Subtype Classification of Intrahepatic Cholangiocarcinoma Using Liver MR Imaging Features and Its Prognostic Value

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Keywords
Cholangiocarcinoma · Recurrence · Survival · Magnetic resonance imaging

Abstract

Introduction: Small-duct (SD) and large-duct (LD) subtypes of cholangiocarcinoma have been investigated for their prognostic factors. This study aimed to evaluate the diagnostic value of liver magnetic resonance imaging (MRI) in differentiating SD and LD types of intrahepatic cholangiocarcinoma (iCCA) and its prognostic value in predicting survival outcomes. Methods: One hundred forty patients with surgically confirmed iCCAs (93 SD type and 47 LD type) who had available preoperative gadoxetic acid-enhanced liver MR images were retrospectively included. MRI features suggestive of the LD type over the SD type were analyzed using multivariate logistic analyses. Postoperative recurrence-free survival (RFS) and overall survival (OS) for 107 patients with available survival data were compared according to MRI features. Results: MRI features suggestive of the LD type included infiltrative contour (odds ratio [OR] 14.2, 95% confidence interval [CI]: 2.5–81.7, \(p = 0.003\)), diffuse biliary dilatation (OR 9.7, 95% CI: 1.2–76.9, \(p = 0.032\)), no arterial phase hyperenhancement (OR 17.8, 95% CI: 2.7–118.6, \(p = 0.003\)), and vascular invasion (OR 4.5, 95% CI: 1.3–15.4, \(p = 0.018\)). When two or more features were combined, sensitivity was 59.6% (28/47), and specificity was 95.7% (89/93) in discriminating the LD type. RFS/OS was significantly shorter in patients with two or more MRI features, compared to those with none or one (310 days vs. 529 days, \(p = 0.011\)/964 days vs. 2,023 days, \(p = 0.010\)). Conclusions: Preoperative liver MRI may help predict the pathological subtype of iCCAs as either the SD type or LD type, allowing preoperative identification of patients with poorer survival outcomes.

Sungeun Park and Youngeun Lee are the co-first authors.
Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, comprising approximately 15% of all primary liver tumors [1]. iCCA is a heterogeneous group of malignancies that can emerge at every point of the biliary tree, from the canals of Hering to the main bile duct (BD) [2]. The strongest risk factors for iCCA are cysts and stones in the BDs, cirrhosis, and hepatitis B and C viruses [3–5]. According to the latest WHO classification, there are two subtypes of iCCA, small-duct (SD) type and large-duct (LD) type, each with distinct clinicopathological features [6]. SD-type iCCAs have been shown to more frequently develop in patients with chronic viral hepatitis without precursor lesions [7, 8], whereas LD-type iCCAs have been more frequently found in patients with chronic BD diseases [9, 10]. Several studies have also demonstrated that LD-type iCCA has a worse prognosis than SD-type iCCA [1, 9, 11]. However, until now, there have been only a limited number of studies that have demonstrated the imaging features of SD-type and LD-type iCCAs. Therefore, accurate subclassification of iCCAs based on imaging features on computed tomography (CT) or magnetic resonance imaging (MRI) would be of clinical value.

Theoretically, distinctly nodular iCCAs in the peripheral liver parenchyma without recognizable LD involvement would more likely be SD-type tumors, while more infiltrative iCCAs involving the Glisson’s capsule of the hilar or segmental BD would more likely be LD-type tumors [12]. However, it may not be so easy to classify these subtypes based on their location (peripheral vs. central) on axial cross-sectional imaging studies, owing to the complex hilar biliary anatomy in three dimensions, parenchymal atrophy related to biliary obstruction, and advanced tumor stage at the time of detection [13, 14]. Recently, Nam et al. [15] reported that arterial hyperenhancement (APHE), round or lobulated contour, and lack of BD encasement were significant CT features suggestive of the SD type, while lymph node enlargement was significantly associated with the LD type. In addition, Rhee et al. [16] reported that the presence of biliary abnormality on MR imaging may suggest the LD type. Yet, at present, it still remains challenging to accurately classify these tumors on imaging. In this regard, this study aimed to evaluate the imaging features of liver MRI so as to differentiate the SD and LD types of iCCA and to predict their survival outcomes.

Materials and Methods

The institutional review board of Seoul National University Hospital (Seoul, South Korea) approved this retrospective study and waived the requirement for written informed consent.

Patients

Between January 2006 and December 2019, patients with a pathological diagnosis of iCCA at surgical resection were retrospectively identified through the database of the Department of Pathology at Seoul National University Hospital. Our study population was selected using the following inclusion criteria: patients with a pathological diagnosis of mass-forming (MF) type iCCA, who underwent preoperative gadobenate dimeglumine-enhanced MRI within 2 months of surgery at our institution.

The exclusion criteria were as follows: (a) intraductal growing (IG) or periductal infiltrating type, (b) rare types of MF type (sarcomatoid type or adenosquamous type), (c) patients who underwent preoperative neoadjuvant treatment, or those with (d) MRI inadequate for image analysis (incomplete study due to motion artifacts or nonvisible masses). Figure 1 shows the patient flowchart.

Pathological Evaluation

One hundred fifty-one patients with MF type iCCAs were reexamined at the pathology department to determine whether they had SD- or LD-type iCCAs. All glass slides for each case were reviewed by two pathologists (Y.L. with 5 years of experience in pathology, H.K. with more than 20 years of experience in hepatopathology), and the iCCAs were classified as either SD type and LD type according to their histopathological features. LD-type iCCAs were characterized by larger caliber ductal structures lined by mucinous columnar epithelium, with some containing extracellular mucin in the duct spaces. SD-type iCCAs, on the other hand, demonstrated smaller ductular-like structures lined by smaller nonmucinous cuboidal cells. For cases that were not readily classifiable based solely on their histomorphology owing to ambiguous features, additional mucin (alcian blue, pH 2.5) and immunohistochemical stains for S100P (1:100, rabbit monoclonal, clone EPR6143, Abcam, Cambridge, UK), NCAM (CD56, 1:100, mouse monoclonal, clone 123C3.D5, Cell-Marque, Rocklin, CA, USA) and N-cadherin (1:100, mouse monoclonal, clone IAR06, Leica Microsystems, Wetzlar, Germany) were performed. For iCCAs in which histological features of LD and SD types were both presented within the same tumor, the mixed tumors of 2 cases were excluded. In addition, 9 patients were thus excluded from the study; 7 cases not classifiable as SD- or LD-type iCCA (ambiguous histology or histology suggestive of other diagnoses on review), and 2 cases which were not evaluable (slides unavailable for review or a totally necrotic tumor). Figure 1 shows the patient flowchart.

MRI Acquisition

In 140 patients, gadoxetic acid-enhanced liver MRI exams were performed at 3.0T (n = 101) or 1.5T (n = 39) scanners. The median time interval between preoperative liver MRI, and surgery was 8 days (range, 1–57 days).

Liver MRI included the following sequences: a respiratory-triggered T2-weighted image, heavily T2-weighted image, diffusion-weighted image (DWI), T1-weighted dual-echo image, and breath-
Liver MRI Features of Small-Duct and Large-Duct Cholangiocarcinoma

Liver MRI Features of Small-Duct and Large-Duct Cholangiocarcinoma

hold T1-weighted fat-suppressed 3D gradient-echo sequences for precontrast and post-contrast imaging including the arterial phase (AP), portal venous phase, transitional phase (TP), and hepatobiliary phase (HBP). For dynamic phase imaging, after obtaining precontrast images, a standard dose (0.025 mmol/kg) of gadoxetic acid (Primovist®: Bayer Healthcare AG, Leverkusen, Germany) was injected intravenously at a rate of 1.0 mL/s using a power injector, followed by a 20-mL saline flush. Using a real-time MR fluoroscopic monitoring system, AP images were acquired 7–8 s after contrast material arrival at the distal thoracic aorta. Subsequently, portal venous phase, TP, and HBP images were obtained approximately 60 s, 3 min, and 20 min, respectively, after starting injection of the contrast medium. Detailed scan parameters are described in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000521747).

MRI Analysis

All liver MRI exams were independently reviewed by two fellowship-trained radiologists (M.H.Y. and E.S.L., with more than 10 years of experience in liver MRI) who were unaware of the pathological subtypes of the tumors. Any discrepancies between the two radiologists were resolved by another observer (I.J. with more than 10 years of experience in liver MRI).

The largest diameter of tumor size was measured on axial images. The radiological level of tumor location (peripheral, mid-, central, or diffuse zone) was determined either by the tumor center or by the nearest margin of the tumor to the hepatic hilum: the peripheral zone was defined as less than 5 cm from the subcapsular portion of the liver; the central zone was defined as involving the proximal segmental portal vein (i.e., P8 proximal branch or P2 proximal branch); and the midzone as the location between peripheral and central zones and the diffuse zone as involving all locations, from peripheral to central zones.

The lesion contour was described as having a round/lobulated or infiltrative appearance. The presence or absence of liver surface change (retraction or bulging) was also evaluated. In addition, the presence or absence of BD dilatation was determined, and if possible, the degree of BD dilatation was categorized as peritumoral dilatation or diffuse (peritumoral, intrahepatic, and/or extrahepatic) BD dilatation. The presence of radiological liver cirrhosis was evaluated.

Enhancement patterns of iCCAs were evaluated on dynamic phases, HBP and DWI, with evaluation of MR imaging features assessed according to the definition of LI-RADS [17]. Arterial enhancement patterns of the tumors were classified as rim APHE, nonrim APHE, and no APHE. Reviewers also assessed whether the tumor had a targetoid appearance: (1) targetoid dynamic enhancement: rim APHE, peripheral "washout," and delayed central enhancement; (2) targetoid appearance on DWI or TP or HBP. The presence of nontargetoid LR-M features (marked diffusion restriction) was also assessed [17]. Peritumoral arterial enhancement was evaluated as liver parenchymal enhancement surrounding the tumors.

The presence of vascular invasion (including encasement of hepatic artery, portal vein, or hepatic vein and tumor in veins), satellite nodules, regional lymph node metastasis or intratumoral necrosis, or mucinous pools was also assessed. Lymph node metastasis was defined as a short diameter of larger than 1 cm or a necrotic lymph node.

Postoperative Survival Outcomes

The survival outcome after curative surgery was available in 107 patients who had R0 resections and follow-up data (75 with SD-type and 32 with LD-type iCCAs). Thirty-three patients (18 with SD-type and 15 with LD-type iCCAs) were excluded from survival analysis due to survival analysis due to R1 resections (n = 19), M1 disease (n = 8),
synchronous cancers (n = 4), and short (<1 month) F/U data (n = 2). Recurrence-free survival (RFS) or overall survival (OS) after hepatic resection was then calculated and compared among the tumor pathological types (SD vs. LD) and MR imaging features. These data were collected by one radiologist (S.P.) using electronic medical records and follow-up imaging studies until February 28, 2021.

**Statistical Analysis**

Radiological features and clinical data were compared between SD- and LD-type iCCAs using the Student's t test for continuous variables and χ² or Fisher's exact test for categorical variables, as appropriate. To compare the radiological features between SD and LD types, a consensus reading of imaging features was used. Levels of interobserver agreement were evaluated using Cohen κ statistics: 0.81–1.0, almost perfect agreement; 0.61–0.8, substantial agreement; 0.41–0.6, moderate agreement; 0.21–0.4, fair agreement; and 0.01–0.2, slight agreement. For continuous variables, intraclass correlation coefficients were used. Significant variables for the differential diagnosis of SD and LD types obtained from univariate analysis were then used as input variables for multivariate analysis, using logistic regression analysis.
Survival outcomes after surgery were evaluated using the Kaplan-Meier method, and pairwise comparisons between subgroups were performed using the log-rank test. All statistical analyses were performed using the SPSS statistical package (version 25.0 for Windows, IBM, Armonk, NY, USA) and MedCalc statistical software (version 19.0, MedCalc Software bvba, Ostend, Belgium). In addition, to quantify discrimination performance, the Harrell concordance index (C-index) was measured and compared between pathology and imaging features [18], using R software, version 4.0.5 (http://www.R-project.org). For all tests, a p value <0.05 was considered to indicate a statistically significant difference.

| MR imaging data                                      | Total (n = 140) | SD type (n = 93) | LD type (n = 47) | p value |
|------------------------------------------------------|-----------------|-----------------|-----------------|---------|
| Median size, cm*                                      | 4.7 (1.2–16.8)  | 4.3 (1.2–16.8)  | 5.2 (1.8–14.2)  | 0.055   |
| Location (center)                                    |                 |                 |                 |         |
| Peripheral                                           | 120 (85.7)      | 82 (88.2)       | 38 (80.9)       | 0.110   |
| Midzone                                              | 13 (9.3)        | 9 (9.7)         | 4 (8.5)         |         |
| Central/diffuse                                      | 7 (5.0)         | 2 (2.2)         | 5 (10.6)        |         |
| Location (perihilar border)                          |                 |                 |                 |         |
| Peripheral                                           | 65 (46.4)       | 53 (57.0)       | 12 (25.5)       | 0.001   |
| Midzone                                              | 26 (18.6)       | 16 (17.2)       | 10 (21.3)       |         |
| Central/diffuse                                      | 49 (35.0)       | 24 (25.8)       | 25 (52.3)       |         |
| Contour                                              |                 |                 |                 |         |
| Round/lobulated                                      | 119 (85.0)      | 90 (96.8)       | 29 (61.7)       | <0.001  |
| Infiltrative                                         | 21 (15.0)       | 3 (3.2)         | 18 (38.3)       |         |
| Liver surface change                                 | 44 (31.4)       | 32 (34.4)       | 12 (25.5)       | 0.285   |
| BD dilatation                                        |                 |                 |                 |         |
| No dilatation                                        | 73 (52.1)       | 64 (68.8)       | 9 (19.1)        | <0.001  |
| Peritumoral dilatation                               | 60 (42.9)       | 27 (29.0)       | 33 (70.2)       |         |
| Diffuse dilatation                                   | 7 (5.0)         | 2 (2.2)         | 5 (10.6)        |         |
| Liver cirrhosis                                      | 44 (31.4)       | 29 (31.2)       | 15 (31.9)       | 0.930   |
| AP enhancement pattern                               |                 |                 |                 |         |
| Nonrim APHE                                          | 33 (23.6)       | 25 (26.9)       | 8 (17.0)        | <0.001  |
| Rim APHE                                             | 84 (60.0)       | 64 (68.8)       | 20 (42.6)       |         |
| No APHE                                              | 23 (16.4)       | 4 (4.3)         | 19 (40.4)       |         |
| Peritumoral arterial enhancement                     | 93 (66.4)       | 55 (59.1)       | 38 (80.9)       | 0.010   |
| Delayed central enhancement                          | 107 (76.4)      | 69 (74.2)       | 38 (80.9)       | 0.381   |
| Portal phase washout pattern                         |                 |                 |                 |         |
| No washout                                           | 86 (61.4)       | 51 (54.8)       | 35 (74.5)       | 0.015   |
| Peripheral washout                                   | 23 (16.4)       | 21 (22.6)       | 2 (4.3)         |         |
| Nonperipheral washout                                | 31 (22.1)       | 21 (22.6)       | 10 (21.3)       |         |
| TP appearance                                        |                 |                 |                 |         |
| No hypointensity                                     | 72 (51.4)       | 39 (41.9)       | 33 (70.2)       | 0.001   |
| Targetoid appearance                                 | 37 (26.4)       | 33 (35.5)       | 4 (8.5)         |         |
| Nontargetoid hypointensity                           | 31 (22.1)       | 21 (22.6)       | 10 (21.3)       |         |
| HBP appearance                                       |                 |                 |                 |         |
| Targetoid appearance                                 | 74 (52.9)       | 55 (59.1)       | 19 (40.4)       | 0.036   |
| Nontargetoid hypointensity                           | 66 (47.1)       | 38 (40.9)       | 28 (59.6)       |         |
| Diffusion-weighted imaging appearance†              |                 |                 |                 | 0.005   |
| n = 133                                              | n = 90          | n = 43          |                 |         |
| Targetoid restriction                                | 73 (54.9)       | 55 (61.1)       | 18 (41.9)       |         |
| Marked diffusion restriction                         | 25 (18.8)       | 19 (21.1)       | 6 (14.0)        |         |
| Restriction but nontargetoid nor marked              | 35 (26.3)       | 16 (17.8)       | 19 (44.2)       |         |
| Vascular invasion                                    | 82 (58.6)       | 41 (44.1)       | 41 (87.2)       | <0.001  |
| Multiplicity                                         | 28 (20.0)       | 14 (15.1)       | 14 (29.8)       | 0.040   |
| Regional lymph node metastasis                       | 29 (20.7)       | 15 (16.1)       | 14 (29.8)       | 0.060   |
| Necrosis or mucin                                    | 52 (37.1)       | 33 (35.5)       | 19 (40.4)       | 0.568   |

Unless otherwise indicated, data are numbers of patients, with percentages in parentheses. Categorical variables were compared using the χ² test or Fisher exact test, as appropriate. APHE, arterial phase hyperenhancement. * Data are continuous variables, reported as median (range) values, and were compared using the Student’s t test. † Percentages were calculated after excluding the nonassessable (missing) cases.
Results

Clinical and Pathological Characteristics

A total of 140 patients (male = 98, mean age 64.4 ± 8.5 years old, range 44–80 years old) were included. After pathological reevaluation of 140 iCCAs, 93 tumors (66.4%) were classified as the SD type and 47 tumors (33.6%) as the LD type. Patients’ clinicopathological findings are described in Table 1. Preoperative tumor markers were significantly elevated in the LD type (p < 0.001 for CA 19-9). Chronic liver disease was more common in the SD type (SD type: 49/93, 52.7% vs. LD type: 6/47, 12.8%, p < 0.001), while biliary dysplasia was more common in the SD type (SD type: 49/93, 52.7% vs. LD type: 6/47, 12.8%, p < 0.001). Chronic liver disease was more common in the SD type (SD type: 39/93, 41.9% vs. LD type: 18/47, 38.3%, p = 0.010). The targetoid appearance was more common with the LD type (SD type: 29/93, 31.2%, vs. LD type: 38/47, 80.9%, p < 0.001). Portal phase peripheral washout pattern and TP targetoid appearance favored SD-type over LD-type iCCAs (Table 2, Fig. 1, 2).

TABLE 1. Preoperative Tumor Markers

| Markers         | SD Type (n=93) | LD Type (n=47) | p-value |
|-----------------|----------------|----------------|---------|
| CA 19-9         | 33.6%          | 66.4%          | <0.001  |
| Chronic liver disease | 52.7%       | 12.8%          | <0.001  |
| Biliary dysplasia | 52.7%        | 12.8%          | <0.001  |

MRI Features

MRI features of SD and LD types are described in Table 2. According to the location of the perihilar border of the 140 iCCAs, the SD type was more frequently found in the peripheral zone than the LD type (SD type: 53/93, 57.0% vs. LD type: 12/47, 25.5%, p = 0.001). Regarding the contour of tumors, the LD type showed a more infiltrative, over round or lobulated margin, than the SD type (SD type: 3/93, 3.2% vs. LD type: 18/47, 38.3%, p < 0.001). Peritumoral or diffuse BD dilatation was also more commonly found with the LD type (SD type: 24/93, 36.6% vs. LD type: 33/47, 70.2%, p < 0.001 and perineural invasion; SD type: 23/93, 24.7% vs. LD type: 31/47, 66.0%, p < 0.001).

TABLE 2. MRI Features

| Feature                      | SD Type (n=93) | LD Type (n=47) | p-value |
|------------------------------|----------------|----------------|---------|
| Targetoid appearance         | 33.6%          | 66.4%          | <0.001  |
| Basal washout pattern        | 52.7%          | 12.8%          | <0.001  |
| Portal washout pattern       | 39/93 (41.9%)  | 18/47 (38.3%)  | 0.010   |
| Basal diffusion restriction   | 49/93 (52.7%)  | 6/47 (12.8%)   | <0.001  |
| Portal diffusion restriction  | 24/93 (25.5%)  | 47/47 (34.0%)  | 0.001   |
| Basal necrosis                | 36/93 (38.3%)  | 15/47 (31.9%)  | 0.001   |
| Portal necrosis               | 23/93 (24.7%)  | 31/47 (66.0%)  | 0.001   |

Multivariate Analysis

On multivariate analysis of MR imaging features which showed significant differences, portal phase peripheral washout pattern and TP targetoid appearance favored SD-type over LD-type iCCAs (p = 0.011 and p = 0.001) (Table 3).

Imaging Feature Combinations

Among the 140 iCCAs, 50 (35.7%) had none of the four significant MR imaging features that were determined to predict the LD type, 58 (41.4%) had one, 21 (15.0%) had two, and 11 (7.9%) three. None satisfied all four features. Table 4 shows the sensitivity, specificity, ac-
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Accuracy, positive predictive value, and negative predictive value of the four significant imaging features and their combination in predicting LD-type iCCAs. When two or more of these four imaging features favoring the LD type were combined, sensitivity and specificity were 59.6% (28/47) and 95.7% (89/93), respectively. When three of these features were satisfied, sensitivity was 23.4% (11/47) and specificity was 100.0% (93/93).

Table 3. Univariate and multivariate analyses of MRI features in discriminating LD-type iCCA

| MR imaging data                  | Univariate | Multivariate |
|----------------------------------|------------|--------------|
|                                  | OR         | 95% CI       | p value | OR         | 95% CI       | p value |
| Median size (cm)                 | 1.130      | 0.995, 1.283 | 0.060   |            |              |         |
| Location (center)                |            |              |         |            |              |         |
| Peripheral                       | 0.143      |              |         |            |              |         |
| Midzone                          | 0.959      | 0.278, 3.311 | 0.947   |            |              |         |
| Central/diffuse                  | 5.395      | 1.001, 29.071| 0.050   |            |              |         |
| Location (perihilar border)      |            |              |         |            |              |         |
| Peripheral                       | 0.002      |              |         |            |              |         |
| Midzone                          | 2.760      | 1.007, 7.567 | 0.048   |            |              |         |
| Central/diffuse                  | 4.601      | 1.985, 10.661| <0.001  |            |              |         |
| Contour                          |            |              |         |            |              |         |
| Round/lobulated                  | 18.621     | 5.116, 67.775| <0.001  | 14.176     | 2.459, 81.708| 0.003*  |
| Infiltrative                     | 0.654      | 0.299, 1.430 | 0.287   |            |              |         |
| BD dilatation                    |            |              |         |            |              |         |
| No dilatation                    | <0.001     |              |         |            |              |         |
| Peritumoral dilatation           | 8.691      | 3.665, 20.610| <0.001  | 2.382      | 0.779, 7.279 | 0.128   |
| Diffuse dilatation               | 17.778     | 2.992, 105.641| 0.002   | 9.673      | 1.217, 76.890| 0.032*  |
| Liver cirrhosis                  | 1.034      | 0.487, 2.199 | 0.930   |            |              |         |
| AP enhancement pattern           |            |              |         |            |              |         |
| Nonrim APHE                      | <0.001     |              |         | 0.006*     |              |         |
| Rim APHE                         | 0.977      | 0.381, 2.503 | 0.961   | 1.569      | 0.423, 5.824 | 0.501   |
| No APHE                          | 14.844     | 3.886, 56.706| <0.001  | 17.848     | 2.685, 118.643| 0.003*  |
| Peritumoral arterial enhancement | 2.917      | 1.264, 6.730 | 0.012   |            |              |         |
| Delayed central enhancement      | 1.469      | 0.620, 3.479 | 0.382   |            |              |         |
| Portal phase washout pattern     |            |              |         |            |              |         |
| No washout                       | 0.139      | 0.031, 0.630 | 0.011   |            |              |         |
| Nonperipheral washout            | 0.694      | 0.291, 1.652 | 0.409   |            |              |         |
| TP appearance                    |            |              |         |            |              |         |
| No hypointensity                 | 0.003      |              |         |            |              |         |
| Targetoid appearance             | 0.143      | 0.046, 0.446 | 0.001   |            |              |         |
| Nontargetoid hypointensity       | 0.563      | 0.232, 1.363 | 0.203   |            |              |         |
| HBP appearance                   |            |              |         |            |              |         |
| Targetoid appearance             | 2.133      | 1.044, 4.357 | 0.038   |            |              |         |
| Nontargetoid hypointensity       |            |              |         |            |              |         |
| Diffusion-weighted imaging appear| 0.007      |              |         |            |              |         |
| Targetoid restriction            |            |              |         |            |              |         |
| Marked diffusion restriction      | 0.965      | 0.334, 2.788 | 0.947   |            |              |         |
| Restriction, but nontargetoid nor| 3.628      | 1.548, 8.504 | 0.003   |            |              |         |
| Vascular invasion                | 8.667      | 3.354, 22.398| <0.001  | 4.477      | 1.298, 15.441| 0.018*  |
| Multiplicity                     | 2.394      | 1.028, 5.572 | 0.043   |            |              |         |
| Regional lymph node metastasis   | 2.206      | 0.958, 5.081 | 0.063   |            |              |         |
| Necrosis or mucin                | 1.234      | 0.600, 2.537 | 0.568   |            |              |         |

OR, odds ratio; APHE, arterial phase hyperenhancement. *Statistically significant results from logistic regression analysis. Variables with p < 0.05 on univariate logistic regression analysis were utilized as input variables for multivariate logistic regression analysis.
Interobserver Agreement of MRI Features

Interobserver agreement for the MRI features ranged between 0.16 and 0.83. Detailed description of interobserver agreements is provided in online supplementary Table 2.

For three of the four MRI imaging features suggestive of LD-type iCCAs, interobserver agreement ranged from moderate to fair agreement: tumor contour, 0.33 (95% CI: 0.12–0.55); arterial enhancement pattern, 0.31 (95% CI: 0.19–0.42); and vascular invasion, 0.46 (95% CI: 0.33–0.59). BD dilatation showed nearly perfect agreement, 0.83 (95% CI: 0.74–0.93).

Prognostic Factor Analysis

In the 107 iCCAs in which follow-up data were available and patients had received R0 resections, median RFS (488 days, 95% CI: 310–683) significantly differed according to the pathological subtype (shown in Fig. 4). The median RFS of the SD type was 538 days (95% CI: 430–2,704), while that of the LD type was 241 days (95% CI: 106–504) with a p value <0.001. Overall median survival (1,541 days, 95% CI: 1,259–3,802) also significantly differed according to the pathological subtype. Median OS of the SD type was 2,803 days (95% CI: 1,447–2,803), while that of the LD type was 567 days (95% CI: 403–1,259 days) with a p value <0.001. Compared to iCCAs without significant MR imaging features, iCCAs with two or more significant MR imaging features showed sig-

Fig. 2. Cholangiocarcinoma of LD type in a 61-year-old woman. a Gadoxetic acid-enhanced AP MR image shows a 4.5-cm mass without AP hyperenhancement. Peritumoral arterial enhancement (dashed arrow) is shown around the tumor (solid arrow). b Portal phase image shows an invasion of the right portal vein (arrow) by the tumor. c Fat-saturated T2 image shows an infiltrative margin of the tumor (arrow). d An LD-type tumor demonstrates dilated ductal structures lined by columnar epithelial cells containing mucin. Extracellular mucin is also present within the ductal spaces. e Follow-up CT shows a recurred tumor, encasing the portal vein and inferior vena cava (arrows). Recurrence occurred 16 months after curative resection.
Table 4. Diagnostic performance of MR imaging features in predicting LD-type iCCA

| MR imaging feature     | Sensitivity      | Specificity | Accuracy   | PPV     | NPV     |
|------------------------|------------------|-------------|------------|---------|---------|
| Infiltrative contour   | 38.3 (18/47)     | 96.8 (90/93) | 77.1 (108/140) | 85.7 (18/21) | 75.6 (90/119) |
| Diffuse BD dilatation  | 10.6 (5/47)      | 97.8 (91/93) | 68.6 (96/140) | 71.4 (5/7)  | 68.4 (91/133) |
| No APHE                | 40.4 (19/47)     | 95.7 (89/93) | 77.1 (108/140) | 82.6 (19/23) | 76.1 (89/117) |
| Vascular invasion      | 87.2 (41/47)     | 55.9 (52/93) | 66.4 (93/140) | 50.0 (41/82) | 89.7 (52/58)  |
| Any two or more        | 59.6 (28/47)     | 95.7 (89/93) | 83.6 (117/140) | 87.5 (28/32) | 82.4 (89/108) |
| Any three              | 23.4 (11/47)     | 100.0 (93/93)| 74.3 (104/140) | 100.0 (11/11)| 72.1 (93/129) |

Data are presented as percentages. Data in parentheses are the number of subjects used to calculate the percentage. PPV, positive predictive value; NPV, negative predictive value; APHE, arterial phase hyperenhancement.

Fig. 3. Cholangiocarcinoma of SD type in a 62-year-old woman. a Axial image of gadoxetic acid-enhanced MRI shows a 3.8-cm round mass with nonrim AP hyperenhancement. b Portal phase image shows no vascular invasion. c Fat-saturated T2 image shows no peritumoral or diffuse BD dilatation. d A SD-type tumor demonstrates smaller cuboidal tumor cells which are arranged in smaller and narrower tubular structures. Mucin production is not evident in the SD type. e Tumor recurrence did not occur during 34 months of the follow-up period after curative resection.

Table 4. Diagnostic performance of MR imaging features in predicting LD-type iCCA

| MR imaging feature     | Sensitivity      | Specificity | Accuracy   | PPV     | NPV     |
|------------------------|------------------|-------------|------------|---------|---------|
| Infiltrative contour   | 38.3 (18/47)     | 96.8 (90/93) | 77.1 (108/140) | 85.7 (18/21) | 75.6 (90/119) |
| Diffuse BD dilatation  | 10.6 (5/47)      | 97.8 (91/93) | 68.6 (96/140) | 71.4 (5/7)  | 68.4 (91/133) |
| No APHE                | 40.4 (19/47)     | 95.7 (89/93) | 77.1 (108/140) | 82.6 (19/23) | 76.1 (89/117) |
| Vascular invasion      | 87.2 (41/47)     | 55.9 (52/93) | 66.4 (93/140) | 50.0 (41/82) | 89.7 (52/58)  |
| Any two or more        | 59.6 (28/47)     | 95.7 (89/93) | 83.6 (117/140) | 87.5 (28/32) | 82.4 (89/108) |
| Any three              | 23.4 (11/47)     | 100.0 (93/93)| 74.3 (104/140) | 100.0 (11/11)| 72.1 (93/129) |

Data are presented as percentages. Data in parentheses are the number of subjects used to calculate the percentage. PPV, positive predictive value; NPV, negative predictive value; APHE, arterial phase hyperenhancement.

Significantly shorter RFS (529 days, 95% CI: 321–1,060, [risk 0 or 1] vs. 310 days, 95% CI: 82–553, [risk 2 or more], p = 0.011) as well as significantly shorter median OS (2,023 days, 95% CI: 743–3,302, [risk 0 or 1] vs. 964 days, 95% CI: 514–1,413, [risk 2 or more], p = 0.010) (shown in Fig. 4).
Table 5. Prognostic value of histology and MR imaging features in predicting survival outcomes, with discrimination performance

| Feature                  | HR (95% CI) | p value* | C-index (95% CI) | p value† |
|--------------------------|-------------|----------|------------------|----------|
| RFS                      |             |          |                  |          |
| Pathology (LD type)      | 2.4 (1.5–3.8) | <0.001   | 0.597 (0.545–0.649) | (−)      |
| Two or more imaging features | 2.0 (1.2–3.6) | 0.013    | 0.543 (0.506–0.580) | 0.046    |
| OS                       |             |          |                  |          |
| Pathology (LD type)      | 3.0 (1.8–5.2) | <0.001   | 0.631 (0.568–0.694) | (−)      |
| Two or more imaging features | 2.2 (1.2–4.1) | 0.012    | 0.550 (0.501–0.599) | 0.010    |

HR, hazard ratio. * p values were obtained from the log-rank test. † p values were obtained from the comparison of C-index between the pathology (LD type) and two or more imaging features.
Table 5 summarizes the hazard ratio (HR) of pathology and the combination of imaging features. The HR of the LD type for RFS was 2.4 (95% CI: 1.5–3.8, p < 0.001), while that of a combination of imaging features was 2.0 (95% CI: 1.2–3.6, p = 0.013). Each C-index was 0.597; 95% CI: 0.545–0.649 for pathology and 0.543; 95% CI: 0.506–0.580 for imaging features. The HR of the LD type for OS was 3.0 (95% CI: 1.8–5.2, p < 0.001), while that of a combination of imaging features was 2.2 (95% CI: 1.2–4.1, p = 0.012), showing a C-index of 0.631; 95% CI: 0.568–0.694 for pathology, 0.550; 95% CI: 0.501–0.599 for imaging features.

Discussion

Our study demonstrated that infiltrative tumor contour, diffuse dilation of the BD, the absence of APHE, and vascular invasion on gadoxetic acid-enhanced liver MRI were independent and significant predictors of LD-type iCCA. Indeed, by combining two or more of these MR imaging features, we were able to obtain a sensitivity of 59.6% and a specificity of 95.7% in predicting LD-type iCCAs, suggesting that MR imaging is able to preoperatively discriminate between the two subtypes of iCCAs [10, 11, 19]. Furthermore, survival outcomes were found to be significantly worse in patients with two or more of these MR imaging features compared to those with none or one of these MR imaging features after curative resection of iCCAs, suggesting that patients with poorer survival outcomes can be identified through imaging. Our study results are in good agreement with several previous pathological studies showing the worse prognosis of LD-type iCCAs in comparison with SD-type iCCAs [1, 9, 11, 20].

The absence of APHE was determined to be one of the major imaging features of LD-type iCCAs according to our study results. These results are in good agreement with previous studies by Fujita et al. [21], in which iCCAs without APHE tended to be of the perihilar type and to have more malignant potential than other iCCAs. Min et al. [22] had also reported that diffuse hypoenhancement and peripheral rim enhancement were associated with a poor prognosis compared with diffuse hyperenhancement in patients with iCCAs. It had also been reported that while iCCAs showing APHE were associated with an increased proportion of the cellular area and less central fibrous stroma, hypoenhancing tumors had sparse cellular components and necrotic changes [21, 23]. Histologically, LD-type tumors demonstrate more desmoplastic stroma containing fibroblasts, while SD-type tumors often show a centrally located dense sclerotic stroma surrounded by a more cellular peripheral portion composed of tumor epithelial cells [24]. Several studies have reported that prominent arterial enhancement on CT and MRI might reflect favorable surgical outcomes in patients with iCCAs [21–23, 25]. However, rim APHE was not shown to be a discriminative feature for LD-type iCCA, which is in well in line with the results of a previous study dealing with CT features [15]. Furthermore, the targetoid appearance of the portal phase, TP, and HBP was not shown to be a discriminative feature. Although it demonstrated no significance on multivariate analysis, the targetoid appearance was related with the SD type on univariate analysis, which is in good agreement with Nam et al’s study [15] that peripheral washout was observed in SD type only. However, it was the opposite result of the previous article [26], and further evaluation is needed.

The presence of diffuse dilation of the BD was found to be another imaging feature suggestive of LD-type iCCAs. This could be related to the origin of LD-type tumors from the large intrahepatic BD and the presence of precursors of intraductal papillary neoplasms or chronic inflammation such as primary sclerosing cholangitis or liver fluke infection [1]. Several previous studies have reported that SD-type tumors originating from small BDs or ductules are associated with chronic liver disease and cirrhosis, whereas LD-type iCCAs are associated with chronic BD diseases, biliary intraepithelial neoplasia, perineural invasion, and lymph node metastasis [10, 12]. Recently, Rhee et al. [16] proposed an image-based classification of iCCAs based on MRI features of the coexistence of biliary abnormalities: ductal type versus parenchymal type. They reported that ductal-type iCCAs were associated with biliary intraepithelial neoplasia and also exhibited a larger tumor size, frequent perineural invasion and lymph node metastasis, and poor OS after surgical resection. Whereas, in their article, the presence of peritumoral BD dilatation was regarded as the ductal type; our study, which used the pathology of SD type and LD type as the reference standard, showed that the presence of diffuse BD dilatation had a more significant relevance with the LD type than that of peritumoral BD dilatation alone.

We also found that an infiltrative margin and vascular invasion on liver MRI were significant factors differentiating LD-type from SD-type iCCAs. This is also in good agreement with previous reports [10, 27] describing the infiltrative growth nature of LD-type tumors. Our pathological data shows a significantly higher proportion of the
infiltrative growth nature in LD-type tumors than SD-type tumors (SD type: 1/93, 1.1% vs. LD type: 15/47, 31.9% \( p < 0.001 \)). MRI infiltrative contour feature was shown more frequently in pathologically combined periductal infiltrative or IG type than pathologically pure MF type (Combined type: 9/16, 56.3%, vs. Pure MF type: 12/124, 9.7%, \( p < 0.001 \)). Indeed, there was a significantly higher proportion (LD type: 11/47, 23.4% vs. SD type 8/93, 8.6%, \( p = 0.016 \)) of positive resection margins in LD-type tumors in our study despite the higher proportion of major surgery (LD type: 36/47, 76.6% vs. SD type: 54/93, 58.1%, \( p = 0.031 \)). Pathological vascular invasion was reported as a prognostic factor for RFS in a previous study [28], although vascular invasion criteria on MRI showed less accuracy in predicting the subtype of iCCA in our study.

In our study, we reviewed all pathology slides and classified them into the SD type and LD type based on histomorphology and immunohistochemistry. Of our cases, there were two iCCAs where the SD and LD morphology coexisted in the same tumor (LD-type iCCA, 60%). Currently, there is no consensus on how to classify such iCCAs, and the relationship between mixed iCCAs and biological behavior remains to be clarified [14, 29]. We could not find an association between this type and the clinicopathological features due to the paucity of such cases, and it would be interesting to see in the future if the predominant histological pattern or the presence of a particular component (e.g., LD pattern) should determine the classification.

Interestingly, SD-type iCCAs more frequently demonstrate a MF gross appearance (98.9%, 92/93). Also, approximately one-fourth of SD-type tumors showed non-rim APHE pattern (26.9%, 25/93), and a half of SD-type tumors arose from the background of chronic liver disease (52.7%, 49/93), which may lead to misdiagnosis of SD-type tumor as hepatocellular carcinoma or combined hepatocellular-cholangiocarcinomas (cHCC-CCA), especially in small tumor sizes [30, 31]. Indeed, SD-type iCCAs may be located closer to cHCC-CCA than LD-type iCCAs on the primary liver cancer spectrum. Histologically, cholangiolocellular carcinoma is currently regarded as a subtype of SD-type iCCA but was classified under the category of CHCC-CCA with stem cell features in the previous edition of the WHO classification, based on the expression of stemness-related markers (e.g., NCAM) and frequent coexistence with HCC components [9, 32, 33]. In addition, the presence of a cholangiolocellular component in iCCAs has been associated with favorable survival in iCCAs [34].

In this study, the prognostic analysis was focused on post-curative resection. Still, surgical resection remains the mainstay of curative treatment for patients with resectable disease in iCCA patients. However, only about 20–40% of patients have a potentially operable disease [35] because most patients with CCA have metastatic or locally advanced disease at presentation. Thus, most of them undergo palliative chemotherapy [36]. In a recent study about the molecular profiles of biliary tract cancer, mutually exclusive and distinct molecular patterns were observed (LD type: KRAS-SMAD4 vs. SD type: BAP1-IDH1/2 alterations) [37]. Also, different clinical outcomes of palliative chemotherapy and immunotherapy responses have been reported between LD and SD types, with the LD type showing a poor response to chemotherapy [37]. Recently, ivosidenib was approved for the SD type with IDH1 mutations [38]. Therefore, further analysis of imaging features combined with molecular markers is needed to predict prognosis, including palliative settings, with improved discriminative powers. In this study, the discrimination power, according to pathological subtype or imaging features, could achieve Harrell’s concordance index less than 0.75 for OS (pathological subtype: 0.631 vs. imaging features: 0.550).

This study has some limitations. First, since we only included patients with iCCAs who underwent surgical resection, our analysis did not evaluate the full spectrum of the TNM stage of iCCA. Second, owing to the retrospective setting of our study, several different MR scanners had been used in our patients, although we had employed similar imaging protocols using the same contrast media. However, our MR images were acquired using gadoxetic acid, extrapolation of our results to MRI with extracellular contrast agents or CT image features may be limited, although there was no specific imaging feature only obtainable using gadoxetic acid, among four significant imaging features. Third, the study patients were collected from a single-center, in an endemic area for HBV and liver fluke infection. Therefore, a more confirmative follow-up study should involve the validation of our findings including patients with disease etiologies such as primary sclerosing cholangitis from multiple centers. Finally, there was a limited degree of interobserver agreement in the subjective interpretation of image features, and quantitative analysis of the enhancement degree of iCCAs on the AP was not performed but rather the qualitative assessment of APHE was used. In conclusion, preoperative liver MRI may help predict the pathological subtype of iCCAs as either the SD type or LD type, allowing preoperative identification of patients with poorer survival outcomes.
Liver MRI Features of Small-Duct and Large-Duct Cholangiocarcinoma

Statement of Ethics

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1810-048-977). The requirement for written informed consent was waived because retrospective pathological and imaging review was performed in this study.

Conflict of Interest Statement

Corresponding author, Jeong Min Lee, is an editorial board member of Liver Cancer. The other authors have no conflicts of interest to declare.

Funding Sources

This research was funded by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2019R1A2C2010056).

References

1 Banales JM, Marin JG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557–88.
2 Banales JM, Cardinale V, Carpio G, Marzio M, Andersen JB, Invernizzi P, et al. Expert consensus document: cholangiocarcinoma – current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol. 2016 May;13(5):261–80.
3 Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. AJR Am J Roentgenol. 2003 Sep;181(3):819–27.
4 Lim JH, Park CK. Pathology of cholangiocarcinoma. Abdom Imaging. 2004 Sep–Oct; 29(5):540–7.
5 Clements O, Eliahou J, Kim JU, Taylor-Robinson SD, Khan SA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a systematic review and meta-analysis. J Hepatol. 2020 Jan;72(1):95–103.
6 Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020 Jan;76(2):182–8.
7 Nakamura Y, Sato Y, Harada K, Sasaki M, Xu J, Ikeda H. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol. 2010 Dec 27;2(12):419–27.
8 Yu TH, Yuan RH, Chen YL, Yang WC, Hsu HC, Jeng YM. Viral hepatitis is associated with intrahepatic cholangiocarcinoma with cholangiolar differentiation and N-cadherin expression. Mod Pathol. 2011 Jun;24(6):810–9.
9 Komuta M, Gouvea O, Vandeaveye V, Akiba J, Van Steenbergen W, Verslype C, et al. Histological diversity in cholangiocellular carcinoma reflects the different cholangiocyte phenotypes. Hepatology. 2012 Jun;55(6):1876–88.
10 Aishima S, Oda Y. Pathogenesis and classification of intrahepatic cholangiocarcinoma: different characters of perihilar large duct type versus peripheral small duct type. J Hepatobiliary Pancreat Sci. 2015 Feb;22(2):94–100.
11 Seo N, Kim DY, Choi JY. Cross-sectional imaging of intrahepatic cholangiocarcinoma: development, growth, spread, and prognosis. AJR Am J Roentgenol. 2017 Aug;209(2):W64–75.
12 Nakamura Y, Kakuda Y. Pathologic classification of cholangiocarcinoma: new concepts. Best Pract Res Clin Gastroenterol. 2015 Apr; 29(2):277–93.
13 Gupta AA, Kim DC, Kriisky GA, Lee VS, CT and MRI of cirrhosis and its mimics. AJR Am J Roentgenol. 2004 Dec;183(6):1595–601.
14 Akita M, Sofue K, Fujikura K, Otani K, Itoh T, Ajiro T, et al. Histological and molecular characterisation of intrahepatic bile duct cancers suggests an expanded definition of perihilar cholangiocarcinoma. HPB. 2019;21(2):226–34.
15 Nam JG, Lee JM, Joo I, Ahn SJ, Park JY, Lee KB, et al. Intrahepatic mass-forming cholangiocarcinoma: relationship between computed tomography characteristics and histological subtypes. J Comput Assist Tomogr. 2018 May/Jun;42(3):340–9.
16 Rhee H, Kim MJ, Park YN, An C. A proposal of imaging classification of intrahepatic mass-forming cholangiocarcinoma into ductal and parenchymal types: clinicopathologic significance. Eur Radiol. 2019 Jun;29(6):3111–21.
17 ACo Radiology. CT/MRI LI-RADS v2018 core. 2018. Available from: https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf?la=en.
18 Harrell FE Jr. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Springer; 2015.
19 Aishima S, Kuroda Y, Nishihara Y, Iguchi T, Taguchi K, Taketomi A, et al. Proposal of progression model for intrahepatic cholangiocarcinoma: clinicopathologic differences between hilar type and peripheral type. Am J Surg Pathol. 2007 Jul;31(7):1059–67.
20 Yoshimitsu K. Differentiation of two subtypes of intrahepatic cholangiocarcinoma: imaging approach. Eur Radiol. 2019 Jun;29(6):3108–10.
21 Fuji N, Asayama Y, Nishie A, Ishigami K, Ushijima Y, Takayama Y, et al. Mass-forming intrahepatic cholangiocarcinoma: enhancement patterns in the arterial phase of dynamic hepatic CT – correlation with clinicopathological findings. Eur Radiol. 2017 Feb;27(2):498–506.
22 Min JH, Kim YK, Choi SY, Kang TW, Lee SJ, Kim JM, et al. Intrahepatic mass-forming cholangiocarcinoma: arterial enhancement patterns at MRI and prognosis. Radiology. 2019 Mar;290(3):691–9.

Author Contributions

Jeong Min Lee and Haeryoung Kim: supervision, writing review, and editing. Sungeun Park and Youngeun Lee: data curation, formal analysis, investigation, and writing original draft. Mi Hye Yu and Eun Sun Lee: data curation. Jin Joo: data curation, writing review, and editing. Jeong Hee Yoon: writing review and editing.

Data Availability Statement

The datasets analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.
23 Kim SA, Lee JM, Lee KB, Kim SH, Yoon SH, Han JK, et al. Intrahepatic mass-forming cholangiocarcinomas: enhancement patterns at multiphasic CT, with special emphasis on arterial enhancement pattern – correlation with clinicopathologic findings. Radiology. 2011 Jul;260(1):148–57.

24 Sigel CS, Drill E, Zhou Y, Basturk O, Askan G, Pak LM, et al. Intrahepatic cholangiocarcinomas have histologically and immunophenotypically distinct small and large duct patterns. Am J Surg Pathol. 2018 Oct;42(10):1334–45.

25 Ariizumi S, Kotera Y, Takahashi Y, Katagiri S, Chen IP, Ota T, et al. Mass-forming intrahepatic cholangiocarcinoma with marked enhancement on arterial-phase computed tomography reflects favorable surgical outcomes. J Surg Oncol. 2011 Aug 1;104(2):130–9.

26 Joo I, Lee JM, Yoon JM. Imaging diagnosis of intrahepatic and perihilar cholangiocarcinoma: recent advances and challenges. Radiology. 2018 Jul;288(1):7–13.

27 Nishihara Y, Aishima S, Hayashi A, Iguchi T, Fujita N, Taketomi A, et al. CD10+ fibroblasts are more involved in the progression of hilar/extrahepatic cholangiocarcinoma than of peripheral intrahepatic cholangiocarcinoma. Histopathology. 2009 Oct;55(4):423–31.

28 Chan KM, Tsai CY, Yeh CN, Yeh TS, Lee WC, Jan YY, et al. Characterization of intrahepatic cholangiocarcinoma after curative resection: outcome, prognostic factor, and recurrence. BMC Gastroenterol. 2018;18(1):180.

29 Hayashi A, Misumi K, Shibahara J, Arita J, Sakamoto Y, Hasegawa K, et al. Distinct clinicopathologic and genetic features of 2 histologic subtypes of intrahepatic cholangiocarcinoma. Am J Surg Pathol. 2016 Aug;40(8):1021–30.

30 Kang Y, Lee JM, Kim SH, Han JK, Choi BI. Intrahepatic mass-forming cholangiocarcinoma: enhancement patterns on gadoxetic acid-enhanced MR images. Radiology. 2012 Sep;264(3):751–60.

31 Kim JH, Joo I, Lee JM. Atypical appearance of hepatocellular carcinoma and its mimickers: how to solve challenging cases using gadoxetic acid-enhanced liver magnetic resonance imaging. Korean J Radiol. 2019;20(7):1019–41.

32 Sia D, Villanueva A, Friedman SL, Llovet JM. Liver cancer cell of origin, molecular class, and effects on patient prognosis. Gastroenterology. 2017 Mar;152(3):745–61.

33 Xue R, Chen L, Zhang C, Fujita M, Li R, Yan SM, et al. Genomic and transcriptomic profiling of combined hepatocellular and intrahepatic cholangiocarcinoma reveals distinct molecular subtypes. Cancer Cell. 2019 Jun 10;35(6):932–47.e8.

34 Rhee H, Ko JE, Chung T, Jee BA, Kwon SM, Nahm JH, et al. Transcriptomic and histopathological analysis of cholangiolocellular differentiation trait in intrahepatic cholangiocarcinoma. Liver Int. 2018 Jan;38(1):113–24.

35 Tan JC, Coburn NG, Baxter NN, Kiss A, Law CH. Surgical management of intrahepatic cholangiocarcinoma: a population-based study. Ann Surg Oncol. 2008;15(2):600–8.

36 Weber SM, Ribero D, O’Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. HPB. 2015;17(8):669–80.

37 Yoon JG, Kim MH, Jang M, Kim H, Hwang HK, Kang CM, et al. Molecular characterization of biliary tract cancer predicts chemotherapy and programmed death 1/programmed death-ligand 1 blockade responses. Hepatology. 2021 Oct;74(4):1914–31.

38 Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClariDH): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020 Jun;21(6):796–807.