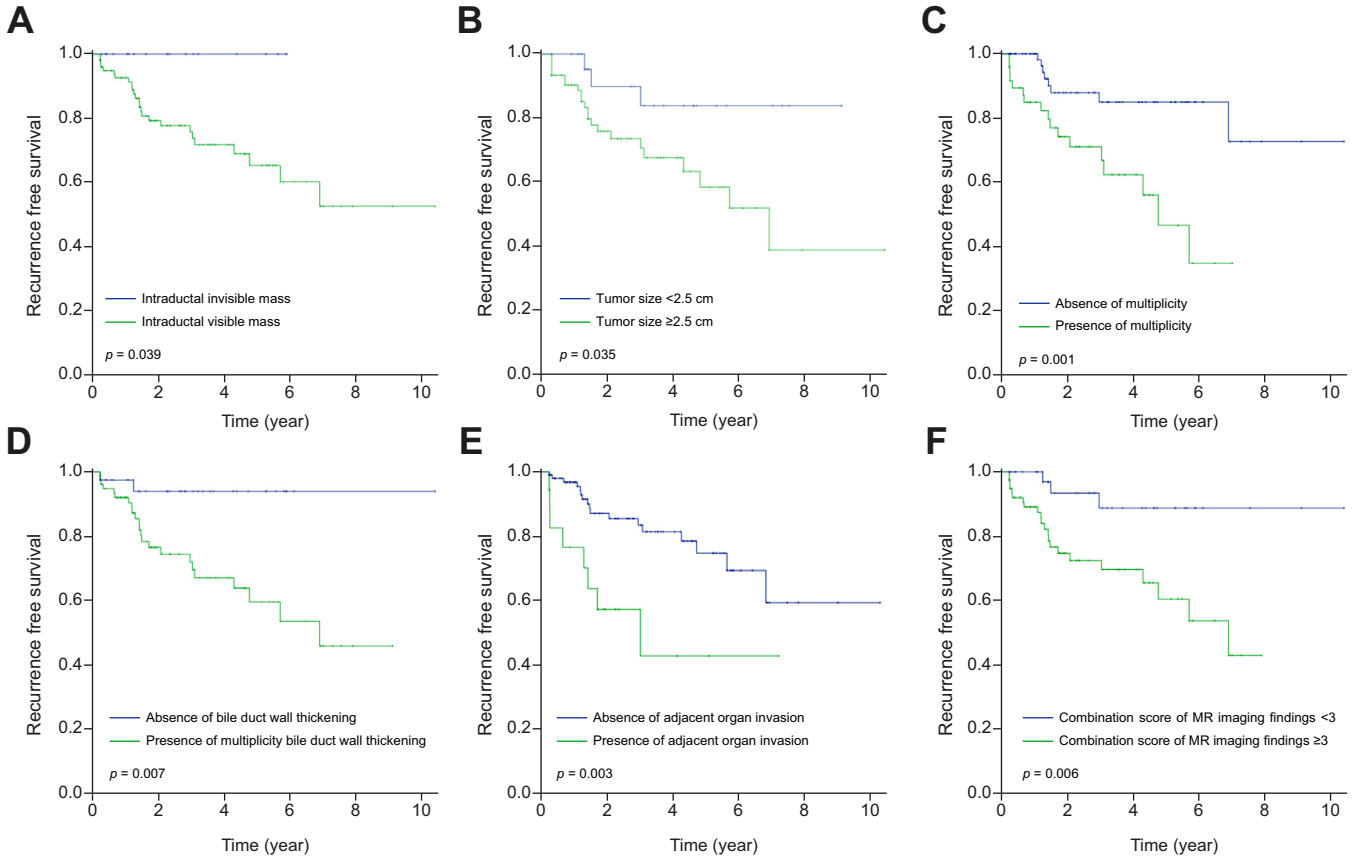

Fig. 4. Kaplan-Meier curves for cumulative recurrence-free survival rates of intraductal papillary neoplasm of the bile duct. (A) With or without intraductal visible mass. (B) Tumor size ≥2.5 cm or <2.5 cm. (C) With or without tumor multiplicity. (D) With or without bile duct wall thickening. (E) With or without adjacent organ invasion. (F) Combination score of significant MR imaging findings ≥3 or <3. Statistical significances were assessed using the log-rank test. MR, magnetic resonance. (This figure appears in colour on the web.)

Table 4. Cox survival analysis of MR imaging predictors of recurrence-free survival.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Intraductal visible mass	8.86	1.24–1,125.20	0.024*	1.40	0.10–201.66	0.828
Tumor size ≥2.5 cm†	5.22	1.56–17.48	0.007*	2.18	0.76–8.46	0.160
Multiplicity of the tumor	3.78	1.61–8.86	0.002*	2.60	1.14–6.42	0.022*
Mucin hypersecretion	2.00	0.91–4.42	0.086			
Bile duct wall thickening	5.84	1.37–24.79	0.017*	2.17	0.69–11.13	0.206
Adjacent organ invasion	3.24	1.39–7.55	0.007*	2.44	0.99–5.57	0.051

HR, hazard ratio; IPNB, intraductal papillary neoplasm of the bile duct; MR, magnetic resonance.
*Statistically significant results from Cox proportional hazards model. All variables with *p* values <0.05 on the univariate analysis were selected for the multivariate analysis.
†The reference category for tumor size ≥2.5 cm is invisible tumor on MR imaging or tumor size <2.5 cm.

ancy is presumed to be due to the inherently high soft-tissue contrast resolution of MR imaging compared with that of US or CT. Furthermore, the discrepancy may also be due to the large proportion of patients with IPNB with an associated invasive carcinoma in our study population. The frequency of intraductal visible mass on MR imaging was significantly higher for IPNB with an associated invasive carcinoma than for IPNB with intraepithelial neoplasia. In the imaging patterns classified into 5 subtypes, most of IPNBs with grossly visible mass, such as types 1, 3, and 4, had an associated invasive carcinoma. This finding is consistent with that of a previous study using cholangiography;[19] that is, benign lesions occasionally displayed biliary stricture or mucobilia without gross neoplasia, whereas the majority of malignant lesions displayed overt intrahepatic intraductal neoplasia. Moreover, IPNBs with intraductal visible mass on MR imaging were associated with significantly worse RFS than those with invisible mass in our study.

A systemic review and meta-analysis of IPNB have reported a median tumor size for IPNB of 2.2–6.0 cm.[4] In 2 previous studies on pathology,[11,20] the patients with malignant or invasive IPNB tended to have a larger mean size of the tumor, but the difference was not statistically significant due to small number of patients. In this multicenter study with a large number of patients, the mean tumor size on MR imaging was significantly larger in IPNB with an associated invasive carcinoma than in IPNB with intraepithelial neoplasia. With a cut-off value of

2.5 cm for tumor size, a larger tumor size showed significantly higher recurrence rates.

According to a systemic review and meta-analysis of IPNB,[4] a considerable proportion (41%) of patients with IPNB had multiple tumors. In our study, 40.8% (49/120) of IPNBs had multiplicity of the tumor on MR imaging, which is comparable with findings of previous reports.[4] One prior study has reported that multiple IPNBs on pathology had a significant correlation with long-term prognosis, and disease free survival rate was significantly lower for multiple IPNB than for single IPNB,[12] which is consistent with our study using MR imaging.

The majority of malignant IPNBs demonstrate invasive tumors in the bile ducts, and it appears as bile duct wall thickening on images.[13,16,21,22] Among various MR imaging findings, our study demonstrated that bile duct wall thickening showed the highest diagnostic accuracy in differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia. Furthermore, prior studies have reported that the degree of tumor invasion had a great impact on the prognosis after surgical resection of IPNB.[14,23] One previous study revealed that the presence of extraductal invasion and depth of extraductal invasive component on pathology were highly correlated with worse outcomes.[8] In our study, bile duct wall thickening that indicates tumor invasion of the bile duct and adjacent organ invasion on MR imaging were associated with lower RFS.

The relationship between IPNB with mucin secretion and tumor invasiveness or prognosis remains controversial. Several studies have reported that macroscopic or microscopic mucin-secreting tumors on pathology were associated with decreased invasion and better survival,[16,24,25] whereas other studies demonstrated that mucin secretion did not have an impact on overall survival of IPNB.[12,17] In our study, mucin hypersecretion based on MR imaging and MR cholangiography did not show any differences in IPNB with intraepithelial neoplasia and in IPNB with an associated invasive carcinoma.

In a previous study using CT,[26] intraductal mass of the IPNB showed equivalent and greater enhancement on AP and it rarely showed intense enhancement on PVP and DP, compared with normal hepatic parenchyma. These findings can be explained by prominent proliferation of the delicate fibrovascular stalks with scarce fibrous stroma in IPNB.[5,26] In our study using MR imaging, the enhancement pattern of IPNB was similar to that in the previous study using CT scan and that of IPNB with or without an associated invasive carcinoma did not show significant differences. In contrast, diffusion restriction was more frequently seen in IPNB with an associated invasive carcinoma than in IPNB with intraepithelial neoplasia. This finding is consistent with the result of a previous study reporting that DW imaging would provide added value in determining tumor invasiveness.[11]

Of note, our series indicates that the majority of IPNB (71.6%) was diagnosed as an invasive carcinoma at presentation, contrary to IPMN of pancreas, in which the non-invasive form is more frequently found. The reported incidence of associated invasive carcinomas in IPNBs varies between 31% and 74%.[8,23,24,27,28] One meta-analysis of IPNB has reported that the invasive component was identified in 43% of IPNB.[19] Hepatolithiasis or clonorchiasis related biliary stricture or cholangitis may suggest the presence of underlying IPNB with intraepithelial neoplasia and make precise diagnosis difficult at the non-invasive state of IPNB. In addition, we only enrolled patients with surgically resected IPNB, and this may have influenced the overestimated incidence of IPNB with an associated invasive carcinoma.

Our study had several limitations. First, it was a retrospective study; therefore, it is prone to potential selection bias. All patients in this study underwent resection and were therefore subject to selection bias. This study only included the patients who had preoperative enhanced MR imaging with MR cholangiography and more than 3 months of follow-up after surgery, consequently, less than 50% of patients could be included in this study and it induces a significant selection bias. In addition, not all patients had identical and controlled follow-up intervals and durations due to our retrospective design, selection bias for the assessment of RFS could be induced. Second, the data were collected over a 10-year period in 2 centers, which may have caused variations in imaging parameters and qualities. However, a long study period for IPNB was inevitable due to the rarity of this disease.

In conclusion, MR imaging with MR cholangiography may be helpful in differentiating IPNB with an associated invasive carcinoma from IPNB with intraepithelial neoplasia. Significant MR imaging findings of IPNB with an associated invasive carcinoma including intraductal visible mass, tumor size ≥2.5 cm, multiplicity of the tumor, bile duct wall thickening, and adjacent organ invasion have a negative impact on RFS.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

M.-J.K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.L. contributed to the study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, and drafting of the manuscript. M.-J.K. contributed to the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. S.K. contributed to the study concept and design and acquisition of data. D.C. contributed to acquisition of data and critical revision of the manuscript for important intellectual content. K.-T.J. contributed to analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Y.N.P contributed to analysis and interpretation of data and critical revision of the manuscript for important intellectual content.

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Supplementary data

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