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Contrast-Enhanced CT and Ultrasonography Features of Intracholecystic Papillary Neoplasm with or without associated Invasive Carcinoma

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Objective: To assess the contrast-enhanced CT and ultrasonography (US) findings of intracholecystic papillary neoplasm (ICPN) and determine the imaging features predicting ICPN associated with invasive carcinoma (ICPN-IC).
Materials and Methods: In this retrospective study, we enrolled 119 consecutive patients, including 60 male and 59 female, with a mean age ± standard deviation of 63.3 ± 12.1 years, who had pathologically confirmed ICPN (low-grade dysplasia [DP] = 34, high-grade DP = 35, IC = 50) and underwent preoperative CT or US. Two radiologists independently assessed the CT and US findings, focusing on wall and polypoid lesion characteristics. The likelihood of ICPN-IC was graded on a 5-point scale. Univariable and multivariable logistic regression analyses were performed to identify significant predictors of ICPN-IC separately for wall and polypoid lesion findings. The performances of CT and US in distinguishing ICPN-IC from ICPN with DP (ICPN-DP) was evaluated using the area under the receiver operating characteristic curve (AUC).
Results: For wall characteristics, the maximum wall thickness (adjusted odds ratio [aOR] = 1.4; 95% confidence interval [CI]: 1.1–1.9) and mucosal discontinuity (aOR = 5.6; 95% CI: 1.3–23.4) on CT were independently associated with ICPN-IC. Among 119 ICPNs, 110 (92.4%) showed polypoid lesions. Regarding polypoid lesion findings, multiplicity (aOR = 4.0; 95% CI: 1.6–10.4), lesion base wall thickening (aOR = 6.0; 95% CI: 2.3–15.8) on CT, and polyp size (aOR = 1.1; 95% CI: 1.0–1.2) on US were independently associated with ICPN-IC. CT showed a higher diagnostic performance than US in predicting ICPN-IC (AUC = 0.793 vs. 0.676; *p* = 0.002).
Conclusion: ICPN showed polypoid lesions and/or wall thickening on CT or US. A thick wall, multiplicity, presence of wall thickening in the polypoid lesion base, and large polyp size are imaging findings independently associated with invasive cancer and may be useful for differentiating ICPN-IC from ICPN-DP.
Keywords: *Gallbladder; Neoplasm; Diagnosis; Computed tomography; Ultrasonography*

INTRODUCTION

Intracholecystic papillary neoplasm (ICPN) is a grossly visible, mass-forming, noninvasive epithelial neoplasm arising in the mucosa and projecting into the lumen of

the gallbladder (GB) [1]. It used to encompass the terms "papillomatosis," "papillary adenoma," "tubulopapillary adenoma," and "intracystic papillary neoplasm." It is a preinvasive neoplasm of the GB, similar in concept to intraductal papillary mucinous neoplasm (IPMN) of the pancreas [2] and intraductal papillary neoplasms of the bile duct [3]. Although ICPNs are remarkably analogous to IPMNs in their exophytic nature, expression of cellular lineages, and the presence of a spectrum of dysplastic changes, mucin production is only a minor feature, contrary to pancreatic IPMNs [4]. Regarding dysplastic changes, the overall frequency of high-grade dysplasia (DP) in ICPN was very high, and < 5% of ICPNs completely lacked high-grade DP [3,4]. In addition, > 50% of ICPNs showed invasive

carcinoma (IC) components at the time of diagnosis [1,4,5], whereas only 40% of pancreatic IPMNs harbored high-grade DP and/or IC [6]. Although the malignancy stratification of pancreatic IPMNs based on imaging features has been well-established through the international consensus Fukuoka guideline [2], no well-organized study on the imaging features of ICPN has been performed to date.

Transabdominal ultrasonography (US) and CT are widely used imaging modalities for the evaluation of GB lesions [7-9]. US and CT are useful for distinguishing malignant GB lesions and between wall-thickening GB cancer and adenomyomatosis [7,8,10]. In particular [11,12], malignant GB lesions can be distinguished from benign lesions based on wall enhancement patterns; however, only a few case reports and case series describing the CT or US features of ICPN have been published [13,14].

ICPN associated with IC (ICPN-IC) is identified in approximately half of all ICPNs. Because the overall outcome of ICPN-IC is definitely better than that of conventional GB carcinomas [4], the correct preoperative diagnosis of ICPN and prediction of ICPN-IC are important for estimating the patient's prognosis. To the best of our knowledge, no previous study has evaluated the characteristic preoperative US or contrast-enhanced CT features of ICPN-IC. Therefore, the aim of this study was to assess the findings of ICPN on contrast-enhanced CT or US and determine the imaging features predicting ICPN-IC.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2007-178-1143), which waived the requirement for obtaining informed consent.

Patients

Using a computerized search of our pathology and radiology information system records between January 2010 and January 2020, we identified 314 consecutive patients who underwent cholecystectomy, with pathologic reports mentioning intracholecystic papillary, intracystic papillary, papillomatosis, or adenoma. According to the 2019 World Health Organization classification of tumors of the digestive system [1], the essential criteria for the ICPN diagnosis are, macroscopically, a mass-forming neoplasm arising in the GB mucosa and, microscopically, intraluminal growth of back-to-back epithelial units in the papillary or tubulopapillary

configuration. Therefore, we excluded patients with pyloric gland adenoma (n = 113), tubular adenoma (n = 51), or adenomatous hyperplasia (n = 7). Among the remaining 125 patients with pathologically confirmed ICPN, five with unavailable preoperative imaging and one with inadequate images for evaluation were excluded. Finally, we enrolled 119 patients, including 60 male and 59 female, with a mean age ± standard deviation (SD) of 63.3 ± 12.1 years (Fig. 1). Among the 119 patients, 66 underwent both CT and US; 41 underwent only CT; and 12 underwent only US. For each patient, the interval between imaging studies and surgery was < 4 months (median, 17 days; range, 0–103 days). Of the 119 patients with ICPN, pathologic results demonstrated associated IC (n = 50), high-grade DP (n = 35), and low-grade DP (n = 34). Among the 50 ICs, 25 were staged as T1
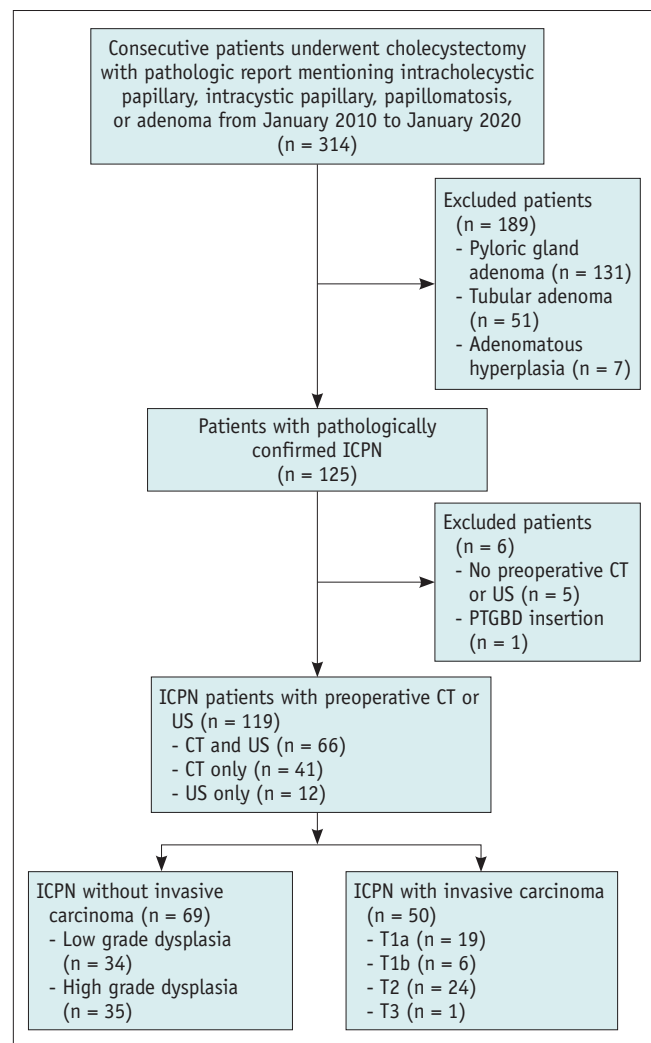
Fig. 1. Flow diagram of the included patients. ICPN = intracholecystic papillary neoplasm, PTGBD = percutaneous transhepatic gallbladder drainage, US = ultrasonography

(T1a = 19 and T1b = 6), 24 as T2, and one as T3 (Table 1). The pathological T-stage was determined according to the eighth edition of the American Joint Committee on Cancer staging system [15].

CT Examination

CT examinations were performed using commercially available multidetector CT scanners: 16-channel scanner Sensation 16 (Siemens Healthcare; n = 12); 64-channel scanners Brilliance 64 (Philips Healthcare), SOMATOM Definition (Siemens Healthcare), and Discovery CT 750 HD (GE Healthcare; n = 43); 256-channel system Brilliance iCT (Philips Healthcare; n = 5); 320-channel system Aquilion ONE (Toshiba Medical Systems; n = 5); and 384-channel dual-source scanners SOMATOM Force (Siemens Healthcare) and IQon (Philips Healthcare; n = 16). The standard CT

protocol for the preoperative evaluation of GB consisted of quadruple phases, including pre-contrast, early arterial, late arterial, and portal venous phases. Each patient received 120 mL non-ionic contrast material (iopromide, Ultravist 370; Schering) at a rate of 2–5 mL/s using an automatic power injector. The imaging delay used for the early arterial phase was 6 seconds, and the delay started after the descending aorta enhancement reached 100 Hounsfield units using the bolus-tracking method. The early and late arterial phases were acquired separately during each breath-hold using a minimum interscan delay of 5–9 seconds. Portal venous phase images were obtained 70 seconds after triggering. CT parameters were as follows: detector configurations of 0.6–0.75 mm; 512 x 512 matrix; tube voltage of 90–120 kVp; tube current of 120–200 mAs; and rotation time of 0.50–0.75 seconds. Axial images

Table 1. Patient and Lesion Characteristics

Characteristic	All Patients (n = 119)	Dysplasia (n = 69)	Invasive Carcinoma (n = 50)	P
Age, years	63.3 ± 12.1	61.4 ± 12.8	66.0 ± 10.7	0.039
> 50	102 (85.7)	55 (79.7)	47 (94.0)	0.028
≤ 50	17 (14.3)	14 (20.3)	3 (6.0)	
Sex				
Male	60 (50.4)	38 (55.1)	22 (44.0)	0.233
Female	59 (49.6)	31 (44.9)	28 (56.0)	
Symptoms				0.070*
Abdominal pain	18 (15.1)	8 (11.6)	10 (20.0)	
Jaundice	1 (0.8)	0 (0.0)	1 (2.0)	
Dyspepsia	4 (3.4)	1 (1.4)	3 (6.0)	
Weight loss	2 (1.7)	1 (1.4)	1 (2.0)	
Vomiting	1 (0.8)	1 (1.4)	0 (0.0)	
Asymptomatic	95 (79.8)	59 (85.5)	36 (72.0)	
Type of surgery				< 0.001
Simple cholecystectomy	93 (78.2)	65 (94.2)	28 (56.0)	
Extended cholecystectomy	25 (21.0)	4 (5.8)	21 (42.0)	
PPPD	1 (0.8)	0 (0.0)	1 (2.0)	
T stage				NA
T1a	NA	NA	19 (38.0)	
T1b	NA	NA	6 (12.0)	
T2	NA	NA	24 (48.0)	
T3	NA	NA	1 (2.0)	
Degree of atypia				NA
Low grade	NA	34 (49.3)	NA	
High grade	NA	35 (50.7)	NA	
Wall thickness, mm†	4.7 ± 3.4	3.6 ± 2.0	6.2 ± 4.2	< 0.001

Data are mean ± standard deviation or patient number (%). *Comparison of the symptomatic case proportion between ICPN with dysplasia and ICPN with invasive carcinoma groups, †Wall thickness was measured in imaging studies, and when it was measured by both CT and ultrasonography, the larger one was recorded. ICPN = intracholecystic papillary neoplasm, NA = not applicable, PPPD = pylorus preserving pancreatoduodenectomy

were reconstructed using a 2.5- to 3-mm slice thickness, and coronal multiplanar reconstruction (MPR) images were obtained at a 3-mm slice thickness on a separate commercially available console system using 3D imaging software. Among the 107 patients with preoperative CT, 81 underwent CT at our institution, whereas the remaining 26 underwent contrast-enhanced CT at other hospitals with CT protocols that met the following inclusion criteria: 1) triple-phase CT consisting of pre-contrast, arterial, and portal venous phases, 2) coronal MPR images, and 3) slice thickness of axial and coronal images ≤ 5 mm.

US Examination

All preoperative abdominal US examinations were performed using a convex probe (2–5 MHz) and/or a high-frequency linear probe (2–8 MHz), with the patient lying in the supine and/or left lateral decubitus position. US was performed using one of the following commercially available US units: LOGIQ E9 and LOGIQ 9, GE Healthcare; Aixplorer, SuperSonic Imagine; iU22, Philips Healthcare; and RS80A, Samsung Medison. For each patient, US was performed by one of the assigned radiologists with clinical experience in US ranging from two to 39 years. Before starting the examination, we carefully reviewed each patient's clinical history, chief complaints, and previously obtained images. During the US examinations, GB was examined with the right intercostal and/or subcostal approach using a convex probe. The US parameters were as follows: frequency of 4 MHz, gain of 27%–33%, dynamic range of 69, and a frame rate of 30 to 45 pictures/s. GB was then evaluated using a high-frequency linear probe according to the operator's requirements. To optimize GB evaluation, real-time spatial compound imaging (three to five compound beams per imaging frame) and speckle reduction techniques of a mild degree were used. Harmonic imaging techniques were used

to improve penetration and spatial resolution.

Imaging Analysis

Two abdominal radiologists (with 9 and 8 years of experience, respectively, in abdominal CT and US, respectively) independently reviewed the CT and US image sets. The images were anonymized and randomly distributed to the reviewers. The reviewers were blinded to the clinical information and radiology reports, except for the diagnosis of ICPN. For CT, in terms of GB wall characteristics, the following features were assessed: 1) maximum GB wall thickness, 2) type of GB wall enhancement pattern (type 1, a heterogeneously enhancing, thick, one-layer pattern; type 2, a strongly enhancing thick inner layer [≥ 2.6 mm] with a weakly enhancing or nonenhancing outer [≤ 3.4 mm]; type 3, others including a weakly enhancing, thin inner layer with a nonenhancing thin outer layer and a weakly enhancing, thin inner layer with a non-enhancing thick outer layer; Fig. 2) [11,12], 3) character of the involved wall border (irregular or smooth), 4) continuity of the mucosal line (continuous or disrupted), 5) loss of the layered pattern of the GB wall (preserved or lost), 6) presence of pericholecystic fat infiltration, and 7) presence of GB stones. When a measurable polypoid lesion (i.e., lesions protruding from the GB wall by ≥ 1 mm in length) was found, its imaging features were also evaluated. In the case of multiple measurable polypoid lesions, the features were evaluated in the largest one as follows: 1) multiplicity (single or multiple), 2) maximum diameter of the largest polyp, 3) shape (pedunculated or sessile), 4) surface contour (smooth or lobulated), 5) presence of tumor base dimpling, and 6) presence of tumor base wall thickening. For US, the type of GB wall enhancement pattern and presence of pericholecystic fat infiltration were omitted from the CT items. In addition, for polypoid lesion evaluation, three items were added:
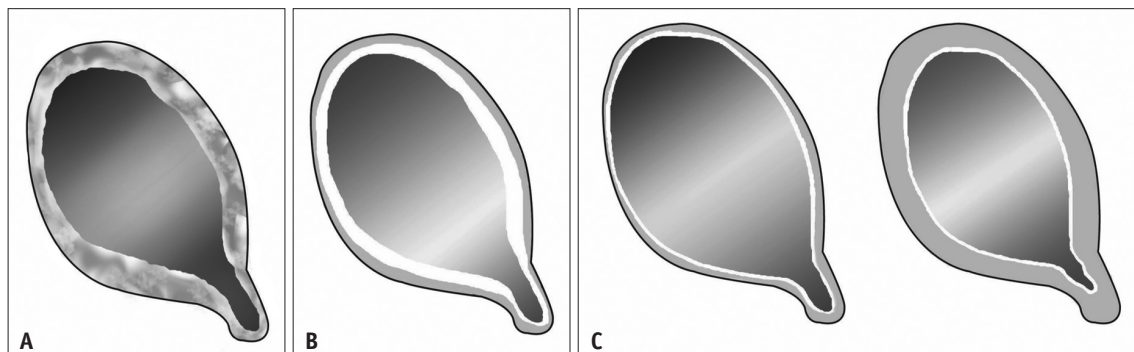
Fig. 2. Diagram showing enhancement patterns of the gallbladder wall.
A. Type 1 enhancement. **B.** Type 2 enhancement. **C.** Type 3 enhancement.

internal echo level (hypoechoic, isoechoic, or hyperechoic compared to the hyperechoic perimuscular connective tissue layer of the GB wall); internal echo pattern (homogeneous or heterogeneous); and presence of hyperechoic or hypoechoic foci in the polyp [16]. Discrepancies in the interpretation of imaging findings by the two reviewers were resolved by a third reviewer with 23 years of clinical experience in abdominal imaging. In addition, reviewers also rated the likelihood of ICPN-IC on the 5-point scale as follows: grade 1, definitely benign lesion, including chronic cholecystitis according to imaging findings, such as a continuous mucosal line, preserved wall layers, a smooth border, type 3 enhancement pattern, and/or small polyp (< 1 cm) without wall irregularity; grade 2, probably benign lesion showing some benign imaging features; grade 3, indeterminate; grade 4, probably malignant lesion showing some imaging findings suggestive of GB cancer; grade 5, definitely malignant lesion according to imaging findings, such as a disrupted mucosal line, loss of wall layers, irregular border, type 1 or 2 enhancement pattern, and/or a large sessile polyp (> 1.4 cm) with basement wall thickening or dimpling [8,11,12,16].

Statistical Analysis

Clinical characteristics were compared between the ICPN-IC and ICPN with DP (ICPN-DP) groups using the chi-square or Fisher's exact test for categorical data and the Mann–Whitney U test for non-normally distributed continuous data. CT and US findings were compared between the ICPN-IC and ICPN-DP groups using the Mann–Whitney U test for non-normally distributed continuous variables and Pearson's chi-square or Fisher's exact test for categorical variables. Inter-reader agreement for the individual interpretation was evaluated using kappa statistics and interpreted as follows: slight, < 0.20; fair, 0.21–0.40; moderate, 0.41–0.60; substantial, 0.61–0.80; and almost perfect, 0.81–1.0 [17]. All other analyses used consensus interpretations. The logistic regression analysis was performed to identify the significant predictors of ICPN-IC. Only variables with p values < 0.050 in the univariable analysis were selected as input variables for the stepwise multivariable analysis. Adjusted odds ratios were reported according to a recommendation for clear reporting [18]. To evaluate the diagnostic performance for discriminating ICPN-IC from ICPN-DP, receiver operating characteristic curves were plotted, and the area under the curve (AUC) was calculated with 95% confidence intervals (CIs) using the method reported by DeLong et al. [19]. The sensitivity and specificity were also calculated according to the reviewer's interpretation, with scores ≥ 4 regarded as positive for IC. The chi-square test was used to compare the sensitivity and specificity of CT and US. Statistical analyses were performed using IBM SPSS Statistics (version 25.0; IBM Corp.) and MedCalc (version 12; MedCalc Software).

RESULTS

IC was observed in 42.0% (50/119) of patients with ICPN. Patients with ICPN-IC were significantly older than those with ICPN-DP (mean age ± SD, 66.0 ± 10.7 vs. 61.4 ± 12.8 years; $p = 0.039$). Table 1 summarizes the baseline characteristics of the enrolled patients.

Common Imaging Findings of ICPN

GB wall thickening was a common finding of ICPN. The mean ± SD of the maximum thickness of the GB wall in all ICPNs was 4.7 ± 3.4 mm. On CT, the distribution of the wall enhancement pattern was as follows: 21.5% (23/107) with type 1, 21.5% (23/107) with type 2, and 57% (61/107) with type 3. Among the 107 patients who underwent CT, 45 had irregular wall borders, 24 had loss of the wall layer, four had pericholecystic fat infiltration, and 21 had gallstones. Among 78 patients who underwent US, 34 had irregular wall borders, 22 had loss of the wall layer, no one had pericholecystic fat infiltration, and 13 had gallstones.

Of the 119 patients with ICPNs, 110 (92.4%) showed measurable polypoid lesions on preoperative CT or US. On CT, the mean size ± SD of the largest polypoid lesion was 18.5 ± 13.2 mm. Of the 98 patients who underwent CT, 43 had multiple lesions, 38 had sessile polyps, 81 had lobulated lesion contours, 21 had lesion base dimpling, and 49 had lesion base wall thickening. On US, the mean size ± SD of the largest polypoid lesion was 22.8 ± 12.5 mm. Of the 74 patients who underwent US, 37 had multiple lesions, 26 had sessile polyps, 69 had lobulated lesion contours, 14 had heterogeneous echogenicity of polyps, and 11 had lesion base dimpling. Imaging patterns of ICPN could be categorized into the following three types: type a, wall thickening (≥ 4 mm) with polypoid lesions; type b, wall thickening without polypoid lesions; and type c, polypoid lesions without wall thickening (Fig. 3). According to this classification, there were 49 patients with type a (ICPN-DP, n = 19; ICPN-IC, n = 30), six patients with type b (ICPN-DP, n = 5; ICPN-IC, n = 1), and 60 patients with type c (ICPN-DP, n = 43; ICPN-IC, n = 17). The remaining four patients

showed no abnormal wall thickening or polypoid lesions on preoperative CT or US (ICPN-DP, n = 2; ICPN-IC, n = 2).

Inter-reader agreements for imaging findings were moderate to perfect (k range, 0.49–1.00) but fair for the internal echo level (k = 0.31). Tables 2 and 3 summarize the inter-reader agreement for each imaging finding.

Imaging Findings Predicting ICPN-IC

GB Wall Characteristics

Among CT findings, the maximum wall thickness of ICPN-IC was significantly higher than that of ICPN-DP (mean ± SD, 6.3 ± 4.4 vs. 3.4 ± 1.9 mm; $p < 0.001$). The type 1 or 2 wall enhancement pattern was more frequently observed in ICPN-IC than in ICPN-DP (64.4% [29/45] vs. 27.4% [17/62]; $p = 0.001$). In addition, an irregular wall border (66.7% [30/45] vs. 24.2% [15/62]; $p < 0.0001$), mucosal discontinuity (40% [18/45] vs. 4.8% [3/62]; $p < 0.001$), loss of the wall layer (40% [18/45] vs. 9.8% [6/62]; $p < 0.001$), and pericholecystic infiltration (8.9% [4/45] vs. 0% [0/62]; $p = 0.027$) were common CT findings of ICPN-IC. In the multivariable analysis, the maximum wall thickness (adjusted odds ratio [aOR] = 1.4; 95% CI: 1.1–1.9) and mucosal discontinuity (aOR = 5.6; 95% CI: 1.3–23.4) were
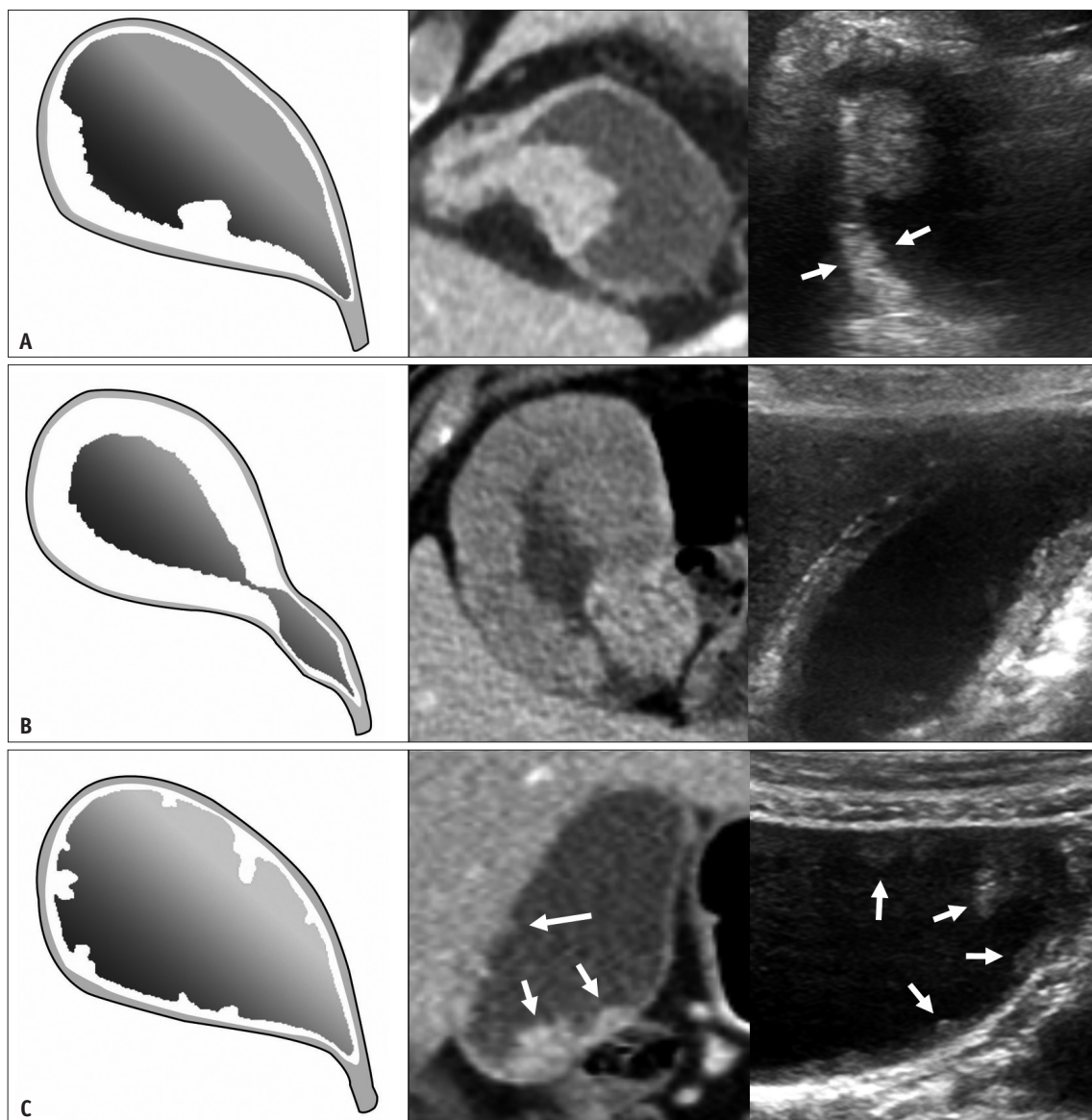
Fig. 3. Schematic drawings with representative CT and ultrasonography images showing three imaging patterns of intracholecystic papillary neoplasm.
A. Wall thickening (arrows) with polypoid lesions. **B.** Wall thickening without polypoid lesion. **C.** Polypoid lesions (arrows) without wall thickening.

Table 2. Predictive GB Wall Characteristics of ICPN-IC in CT and US

Image Findings	Invasive Carcinoma	Dysplasia	Inter-Reader Agreement (95% CI)	Univariable Analysis P	Multivariable Analysis Adjusted Odds Ratio (95% CI)	P
CT variable (n = 107)	(n = 45)	(n = 62)				
Maximum wall thickness, mm*	6.3 ± 4.4	3.4 ± 1.9	0.92 (0.88–0.95)	< 0.001	1.4 (1.1–1.9)	0.009
Wall enhancement pattern†			0.57 (0.43–0.72)	0.001	Eliminated	Eliminated
Type 1	15	8				
Type 2	14	9				
Others	16	45		Reference		
Irregular wall-border‡	30	15	0.84 (0.71–0.98)	< 0.001	Eliminated	Eliminated
Mucosal discontinuity‡	18	3	0.85 (0.71–0.99)	< 0.001	5.6 (1.3–23.4)	0.018
Loss of wall layer‡	18	6	0.82 (0.67–0.97)	< 0.001	Eliminated	Eliminated
Pericholecystic infiltration‡	4	0	0.71 (0.41–1.00)	0.027	Eliminated	Eliminated
Gall stone‡	7	14	1.00 (1.00–1.00)	0.366		
US variable (n = 78)	(n = 33)	(n = 45)				
Maximum wall thickness, mm*	3.9 ± 1.9	3.2 ± 1.8	0.88 (0.82–0.93)	0.037	Eliminated	Eliminated
Irregular wall-border‡	17	17	0.78 (0.54–1.00)	0.227		
Mucosal discontinuity‡	5	1	0.65 (0.20–1.00)	0.235		
Loss of wall layer‡	11	11	0.49 (-0.11–1.00)	0.389		
Gall stone‡	6	7	0.95 (0.86–1.00)	0.758		

Data are mean ± standard deviation or patient number. *For continuous variables, an increase by 1 considered when calculating odds ratios, †For wall enhancement pattern, type 1 + type 2 was compared with others (the reference) to perform analysis, ‡For categorical variables, the absence of the image findings was the reference when calculating odds ratios. CI = confidence interval, GB = gallbladder, ICPN-IC = intracholecystic papillary neoplasm associated with invasive carcinoma, US = ultrasonography

significant CT imaging features predicting ICPN-IC (Fig. 4). Regarding US variables, the maximum wall thickness of ICPN-IC was significantly thicker than that of ICPN-DP (mean ± SD, 3.9 ± 1.9 vs. 3.2 ± 1.8 mm; p = 0.037). No other significantly different US features were found between ICPN-IC and ICPN-DP. Table 2 summarizes the GB wall characteristics predicting ICPN-IC.

Polypoid Lesion Characteristics

On preoperative CT, 40 of the 45 ICPN-ICs and 56 of the 62 ICPN-DPs showed measurable polypoid lesions. The common CT findings of ICPN-IC distinguished from ICPN-DP included multiple lesions (67.5% [27/40] vs. 27.6% [16/58]; p < 0.001), larger size (mean ± SD, 23.5 ± 17.0 vs. 15.1 ± 8.3 mm; p = 0.001), sessile shape (57.5% [23/40] vs. 25.9% [15/58]; p = 0.002), lobulated contour (92.5% [37/40] vs. 75.9% [44/58]; p = 0.033), presence of tumor base dimpling (32.5% [13/40] vs. 13.8% [8/58]; p = 0.027), and presence of tumor base wall thickening (77.5% [31/40] vs. 31.0% [18/58]; p < 0.001). In the multivariable analysis, multiplicity of polypoid lesions (aOR = 4.0; 95% CI: 1.6–10.4) and the presence of tumor base wall

thickening (aOR = 6.0; 95% CI: 2.3–15.8) were significant predictive imaging features of ICPN-IC (Fig. 5). In US, larger size (mean ± SD, 28.3 ± 15.8 vs. 18.6 ± 7.0 mm; p = 0.001), heterogeneous internal echogenicity (31.3% [10/32] vs. 9.5% [4/42]; p = 0.018), and the presence of tumor base dimpling (28.1% [9/32] vs. 4.8% [2/42]; p = 0.007) were significantly common findings of ICPN-IC. In the multivariable logistic regression analysis, only lesion size (aOR = 1.1; 95% CI: 1.0–1.2) was a significant predictor of ICPN-IC (Fig. 5). Table 3 summarizes the imaging findings predicting ICPN-IC with polypoid lesions.

Diagnostic Performances of CT and US in Distinguishing ICPN-IC from ICPN-DP

The pooled AUCs of CT (n = 107) and US (n = 78) differed significantly in distinguishing ICPN-IC from ICPN-DP (0.793 [95% CI: 0.733–0.845] vs. 0.676 [95% CI: 0.597–0.749]; p = 0.002; Fig. 6). The sensitivity of CT was significantly higher than that of US (60.0% vs. 37.9%; p = 0.007). The specificity did not differ significantly between CT and US (85.5% vs. 87.8%; p = 0.629).

Table 3. Predictive Polypoid Lesion Characteristics of ICPN-IC in CT and US

| Image Findings	Invasive Carcinoma	Dysplasia	Inter-Reader Agreement (95% CI)	Univariable Analysis	Multivariable Analysis	
				P	Adjusted Odds Ratio (95% CI)	*P*
CT variable (n = 98)	(n = 40)	(n = 58)				
Multiplicity			0.74 (0.60–0.89)			
Single	13	42		Reference	Reference	
Multiple	27	16		< 0.001	4.0 (1.6–10.4)	< 0.001
Size (largest one), mm*	23.5 ± 17.0	15.1 ± 8.3	0.95 (0.92–0.97)	0.001	Eliminated	Eliminated
Shape			0.75 (0.60–0.89)			
Pedunculated	17	43		Reference		
Sessile	23	15		0.002	Eliminated	Eliminated
Surface contour			0.56 (0.36–0.77)			
Smooth	3	14		Reference		
Lobulated	37	44		0.033	Eliminated	Eliminated
Tumor base dimpling†	13	8	0.76 (0.60–0.92)	0.027	Eliminated	Eliminated
Tumor base wall thickening†	31	18	0.75 (0.62–0.89)	< 0.001	6.0 (2.3–15.8)	< 0.001
US variable (n = 74)	(n = 32)	(n = 42)				
Multiplicity			0.66 (0.49–0.83)			
Single	12	25		Reference		
Multiple	20	17		0.060		
Size (largest one), mm*	28.3 ± 15.8	18.6 ± 7.0	0.95 (0.92–0.97)	0.001	1.1 (1.0–1.2)	0.008
Shape			0.82 (0.68–0.96)			
Pedunculated	18	30		Reference		
Sessile	14	12		0.175		
Surface contour			0.74 (0.39–1.00)			
Smooth	1	4		Reference		
Lobulated	31	38		0.381		
Internal echo level			0.31 (0.10–0.52)			
Hypoechoic	18	21		Reference		
Isoechoic	14	21		0.594		
Internal echo pattern			0.74 (0.54–0.94)			
Homogeneous	22	38		Reference		
Heterogeneous	10	4		0.018	Eliminated	Eliminated
Foci†	6	4	0.69 (0.47–0.90)	0.313		
Tumor base dimpling†	9	2	0.75 (0.52–0.98)	0.007	5.5 (0.9–32.1)	0.059
Tumor base wall thickening†	8	8	0.71 (0.52–0.91)	0.538		

Data are mean ± standard deviation or patient number. *For continuous variables, an increase by 1 considered when calculating odds ratios, †For categorical variables, the absence of the image findings was the reference when calculating odds ratios. CI = confidence interval, ICPN-IC = intracholecystic papillary neoplasm associated with invasive carcinoma, US = ultrasonography

DISCUSSION

In this study, ICPN-IC was identified in 42.0% of all ICPNs (50/119). In addition, ICPNs appeared in the form of wall thickening and/or polypoid lesions on preoperative CT or US. The mean maximum wall thickness of GB was 4.7 mm, and 92.4% of ICPNs (110/119) had measurable polypoid lesions.

The maximum wall thickness (aOR = 1.4) and mucosal discontinuity (aOR = 5.6) were independently associated with ICPN-IC on CT. Our results were similar to those of previous studies showing that GB cancers had thicker walls and showed mucosal discontinuity more frequently than benign inflammatory conditions on CT or US [12,20]. Furthermore, ICPN-IC more frequently showed type 1 or 2 wall enhancement patterns on CT than ICPN-DP (64.4%
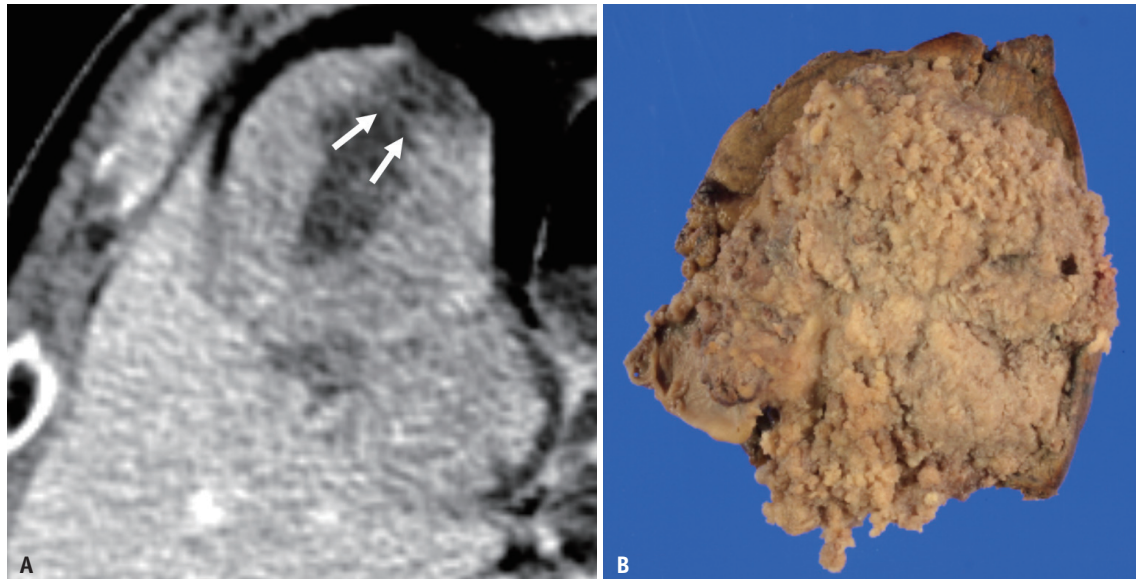
Fig. 4. Intracholecystic papillary neoplasm with associated invasive carcinoma in a 78-year-old male.
A. Axial contrast-enhanced CT image shows diffuse wall thickening (maximum wall thickness, 24 mm) of the GB with mucosal discontinuity (arrows). **B.** Pathologic specimen shows numerous diffuse papillary lesions along the GB wall. GB = gallbladder
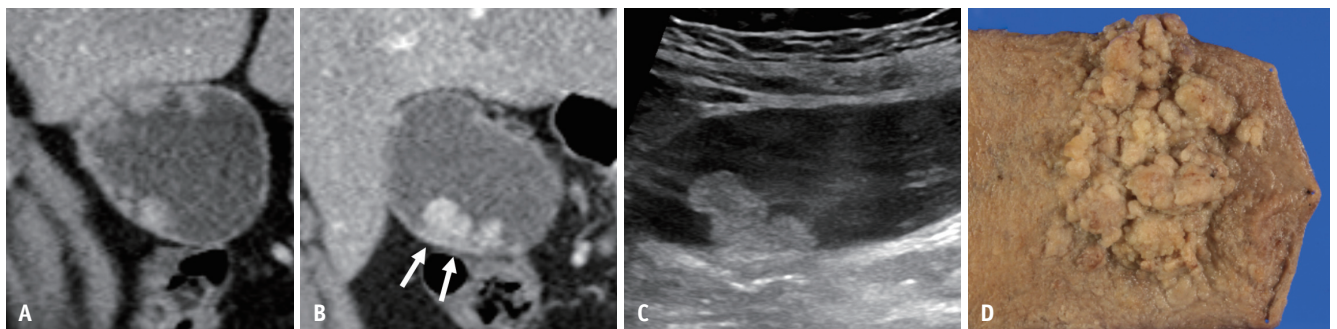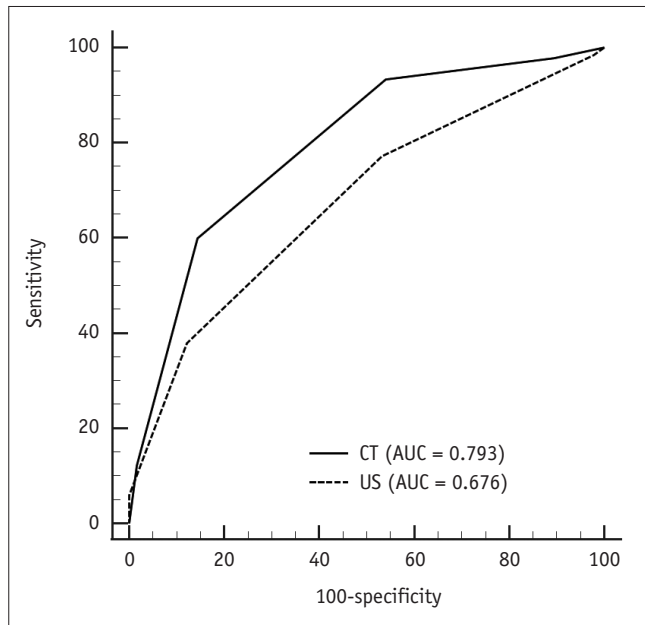

Fig. 5. Intracholecystic papillary neoplasm with associated invasive carcinoma in a 56-year-old female.
A, B. Coronal contrast-enhanced CT images demonstrate multiple polypoid lesions. The largest lesion shows lesion base wall thickening (arrows).
C. Ultrasonography shows the largest lesion (3.3 cm) in the GB body. **D.** Pathologic specimen shows multiple papillary lesions in the GB body.
GB = gallbladder

vs. 27.4%). This result was also consistent with that of previous studies demonstrating that GB cancer more frequently showed type 1 or 2 wall enhancement patterns on contrast-enhanced CT than benign inflammatory lesions [11,12,20].

Regarding polypoid lesions, tumor base wall thickening was an independent predictor of ICPN-IC on preoperative CT. Kim et al. [21] reported that base wall thickening of polypoid tumors could suggest T2-stage GB cancer, similar to our study result showing that 50% of ICPN-IC (25/50) cases were staged as ≥ pT2. In contrast, multiplicity was a significant predictor of ICPN-IC on CT. However, in several previous studies, multiplicity was observed in non-neoplastic polyps more frequently than in neoplastic polyps [5,7,22]. The reason for this discrepancy may be

that ICPN often appears in the form of papillomatosis. As papillomatosis refers to the presence of multiple premalignant lesions, multiplicity may be common in ICPN-IC. On US, a larger size was a feature of ICPN-IC in contrast with ICPN-DP (mean ± SD, 28.3 ± 15.8 vs. 18.6 ± 7.0 mm). In previous studies [23-25] and guidelines [26], the polyp size was a significant predictor of GB cancer, with an optimal cutoff value ≥ 10 or ≥ 15 mm, similar to our study findings.

CT and US showed moderate diagnostic performances in differentiating ICPN-IC from ICPN-DP (AUC = 0.793 and 0.676, respectively). In addition, the AUC of CT was significantly greater than that of US ($p < 0.05$). In previous studies [7,8], high-resolution US was an excellent modality for the characterization and staging of

Fig. 6. AUC of CT and US for differentiating ICPN-IC from ICPN-DP. CT showed significantly better performance than US (0.793 vs. 0.676; *p* = 0.002). AUC = area under the receiver operating characteristic curve, ICPN-DP = intracholecystic papillary neoplasm with dysplasia, ICPN-IC = intracholecystic papillary neoplasm associated with invasive carcinoma, US = ultrasonography

GB cancer through demonstration of the GB wall layers. Although approximately 90% (70/78) of patients with ICPN underwent high-resolution US in our study, US showed a lower diagnostic performance than CT. Considering the multiplicity of ICPNs and high operator dependency of US, localizing and visualizing areas with IC components on US may be difficult. In contrast, CT could be advantageous in distinguishing ICPN-IC because it is operator-independent and superior in visualizing the entire GB. When ICPN is suspected on US examination, further evaluation with contrast-enhanced CT may be helpful in detecting ICPN-IC. In addition, although we investigated differences between ICPN-IC and ICPN-DP, distinguishing between ICPN and other benign polypoid lesions and/or wall thickening could be more important. Further, distinguishing between high- and low-grade DP, as in the case of IPMN [27,28], may be important. Further studies involving a sufficient number of patients with low-grade DP are required to investigate differences in the prognosis and imaging features between ICPN-IC with high-grade DP and ICPN with low-grade DP.

Our study had several limitations. First, the retrospective study design may have resulted in a selection bias. Second, because not all patients underwent both CT and US, comparison of the two modalities may be inaccurate. Third,

other benign or malignant GB lesions, such as pyloric gland adenomas or conventional GB cancers, were not included. Despite these limitations, the imaging patterns of ICPN presented in our study may be helpful in distinguishing ICPN from other GB lesions. Therefore, further studies are required to confirm the results of the present study. Fourth, because the US images were reviewed retrospectively rather than in real time, US performance could be underestimated.

In conclusion, ICPN showed polypoid lesions and/or wall thickening on CT or US. A thick GB wall, multiplicity, the presence of wall thickening in the polypoid lesion base, and a large polyp size were imaging findings independently associated with invasive cancer and potentially useful in differentiating ICPN-IC from ICPN-DP.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to the patients' personal medical information but are available from the corresponding author on reasonable request.

Conflicts of Interest

Jung Hoon Kim who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Jung Hoon Kim. Data curation: Jae Hyun Kim. Formal analysis: Jae Hyun Kim. Investigation: Hyo-Jin Kang, Jae Seok Bae. Methodology: Jung Hoon Kim, Jae Hyun Kim. Project administration: Jung Hoon Kim. Resources: Jung Hoon Kim. Supervision: Jung Hoon Kim. Visualization: Jae Hyun Kim. Writing—original draft: Jae Hyun Kim, Jung Hoon Kim. Writing—review & editing: all authors.

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