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LI-RADS Category Can Be a Post-Surgical Prognostic Factor for Intrahepatic Cholangiocarcinoma in Patients with Liver Cirrhosis or Chronic Hepatitis B

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Keywords
Cholangiocarcinoma · Liver Imaging Reporting and Data System · Recurrence · Survival · Magnetic resonance imaging

Abstract

Introduction: The Liver Imaging Reporting and Data System (LI-RADS) categorization has been proposed as a potential prognostic indicator for primary liver neoplasms in patients with liver cirrhosis or chronic hepatitis B. This multicenter study aimed to determine whether LI-RADS categorization can offer additional post-surgical prognostic value for intrahepatic cholangiocarcinoma (ICCA) when used in conjunction with the American Joint Committee on Cancer (AJCC) guidelines. ***Methods:*** Patients with high risk for hepatocellular carcinoma, surgically confirmed ICCAs, and available preoperative MRI were enrolled. LI-RADS categorization of ICCAs was performed using MRI features, and multivariate analyses were conducted incorporating LI-RADS category, AJCC staging, and clinicopathologic factors to evaluate their predictive value for postoperative recurrence-free survival (RFS) and overall survival (OS). In patients with early recurrence (<2 years), the percentages of AJCC stage I and LR-M or LR tumor-in-vein (TIV) were calculated, respectively. ***Results:*** Among the 166 ICCAs analyzed, 13.3% (22/166) were classified as LR-4/5, 77.7% (129/166) as LR-M, and 9.0% (15/166) as LR TIV. Classifications according to the 8th AJCC guidelines for patients with available post-surgical pathologic data and follow-up imaging were 40.6% (63/155) stage I tumors, 23.9% (37/155) stage II, and 35.5% (55/155) stage III. Multivariate analysis revealed that LI-RADS category (LR-M or LR-TIV) was a significant factor for predicting both RFS (hazard ratio [HR] = 2.86, $p = 0.02$) and OS (HR = 3.18, $p = 0.03$). Additionally, AJCC staging (II or III) was a significant factor for RFS (HR = 3.90, $p < 0.001$) and OS (HR = 3.29, $p < 0.001$), male sex was a significant factor for RFS (HR = 1.89, $p = 0.006$) and OS (HR = 2.23, $p =$

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0.002), and positive resection margin was a significant factor for OS (HR = 1.91, $p = 0.03$). Among the 80 patients with early recurrence, 97.5% displayed LR-M or LR-TIV features, while 11.3% were AJCC stage I patients. ***Conclusion:*** The MRI-based preoperative LI-RADS categorization of ICCA provides additional post-surgical prognostic value beyond the AJCC guidelines, with significant implications for both RFS and OS.

Introduction

Intrahepatic cholangiocarcinoma (ICCA) is the second most common primary malignancy, accounting for 15% of primary liver cancers, and its incidence is increasing globally [1]. ICCAs, which can arise from the canal of Hering to the hilar bile duct, are heterogeneous tumors, showing diverse clinicopathologic features and genetic mutations depending on the cell lineages of their origin [1–3]. Furthermore, although chronic inflammation of the bile duct due to pathology such as liver flukes, intrahepatic stone disease, and primary sclerosing cholangitis is known to be a common risk factor for ICCA, chronic hepatitis B and C infections are also important risk factors [4–6]. It was reported that about 8–10% of all ICCAs occur in patients with liver cirrhosis [7]. Currently, surgical resection with a negative margin (R0 resection) is considered the only curative treatment option [8]. However, the cumulative tumor recurrence rates and patient survival rates after curative surgical resection are approximately 70% and 30% at 5 years, respectively, and the prognosis is still very poor [9–11]. Therefore, identification of preoperative predictive markers is critical for guiding management and selecting optimal surgical candidates for ICCA [12–14]. The American Joint Committee on Cancer (AJCC) staging system which is the most prevalent for ICCA plays a crucial role in prognostic classification and treatment guidance [11]. According to the 8th edition of the AJCC system, if there is no metastasis or regional LN metastasis, the stage is determined by the tumor size and number, vascular invasion, or adjacent organ invasion. Factors like larger tumor size, multiple tumors, lymph node metastasis, vascular invasion, and poor tumor differentiation are established as risk factors for reduced overall survival (OS) [9].

Accurately diagnosing ICCA in patients with liver cirrhosis or chronic hepatitis B presents is notably challenging, and predicting their prognosis adds further complexity [15]. ICCAs typically exhibit rim arterial phase hyperenhancement (APHE) and are categorized as Liver Imaging Reporting and Data System (LI-RADS) category M (LR-M). However, it is important to note that approximately 20% of ICCAs may present with nodular APHE, leading to their categorization as LI-RADS category 4 or 5 (LR-4/5) [16, 17]. Nonetheless, there is growing evidence that the LI-RADS category provides valuable prognostic information for primary liver cancers, including ICCAs [17, 18]. However, it is worth mentioning that many studies have primarily focused on imaging variables and have not fully integrated all available pathologic and radiologic information for prognosis prediction. In this study, our objective was to investigate whether preoperative LI-RADS categorization of ICCAs can offer supplementary prognostic information following surgery, in conjunction with the conventional AJCC staging system.

Methods

This study was conducted at three tertiary referral institutions and was approved by the Institutional Review Board of each institution. The need for informed consent was waived by the Institutional Review Board of Seoul National University Hospital, Asan Medical Center, and Konkuk University Medical Center.

Study Population

This retrospective study included patients who underwent surgical resection for mass-forming ICCA at one of three tertiary referral hospitals between January 2009 and December 2019. Patients were included if they (a) were aged ≥18 years, (b) were at risk of hepatocellular carcinoma (HCC) as per the LI-RADS criteria [19], and (c) underwent dynamic contrast-enhanced MRI. Patients were excluded if they (a) had previous other malignancy, (b) had synchronous HCC, (c) had been treated before surgery, (d) had undergone palliative surgical resection, or (e) had suboptimal image quality (Fig. 1). Clinical information, including demographic characteristics, laboratory results, and clinical outcomes, was obtained from the patients' electronic medical records.

In prior studies, we reported on 50 patients [20] and 41 patients [16] included in the current study. The prior reports evaluated tumor response and imaging features regarding pathologic subtypes. The current study expands on this by having a larger patient number and includes analyses of survival in conjunction with AJCC staging system.

MRI Techniques

All patients underwent multiphase liver MRI on a 1.5-T or 3.0-T scanner, and all examinations met the technical acquisition standards of the LI-RADS criteria [8]. The MRI examination included T1-weighted dual gradient-echo in- and opposed-phase imaging, T2-weighted navigator-triggered turbo spin-echo imaging, diffusion-weighted single-shot spin-echo echo-planar imaging, and breath hold T1-weighted fat-suppressed 3D gradient-echo sequence for pre-contrast and post-contrast imaging. Details

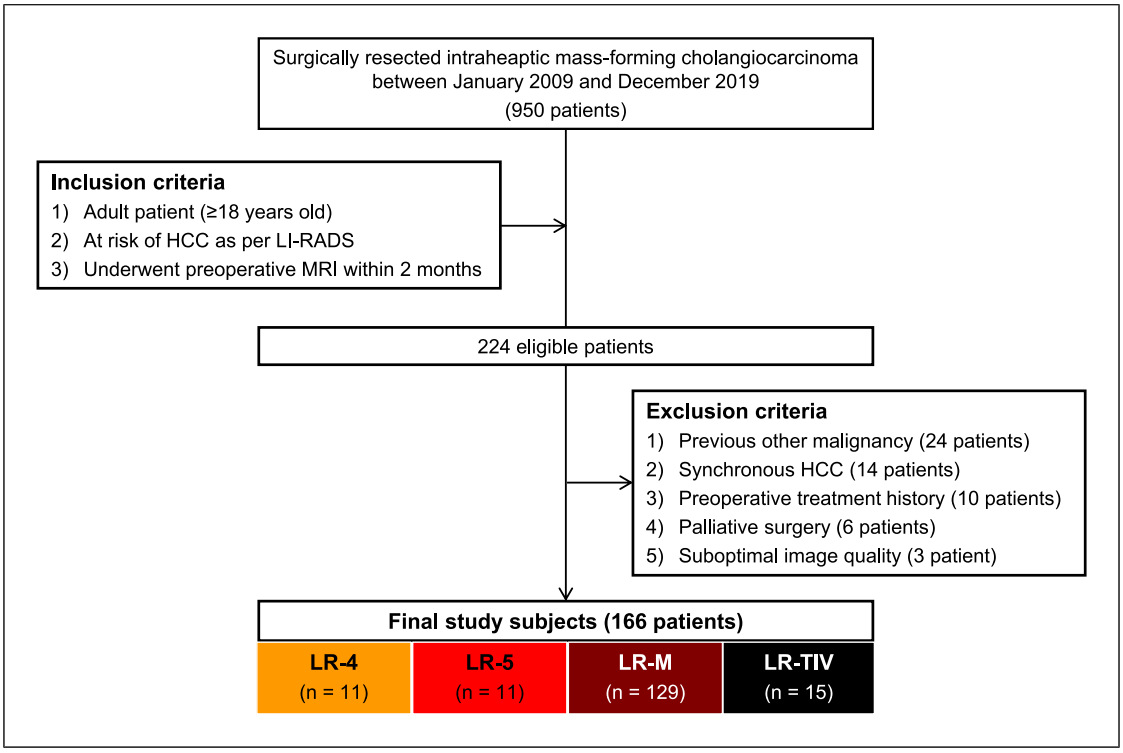


Fig. 1. Flow diagram of patient enrollment.

of the MRI techniques are summarized in the online supplementary methods (for all online suppl. material, see https://doi.org/10.1159/000539794).

Image Analysis and LI-RADS Category Assignment

Three board-certified abdominal radiologists, with 8, 5, and 3 years of hepatic imaging experience respectively, independently conducted all image analyses. Because this study was mainly focused on the LI-RADS category of the index tumor and not on the diagnostic performance in tumor detection, the readers were informed that all patients had ICCAs, and were told the size and location of the index tumor to be analyzed. However, they were blinded to other clinical information. An investigator not involved in the image analysis prepared the list of index tumors. In cases with multiple tumors, the largest was chosen as the index tumor. If any interpretations demonstrated discrepancies among the readers, they re-evaluated the images together and reached a consensus.

Using the LI-RADS lexicon [21], major features, ancillary features, targetoid appearances (rim APHE, peripheral washout, delayed central enhancement, targetoid restriction, or targetoid TP/HBP appearance), and nontargetoid appearances (infiltrative appearance, marked diffusion restriction, necrosis or severe ischemia, or peritumoral bile duct dilatation) were analyzed. Then, the LI-RADS category was assigned to each tumor according to the LI-RADS v2018 criteria [8]. When any targetoid appearance was noted, the tumor was categorized as LR-M, unless the tumor was already categorized as LR-1, LR-2, or LR-TIV [8]. Tumors with nontargetoid LR-M features were assigned as LR-M if they did not meet the LR-5 criteria [8].

Pathologic Analysis

ICCA was pathologically diagnosed using the surgical specimen, in accordance with the 2019 WHO classification [22]. Tumor size, number, microvascular or macrovascular invasion, visceral peritoneal invasion, and extrahepatic organ invasion were evaluated, and pathologic T stage was determined according to the AJCC system. The presence of lymph node metastasis was also evaluated (pN0 or pN1 stage). In patients who did not undergo lymphadenectomy (Nx stage), the following composite reference standards were used to determine the N stage: development of suspicious regional lymph nodes on follow-up imaging tests such as CT, MRI, or positron emission tomography within 3 months after surgery was classified as N1; and absence of suspicious regional lymph nodes on follow-up imaging tests for at least 1 year after surgery was classified as N0 [23].

Outcome Assessment

After surgical resection, patients were followed every 1–3 months for the first 2 years and every 3–6 months thereafter, up to death or the last follow-up date (February 28, 2023). Routine follow-up included contrast-enhanced dynamic CT or MRI and assessment of serologic tumor markers. Patients with symptoms indicative of any extrahepatic metastasis were also evaluated by positron emission tomography, chest CT, brain CT or MRI, or bone scan. OS was defined as the interval between surgical resection and death, and recurrence-free survival (RFS) was defined as the interval between surgical resection and tumor recurrence or death.

Table 1. Clinical characteristics of the 166 patients included in this study

Variables	Value
Age, mean±SD, years	59±10
Sex, *n* (%)	
Men	114 (68.7)
Women	52 (31.3)
Liver disease, *n* (%)	
Liver cirrhosis	74 (44.6)
HBV infection	31 (18.7)
HCV infection	5 (3.0)
Alcohol	10 (6.0)
Steatosis	7 (4.2)
Unknown etiology	21 (12.7)
Chronic hepatitis B without cirrhosis	92 (55.4)
Tumor marker	
CA19-9, median (IQR)	19.1 (8.7, 65.8)
CEA, median (IQR)	2.1 (1.4, 3.5)
Type of surgery, *n* (%)	
Major hepatectomy	98 (59.0)
Minor hepatectomy	68 (41.0)
Resection margin status, *n* (%)	
R0	147 (88.6)
R1	16 (9.6)
R2	3 (1.8)
Perioperative chemotherapy, *n* (%)	
Neoadjuvant chemotherapy	0 (0.0)
Adjuvant chemotherapy	49 (29.5)
Tumor size, mean±SD, cm	4.9±2.9
Tumor grade, *n* (%)	
Well differentiated	11 (6.6)
Moderately differentiated	111 (66.9)
Poorly differentiated	38 (22.9)
Not available	6 (3.6)
Multiplicity, *n* (%)	15 (9.0)
Vascular invasion, *n* (%)	80 (48.2)
Pathologic T staging, *n* (%)	
T1a	58 (34.9)
T1b	13 (7.8)
T2	62 (37.3)
T3	28 (16.9)
T4	5 (3.0)
Pathologic N staging, *n* (%)	
N0	32 (19.3)
N1	27 (16.3)
Nx	107 (64.4)
N staging using the composite reference standard, *n* (%)	
N0	121 (72.9)
N1	34 (20.5)
Nx	11 (6.6)
8th AJCC stage (*n* = 155)[a]	
I	63 (40.6)
II	37 (23.9)
III	55 (35.5)

AJCC, American Joint Commission on Cancer; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range. [a]The 8th AJCC stage was classified after exclusion of patients with Nx (*n* = 11).

Statistical Analysis

Continuous variables are expressed as median and interquartile range [IQR] or mean and standard deviation and were compared using unpaired two-tailed *t* tests. Categorical variables are expressed as frequencies and percentages and were compared using Fisher's exact test or the χ^2 test. Inter-reader agreement on imaging features and LI-RADS categorization was evaluated using Fleiss kappa statistics.

OS and RFS were analyzed by the Kaplan-Meier method according to the AJCC stage (stage I, II, and III) and the LI-RADS category (LR-4/5, LR-M, and LR-TIV) and were pairwise compared with the log-rank test. The Cox proportional hazards regression model was used for univariable and multivariable analyses of factors related to OS and RFS after surgical resection, including demographic characteristics, tumor markers, tumor size, multiplicity, vascular invasion, AJCC stage, tumor grade, resection margin, and LI-RADS category. Factors found to differ significantly on univariable analyses were included in a multivariable analysis with a stepwise backward elimination method. Spearman correlation analysis was performed to assess the correlations between variables and evaluate whether multicollinearity effects among the covariates were present or not. In addition, OS and RFS were compared according to the number of significant factors (i.e., $n \leq 1$, $n = 2$, or $n \geq 3$). Statistical analyses were performed using SPSS (version 23.0, IBM), and a p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 224 potentially eligible patients, 57 were excluded, including 24 who had previous other malignancy, 14 who had synchronous HCC, 10 who had been treated before surgery, six who had undergone palliative surgical resection, and three with a suboptimal image quality. The study therefore included 166 patients (mean age, 59 ±

Table 2. Imaging characteristics of the 166 intrahepatic cholangiocarcinomas

Variables	Value
Lesion size, *n* (%)	
≤5.0 cm	112 (67.5)
>5.0 cm	54 (32.5)
Major features, *n* (%)	
Non-rim APHE	39 (23.5)
Non-peripheral washout	21 (12.7)
Enhancing capsule	7 (4.2)
TIV, *n* (%)	15 (9.0)
Targetoid appearance, *n* (%)	
Rim APHE	95 (57.2)
Peripheral washout	19 (11.4)
Delayed central enhancement	115 (69.3)
Targetoid restriction	63 (37.8)
Targetoid TP/HBP appearance	55 (33.1)
Nontargetoid LR-M features, *n* (%)	
Infiltrative appearance	26 (15.7)
Necrosis or severe ischemia	20 (12.0)
Marked diffusion restriction	70 (42.2)
Bile duct dilatation	61 (36.7)
Ancillary features, *n* (%)	
Corona enhancement	82 (49.4)
Fat in mass	1 (0.6)
Restricted diffusion	161 (97.0)
Mild-moderate T2 hyperintensity	159 (95.8)
TP hypointensity[a]	40 (27.8)
HBP hypointensity[a]	142 (98.6)
HBP hyperintensity[a]	1 (0.7)
LI-RADS category, *n* (%)	
LR-4 or 5	22 (13.3)
LR-M	129 (77.7)
LR-TIV	15 (9.0)

APHE, arterial phase hyperenhancement; TP, transitional phase; HBP, hepatobiliary phase; LR-4, LI-RADS category 4; LR-5, LI-RADS category 5; LR-M, LI-RADS category M; LR-TIV, LI-RADS category tumor-in-vein. [a]TP hypointensity, HBP hypointensity, and HBP hyperintensity were reviewed on hepatobiliary contrast-enhanced MR.

10 years) (Fig. 1), the clinical characteristics of whom are presented in Table 1. Ninety-two (55.4%) patients had chronic hepatitis B without cirrhosis, whereas 74 (44.6%) had liver cirrhosis. The median serum carbohydrate antigen 19-9 and carcinoembryonic antigen values were 19.1 U/mL (IQR, 8.7–65.8) and 2.1 ng/mL (IQR, 1.4–3.5), respectively.

Major hepatectomy was performed in 98 (59.0%) patients, and the surgical resection margin was negative in 147 (88.6%) patients. The mean tumor size was 4.9 ± 2.9 cm. Of the 166 included patients, 38 (22.9%) had a poorly-differentiated tumor grade, 15 (9.0%) had multiplicity, and 80 (48.2%) had vascular invasion in the pathologic analysis. Pathologic N staging was available for 59 (35.5%) patients who underwent lymphadenectomy, and N staging based on the composite reference standard was determined in 155 (93.4%) patients. According to the AJCC staging system, there were 63 (40.6%), 37 (23.9%), and 55 (35.5%) patients classified as stage I, II, and III, respectively. None received neoadjuvant chemotherapy, whereas 49 (29.5%) received adjuvant chemotherapy.

MRI Features and LI-RADS Categories

Hepatobiliary contrast agent (gadoxetic acid) was used as the MRI contrast in 144 (86.7%) patients. The median interval between MRI and surgery was 17 days (IQR, 6–24). In the 166 CCAs, the frequencies of the major features of non-rim APHE, washout, and enhancing capsule were 23.5%, 12.7%, and 4.2%, respectively (Table 2). Tumor-in-vein (TIV) was noted in 9.0% of 166 CCAs. Among the targetoid mass features, delayed central enhancement was the most common imaging feature (69.3%), followed by rim APHE (57.2%). Based on the results of the image analysis, 129 (77.7%) of 166 CCAs were categorized as LR-M (Fig. 2), 15 (9.0%) as LR-TIV, 11 (6.6%) as LR-4, and 11 (6.6%) as LR-5 (Fig. 3). The kappa values for inter-reader agreement ranged from 0.53 to 0.78 for major features, from 0.49 to 0.68 for targetoid mass features, and from 0.46 to 0.73 for nontargetoid mass features (online suppl. Table S1). Inter-reader agreement for LI-RADS category was substantial, with a kappa value of 0.74.

Survival Outcomes

Over a median follow-up period of 48 months (range, 2–166 months), 97 (58.4%) patients died, and 111 (66.9%) experienced tumor recurrence. Both median RFS and OS differed significantly according to AJCC stage ($p < 0.001$ for both) and LI-RADS category ($p < 0.001$ for both) (Fig. 4). In particular, patients with LR-M and LR-TIV showed worse RFS (median 18 vs. 51 months for LR-M, $p < 0.001$; 3 vs. 51 months for LR-TIV, $p < 0.001$) and OS (48 vs. 84 months for LR-M, $p < 0.001$; 14 vs. 84 months for LR-TIV, $p < 0.001$) compared to those with LR-4/5, respectively.

Univariable analysis found nine factors (sex, tumor size, multiplicity, vascular invasion, AJCC stage, tumor grade, resection margin, adjuvant chemotherapy, and LI-RADS category) associated with RFS and eight factors (sex, tumor size, multiplicity, vascular invasion, AJCC

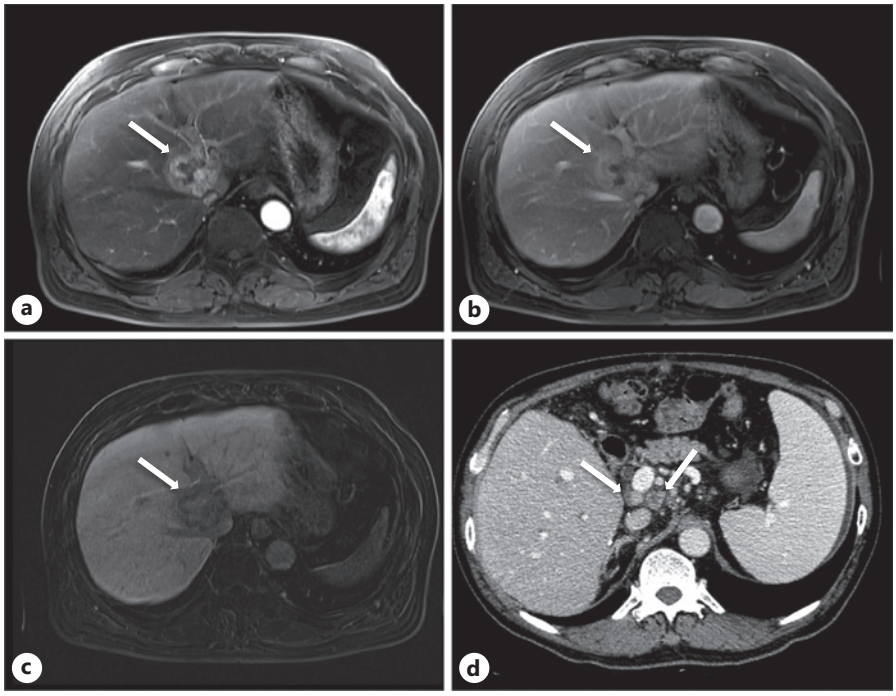


Fig. 2. Mass-forming intrahepatic cholangiocarcinoma in a 59-year-old man with chronic hepatitis B virus infection. **a–c** Gadoxetic acid-enhanced MRI shows a 4.5 cm rim arterial phase hyperenhancing mass (**a**, arrow) in segment IV with delayed central enhancement and peripheral washout (**b**, arrow). It also shows a targetoid hepatobiliary phase appearance (**c**, arrow). The lesion was TNM stage I (T1a, N0, M0), according to the AJCC 8th edition, whereas it was categorized into LI-RADS category M on gadoxetic acid-enhanced MRI. At 19 months after hepatic resection, the tumor recurred as lymph node metastases (**d**, arrows). This patient died 47 months after surgery.

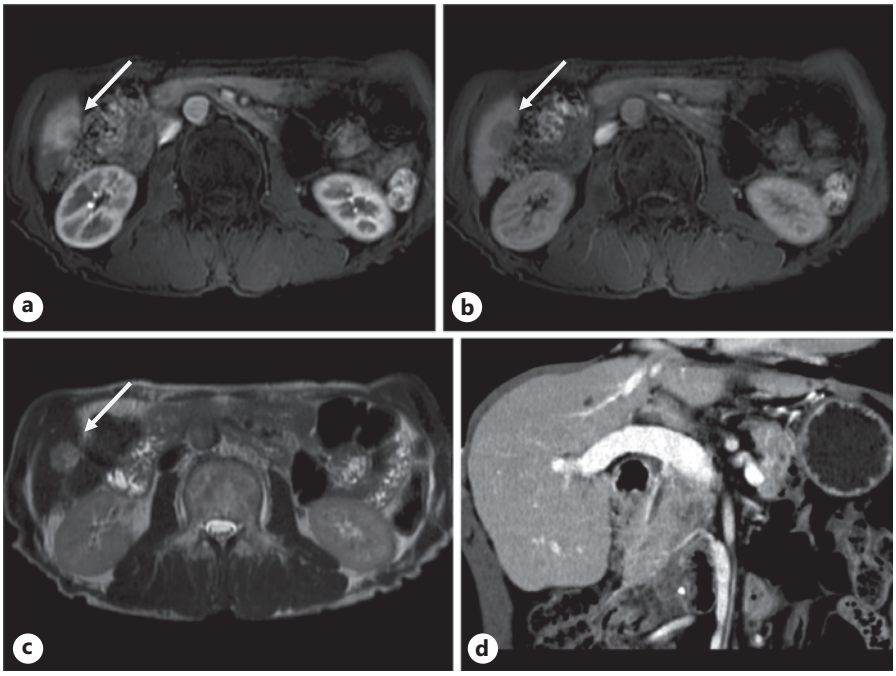
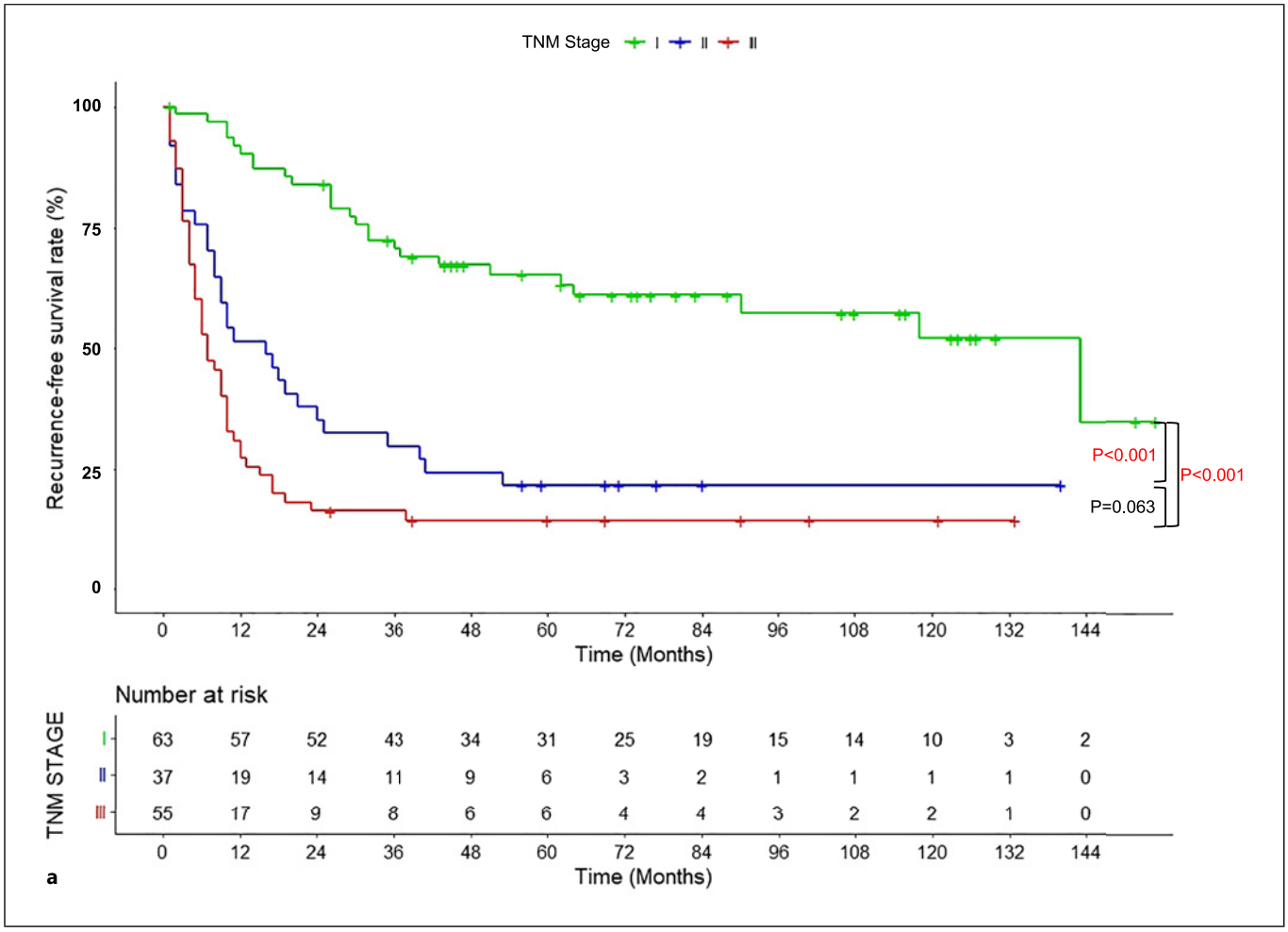


Fig. 3. Mass-forming intrahepatic cholangiocarcinoma in a 60-year-old man with chronic hepatitis B virus infection. **a–c** Gadoxetic acid-enhanced MRI shows a 1.9 cm non-rim arterial phase hyperenhancing mass (**a**, arrow) in segment VI with arterial corona enhancement and non-peripheral portal washout (**b**, arrow). It also shows a non-infiltrative appearance (**c**, arrow). The lesion was TNM stage I (T1a, N0, M0), according to the AJCC 8th edition, and was categorized into LI-RADS category 5 on gadoxetic acid-enhanced MRI. The tumor did not recur, and the patient survived for 55 months following the hepatic wedge resection (**d**, contrast-enhanced CT at 55 months after surgery).

stage, resection margin, adjuvant chemotherapy, and LI-RADS category) associated with OS (Table 3). Tumor size, multiplicity, and the presence of vascular invasion were excluded from the multivariable analysis to avoid multicollinearity effects among the covariates. Multivariable analysis showed that male sex (adjusted hazard ratio [aHR], 1.89; 95% confidence interval [CI], 1.20–2.96; $p = 0.006$), AJCC stage II or III (aHR, 3.90; 95% CI, 2.43–6.28; $p < 0.001$), and LR-M or LR-TIV (aHR, 2.86; 95% CI, 1.23–6.64; $p = 0.02$) were independent



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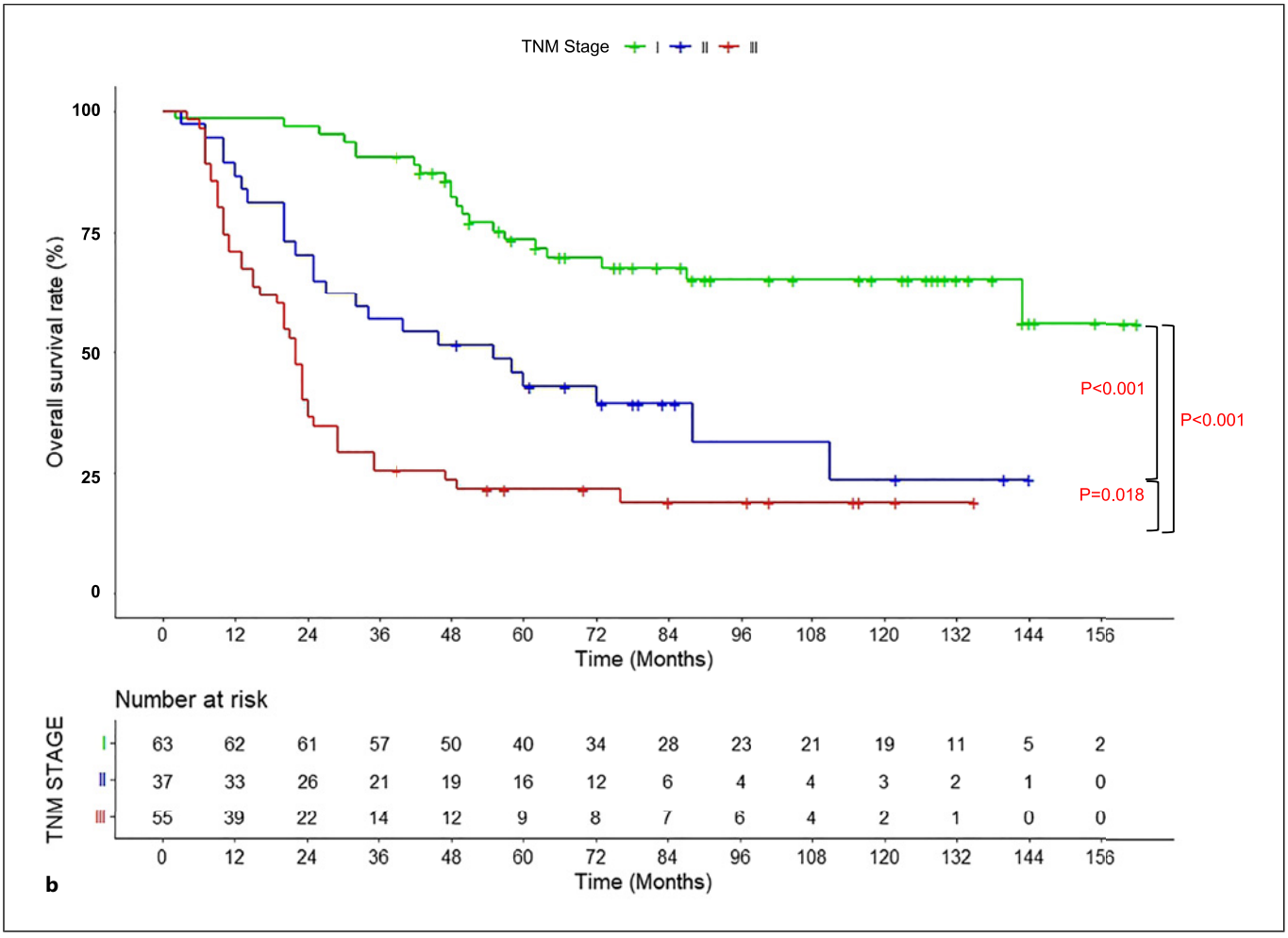
factors for worse RFS, and that male sex (aHR, 2.23; 95% CI, 1.35–3.69; $p = 0.002$), AJCC stage II or III (aHR, 3.29; 95% CI, 1.96–5.53; $p < 0.001$), positive resection margin (aHR, 1.91; 95% CI, 1.08–3.36; $p = 0.03$), and LR-M or LR-TIV (aHR, 3.18; 95% CI, 1.14–8.87; $p = 0.03$) were independent factors for worse OS.

Early tumor recurrence (<2 years) occurred in 80 patients (online suppl. Table S2). Of these 80 patients, there were 9, 24, and 47 patients classified as AJCC stage I, II, and III, respectively. According to LI-RAD category, there were 64 and 14 patients classified as LR-M and LR-TIV. In particular, eight of the nine AJCC stage I patients (88.9%) demonstrated LR-M features. The survival outcomes of the patients were also stratified by the number of significant factors: the median RFS and OS were significantly shorter in the group with three or more factors than in the group with one or no factor (8 vs. 62 months, $p < 0.001$ for RFS; 23 vs. 79 months, $p < 0.001$ for OS) and the group with two factors (8 vs. 29 months, $p = 0.001$ for RFS; 23 vs. 63 months, $p = 0.024$ for OS) (online suppl. Fig. S1).

Discussion

This study demonstrates that LI-RADS categorization of ICCA in patients at risk (liver cirrhosis or chronic hepatitis B) was an independent and significant prognostic factor predicting post-surgical RFS and OS, as was the AJCC staging system based on post-surgical pathology. In our study, ICCAs categorized as LR-4 or 5 showed a better prognosis than ICCAs with LR-M or TIV. Moreover, LI-RADS category could be useful to predict an early recurrence after the resection for ICCAs. The AJCC staging system is indispensable for cancer staging and prognosis



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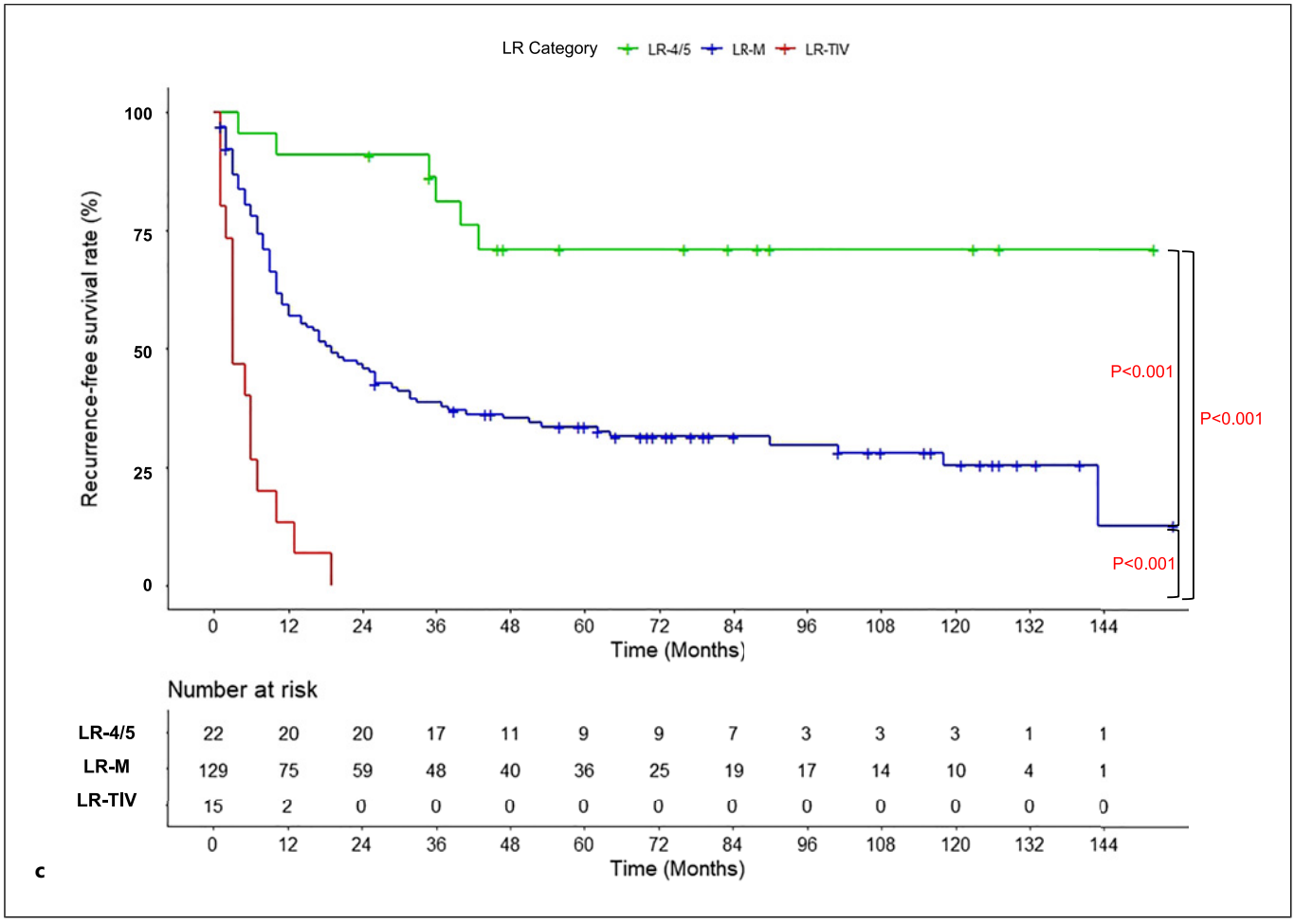
prediction, including in primary liver cancers [8]. However, considering the generally very poor prognosis for ICCAs and the fact that the AJCC staging is pathology-based, the identification of preoperative imaging phenotypes that may represent histologic prognostic indicators would be beneficial for guiding management [24]. Although a previous study showed that the degree of arterial enhancement, tumor size, and LN metastasis were significant factors for predicting RFS [25], the additional value of these imaging features in complementing the AJCC staging system remained unclear. This ambiguity suggests the need for further investigation into how these imaging characteristics might enhance the predictive accuracy of the AJCC staging criteria. Our study reveals that adding the LR-category to the AJCC staging system enhances prognostic accuracy in ICCA. This marks the first instance of combining the 8th AJCC pathologic staging with LI-RADS categories for improved prognosis prediction in ICCA.

For early-stage ICCA, surgical resection remains the primary curative treatment method. According to the BILCAP trial, adjuvant capecitabine for a 6-month period has been established as the standard of care, regardless of margin or nodal status [26]. While the role of neoadjuvant chemotherapy in ICCAs is still on debate, growing evidence suggests its potential in achieving longer OS [27, 28]. According to a multi-institutional review [29], 22% of patients who underwent resection for ICCA had very early recurrence (defined as within 6 months of surgery). Neoadjuvant therapy may help reduce the risk of early recurrence or progression by eliminating micrometastatic disease [30]. Identified risk factors for early recurrence include a larger tumor size, high tumor burden, KRAS mutation, vascular invasion, nodal involvement, the presence of cirrhosis, and elevated preoperative levels of tumor markers [31]. In our study, most of patients experiencing early recurrence exhibited



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LR-M or LR-TIV features (97.5%, 78 out of 80 cases). Additionally, a significant proportion of patients diagnosed with stage I cancer and encountering early recurrence showed LR-M or LR-TIV features (88.9%, 8 out of 9 cases). The LIRADS criteria, which assess tumor characteristics based on imaging phenotype, may serve as a potential predictive factor for early recurrence. Given the heterogeneity of ICCAs, incorporating these criteria alongside the AJCC criteria could be beneficial. However, to establish the efficacy and applicability of this approach, further validation via larger-scale studies is crucial.

In recent years, a few studies have shown that LI-RADS can be used for not only differential diagnosis, but also for potential prognostication for primary liver cancers including HCC, ICCA, and combined HCC-CCA [17, 18]. ICCA is a highly biologically-heterogeneous malignancy, influenced by a complex interplay of molecular, pathologic, and anatomic factors [1, 6, 32]. This intricate diversity necessitates distinct therapeutic approaches tailored to individual cases, which in turn significantly impacts therapeutic outcomes [8, 33]. However, the AJCC staging system lacks information about heterogeneity of ICCAs. The classification of LR categories enhances our understanding of the tumor's characteristics and aids in prognostic predictions. In our study, ICCAs categorized as LR-4 or 5 showed a better prognosis than ICCAs with LR-M or TIV, which is in accord with previous studies [17, 34]. In particular, LR-TIV was more strongly associated with poor prognosis. Because patients with TIV were more likely to have tumor vascular invasion and lymph node metastasis, the development of TIV could significantly reduce the survival rate [35]. Our study results are also in good agreement with a recent study by Hwang et al. [17], which reported that 17.7% of ICCAs were categorized as LR-4 or 5, and LR-M category and a tumor size >3 cm on MRI were independent factors for poor RFS. Other studies [25, 36] also reported that arterially hypervascular ICCAs were

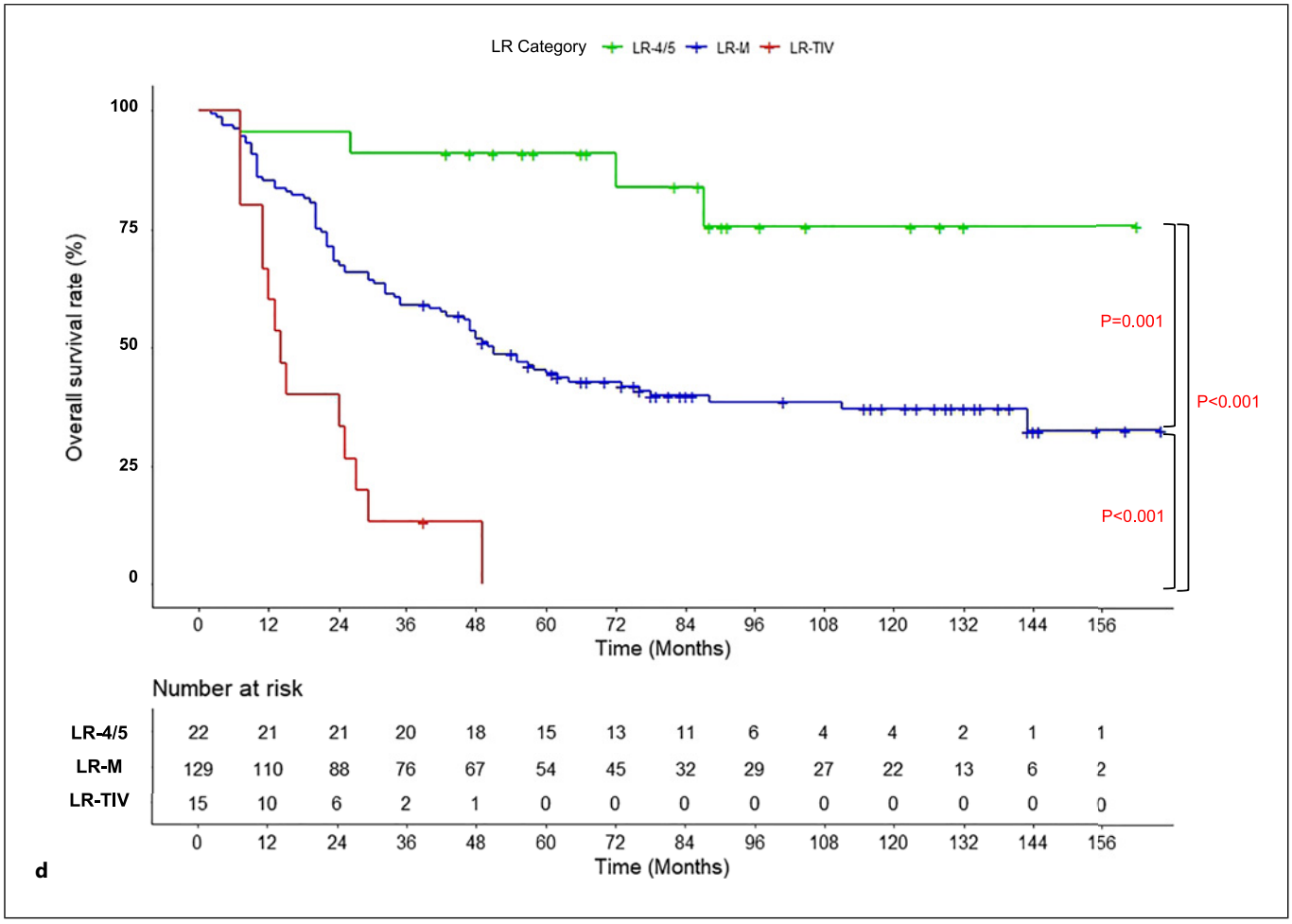

Fig. 4. Kaplan-Meier analyses of RFS and OS according to AJCC stage (**a**, **b**) and LI-RADS category (**c**, **d**).

more frequently small duct type ICCAs, occurred more commonly in chronic hepatitis B patients, and showed better post-surgical outcomes than hypovascular ICCAs [12, 16, 22, 33, 37]. Similarly, a study by Kierans et al. [38] reported that the clinical outcomes of HCCs and ICCAs presenting with LR-M features, including OS and disease-specific survival, were similar. Therefore, both the current study and previous studies provide strong evidence indicating that imaging phenotype is related to tumor biology in primary liver cancers. Moreover, our study additionally demonstrated that the LI-RADS category of ICCA determined on the basis of preoperative MRI was able to provide additional post-surgical prognostic value in conjunction with the AJCC guidelines for ICCA, with significant implications for both RFS and OS.

In our study, alongside LR-M or LR-TIV, factors like male sex, AJCC stage II or III, and a positive resection margin, independently indicated a poorer OS. A recent systematic review highlighted that female patients exhibited higher median OS and progression-free survival compared to their male counterparts [39]. The underlying causes for this superior prognosis in women remain uncertain. Differences in lifestyle, such as smoking, or differences in etiological factors, drug metabolism, and/or epigenetic changes, may contribute to the disparities in treatment response [32, 40]. A positive resection margin is a well-known strong independent predictor of poor outcome [41, 42]. According to one study [41], R1 resection was an independent predictor of poor survival in pN0 patients, whereas in pN1 patients, survival was similar between R0 and R1 resections. However, in this previous study assessing the effect of the resection margin, the presence of LN metastasis was not considered. In our study, resection margin was a significant factor for OS but not for RFS. A method that integrates staging, resection

Table 3. Univariable and multivariable analyses of factors affecting RFS and OS

Variables	RFS				OS			
	univariable analysis		multivariable analysis		univariable analysis		multivariable analysis	
	HR (95% CI)	*p* value	adjusted HR (95% CI)	*p* value	HR (95% CI)	*p* value	adjusted HR (95% CI)	*p* value
Age (≥60)	0.81 (0.56, 1.18)	0.81			1.01 (0.68, 1.50)	0.98		
Sex (male)	1.80 (1.17, 2.78)	0.008	**1.89 (1.20, 2.96)**	**0.006**	2.03 (1.25, 3.30)	0.004	**2.23 (1.35, 3.69)**	**0.002**
Liver disease								
HBV infection	0.90 (0.60, 1.36)	0.90			0.87 (0.56, 1.34)	0.52		
Liver cirrhosis	1.18 (0.80, 1.74)	0.40			1.36 (0.90, 2.05)	0.15		
Tumor markers								
CA19-9 (≥37 U/mL)	1.41 (0.92, 2.17)	0.12			1.48 (0.94, 2.34)	0.09		
CEA (≥5 ng/mL)	1.03 (0.55, 1.94)	0.93			1.27 (0.67, 2.39)	0.47		
Tumor size (5 cm)[a]	2.74 (1.87, 4.02)	<0.001			2.46 (1.64, 3.69)	<0.001		
Multiplicity[a]	2.81 (1.59, 4.97)	<0.001			2.05 (1.09, 3.86)	0.03		
Vascular invasion (present)[a]	3.68 (2.48, 5.47)	<0.001			3.64 (2.38, 5.56)	<0.001		
8th AJCC stage (II or III)	4.49 (2.82, 7.17)	<0.001	**3.90 (2.43, 6.28)**	**<0.001**	4.08 (2.46, 6.75)	<0.001	**3.29 (1.96, 5.53)**	**<0.001**
Tumor grade (poorly differentiated)	1.69 (1.11, 2.59)	0.015	1.07 (0.68, 1.69)	0.76	1.45 (0.92, 2.27)	0.11		
Resection margin (R1 or R2)	2.17 (1.30, 3.62)	0.003	1.58 (0.93, 2.70)	0.09	2.48 (1.43, 4.27)	0.001	**1.91 (1.08, 3.36)**	**0.03**
Adjuvant chemotherapy	1.68 (1.13, 2.50)	0.01	0.86 (0.56, 1.33)	0.50	1.56 (1.02, 2.37)	0.04	0.91 (0.57, 1.44)	0.68
LI-RADS category (LR-M or LR-TIV)	4.28 (1.88, 9.75)	0.001	**2.86 (1.23, 6.64)**	**0.02**	5.06 (1.86, 13.77)	0.002	**3.18 (1.14, 8.87)**	**0.03**
LR-M versus LR-4/5	3.89 (1.70, 8.89)	0.001			4.58 (1.68, 12.52)	0.003		
LR-TIV versus LR-4/5	18.04 (6.82, 47.72)	<0.001			16.69 (5.39, 51.65)	<0.001		

AJCC, American Joint Commission on Cancer; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus; HR, hazard ratio; LR-M, LI-RADS category M; LR-TIV, LI-RADS category tumor-in-vein; RFS, recurrence-free survival; OS, overall survival. Factors with statistical significance are expressed in bold. [a]Because pathologic TNM stage was based on tumor size, multiplicity, and the presence of vascular invasion, these features were excluded from the multivariable analysis to avoid a multicollinearity effect among the covariates.

margin, and imaging characteristics should be devised and validated to ascertain the significance of each prognostic element.

This study has several limitations. First, there may be a selection bias due to its retrospective nature. Patients who had hepatic resection for curative purpose were included,

whereas patients who could not undergo surgery were excluded, with the reasons for not undergoing surgery probably being advanced stage or poor liver function. Second, patients who had a high risk for HCC were included, with the intention of applying the LI-RADS categorization. Furthermore, the study population was recruited from an area with endemic hepatitis B virus infection. Therefore, the patients included in our study may not be representative of the general population with ICCA. Third, while agreement for LI-RADS categorization was substantial (kappa = 0.74), it was not perfect. In particular, the agreement of peripheral washout and marked diffusion restriction was not good. Considering that LI-RADS categorization is determined by qualitative assessments, our results should be understood with consideration of this limitation. Last, because of the retrospective nature of the study, several different MRI scanners, protocols, and contrast media were used. Last, a subtype re-classification according to pathology (small duct type or large duct type) was not performed and could not be used as a clinicopathologic factor in this study.

In conclusion, the MRI-based preoperative LI-RADS categorization provides additional post-surgical prognostic value beyond the AJCC guidelines for ICCA, with significant implications for both RFS and OS. Our results underscore the importance of incorporating LI-RADS categorization alongside the traditional AJCC staging system to enhance prognostic assessment and provide information for clinical decision-making for patients with ICCA.

Statement of Ethics

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2206-226-1339), Asan Medical Center (IRB No. 2022-1215), Konkuk University Medical Center (IRB No. 2022-07-003). The need for informed consent was waived by the Institutional Review Board of Seoul National University Hospital, Asan Medical Center, and Konkuk University Medical center.

Conflict of Interest Statement

Corresponding author, Jeong Min Lee, is an editorial board member of Liver Cancer. Jeong Min Lee received grant from Samsung Medison, Siemens Healthineers, Philips Healthcare, GE Healthcare, Bayer, Guerbet, CMS, Canon Healthcare, and Dongkuk Pharma; payment for lectures from Samsung Medison, GE Healthcare, Philips Healthcare, and Starmed, outside the submitted work. The other authors have no conflicts of interest to declare.

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Author Contributions

Sungeun Park contributed to acquisition of data, analysis and interpretation of data, and drafting the manuscript. Boyeon Koo contributed to acquisition of data, analysis and interpretation of data, and drafting the manuscript. Boryeong Jeong contributed to analysis and interpretation of data. Sang Hyun Choi contributed to study concept and design, study supervision, analysis and interpretation of data, and drafting the manuscript. Jeong Min Lee contributed to study concept and design, study supervision, and critical revision of the manuscript for important intellectual content. All authors contributed substantially to critically reviewing or revising the manuscript for important intellectual content and approved the final manuscript.

Data Availability Statement

The datasets analyzed during the current study are not publicly available due to the datasets containing information that could compromise the privacy of research participants but are available from the corresponding author [J.M.L. or S.H.C.] on reasonable request.

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