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Outcomes and Role of Lymphadenectomy in Hypervascular Intrahepatic Cholangiocarcinoma Based on CT-Vascularity

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ABSTRACT

Background: This study aimed to evaluate the outcomes and role of lymphadenectomy in hypervascular intrahepatic cholangiocarcinoma (ICC) quantified using the arterial phase of contrast-enhanced computed tomography (CT).

Methods: Consecutive patients with mass-forming (MF) or predominantly MF type ICC who underwent surgical resection from 2000 to 2019 were retrospectively analyzed. Using the image of the late arterial phase, CT-vascularity was calculated by dividing the CT value of the tumor (Hounsfield units) with that of the liver parenchyma. According to the CT-vascularity, patients were divided into hypervascular (CT-vascularity > 1) and non-hypervascular (CT-vascularity ≤ 1) groups. Clinicopathologic features and survival outcomes were compared between the two groups. Further, the prognostic impact of lymphadenectomy was assessed in the hypervascular group.

Results: Of the 135 patients with MF-ICC, the hypervascular group, and non-hypervascular group comprised 47 (34.8%) and 88 patients (65.2%), respectively. The hypervascular group displayed clinical features typically associated with hepatocellular carcinoma (HCC) (i.e., viral hepatitis or history of HCC) and less aggressive tumor characteristics such as lower proportions of regional lymph node metastasis. The overall survival (OS) and recurrence-free survival (RFS) of the hypervascular group were significantly better than those of the non-hypervascular group (all, $p < 0.001$), and these results were retained after adjusting for known prognostic factors. Further, implementation of lymphadenectomy was not associated with benefit for OS and RFS in the hypervascular group ($p = 0.819$, $p = 0.912$).

Conclusion: Hypervascular ICC itself represents a favorable prognosis, and there is a possibility of omitting lymphadenectomy in this subgroup.

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; IG, intraductal growth; LN, lymph node; MF, mass-forming; MRI, magnetic resonance imaging; OS, overall survival; PET, positron emission tomography; PI, periductal infiltrative; RFS, recurrence-free survival; ROI, region of interest.

Previous Presentation: This paper is not presented elsewhere.

1 | Introduction

Intrahepatic cholangiocarcinoma (ICC) accounts for 5%–10% of primary liver cancers and is the second most common primary liver malignancy in adults after hepatocellular carcinoma (HCC) [1–3]. Surgical resection is currently considered the first-line treatment for resectable ICC [4]. In addition to prioritizing R0 resection, lymphadenectomy, which may help determine accurate tumor staging, provide local control of the regional lymph node area, or possibly eradicate occult lymph node metastases, should be considered for ICC surgery [5, 6]. Despite its importance, some studies have reported potential risks of complications with lymphadenectomy [7, 8], or adequacy of lymphadenectomy might not be fully achieved in minimally invasive surgery [9, 10]. In this context, the omission of lymphadenectomy should be debated, and its candidate may be the low-risk group of lymph node (LN) metastasis, given the role of lymphadenectomy.

It has been reported that some cases of ICC show a hypervascular appearance in the arterial phase of contrast-enhanced computed tomography (CT), and such cases (so-called, hypervascular ICC) represent a better prognosis compared to the non-hypervascular ICC [11, 12]. Hypervascular ICC seemed to be associated with a low risk of LN metastasis [13]. Indeed, it should be noted that hypervascular ICC can be radiographically misdiagnosed as HCC [14]; consequently, a significant number of patients with hypervascular ICC may have been incidentally omitted for lymphadenectomy. These data might allow us to investigate the prognostic value of lymphadenectomy in patients with hypervascular ICC even in a single institution with consistent surgical policies.

Therefore, the objective of this study was (i) to characterize and evaluate the outcomes of hypervascular ICC and (ii) to assess the prognostic impact of lymphadenectomy in these patients. In this study, vascularity was quantified using the arterial phase of contrast-enhanced CT to emphasize objectivity [15, 16].

2 | Patients and Methods

2.1 | Study Design

This study was a retrospective, single-center, observational study. The protocol was approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (approval code. R3809), and informed consent was considered to have been obtained from patients using an opt-out method.

2.2 | Patients

Data of patients with ICC who underwent surgical resection at the Department of Surgery, Kyoto University, Japan between 2000 and 2019, were retrieved from institutional databases and electronic medical records. Because several cases showed the combined history of HCC and ICC, we conducted a re-review of different databases. Inclusion criteria were patients with histologically confirmed mass-forming (MF) type or predominantly MF type (i.e., MF + periductal infiltrative [PI] type or MF + intraductal growth [IG] type) ICC. Patients with multiple or para-aortic LN metastasis, who were judged as operable or benefited from resection, were included in this study. Meanwhile, those with bulky para-aortic LN metastasis detected on CT, magnetic resonance imaging (MRI), or ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging were considered to be in unresectable status [17] and were not included in this study. Exclusion criteria were: (i) preoperative CT data not available; (ii) patients who had previously undergone at least one surgical resection for ICC; (iii) patients with histologically other types of ICC (PI type or IG type), and (iv) patients with apparent distant metastasis other than para-aortic LN metastasis.

The clinical and pathological features of the primary tumor were assessed by at least two dedicated radiologists and hepatobiliary pathologists, respectively. Definitions of follow-up protocols, and recurrence criteria were reported earlier [18–20]. Treatments after recurrence were determined during the multidisciplinary team conference. The last follow-up was updated in December 2022.

2.3 | CT Image Acquisition and Categorization

Abdominal CT scans were conducted using multidetector-row CT scanners (Aquilion 16, Aquilion 64, Aquilion ONE, and PRIME; Canon Medical Systems, Tochigi, Japan) with 16-, 64-, or 320-detector configurations. Contrast media with 600 mg iodine/kg body weight were injected in 30 s via an automatic injector. All CT images were viewed on a multimodal image archiving and communication system (Centricity Universal Viewer Zero Footprint, GE Healthcare, Tokyo, Japan). The late arterial phase was assessed as the hepatic arterial phase, as it is useful for detecting hypervascular hepatic neoplasms [13]. The CT image was captured at a fixed delay of 35 s after the start of contrast agent injection.

To reduce the bias of preoperative diagnosis, this study emphasized to objectively identify hypervascular ICC using CT-vascularity reported by a Japanese group [15, 16]. The mean CT values (Hounsfield units, HU) of the region of interest (ROI) in the late arterial phase were used to assess enhancement. The tumor shape was precisely outlined, and the mean CT value was measured on three axial slices, including the maximum tumor size. To measure non-tumor liver parenchyma CT values, regions were selected in the right (2 regions) and left liver lobes (1 region), and mean CT values were calculated (Figure S1). The CT ratio was determined by dividing the mean tumor CT value by the mean non-neoplastic liver parenchyma CT value. Regions with fatty changes, blood vessels, cysts, or artifacts were avoided during ROI selection. Hypervascular ICC was defined as CT-vascularity equal to or greater than 1, while non-hypervascular ICC had CT-vascularity less than 1 [15, 16]. Three independent surgeons (X.L, T.Y, and Y.H) assessed CT-vascularity, and its validity was compared with diagnoses by radiologists. Two blinded radiologists (K.S and H.I) categorized patients into hyper-enhancement, rim-enhancement, or hypo-enhancement groups following Fujita et al.'s criteria [13].

2.4 | Operative Procedures and Treatment Strategy

The surgical treatment strategy for ICC in our institution was previously reported [18–20]. The surgical indication is determined comprehensively considering the patient's performance status; functional reserve of the liver; and the future live remnant volume. For ICC surgery, we routinely perform sampling of para-aortic LNs (station 16), and lymphadenectomy around the hepatoduodenal ligament (station 12), posterior pancreatic region (station 13), and common hepatic artery (station 8). In the left-sided tumors, lymphadenectomy around the area of the lesser curvature of the stomach (stations 1, 3, and 7) was performed before 2009, and currently, our practice is sampling the regional LNs of these areas to avoid delayed gastric emptying. The criteria of omitting lymphadenectomy were as follows; (i) patients with cirrhotic liver, (ii) elderly patients with low-performance status, and (iii) patients with low risk of LN metastasis. ICC with a very low risk of LN metastasis was defined as solitary, peripheral type, clinical node-negative, and ≤ 3 cm tumor based on our report and previous study [21, 22]. Meanwhile, biliary and/or vascular resection and reconstruction were planned when necessary.

2.5 | Statistical Analysis

Categorical variables were presented as numbers and percentages, compared using the chi-square test (or Fisher's exact test if necessary). Continuous variables were expressed as median (range) and compared using the Mann-Whitney *U* test. Overall survival (OS) measured from surgery to death or follow-up completion, recurrence-free survival (RFS) measured from surgery to death/recurrence or follow-up completion. Kaplan-Meier analysis estimated survival outcomes, compared via the log-rank test, and expressed as actuarial values. Multivariate analysis, using the Cox hazard model for variables with $p < 0.05$ in univariate analysis, identified independent prognostic factors for OS and RFS. In cases of collinearity, choices were based on *p*-values and clinical reasoning. A *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed using JMP version 16.1 software (SAS Institute, Cary, NC, USA).

3 | Results

A total of 170 surgical resections for ICC were performed at Kyoto University Hospital during the study period. According to the research criteria, 135 patients were enrolled in this study. Of these, 47 patients were recruited as the hypervascular group (34.8%) and 88 patients (65.2%) were the non-hypervascular group (Figure 1).

3.1 | Clinical Characteristics According to the CT-Vascularity

First, we assessed the association of CT-vascularity and findings by radiologists as shown in Figure S2. As expected, radiologists-judged hypervascular ICC was significantly associated with higher CT-vascularity; meanwhile, radiologists-judged rim-enhancement ICC and hypovascular ICC were associated with lower CT-vascularity ($p < 0.001$).

The baseline demographic and clinicopathological data of the study population are shown in Table 1. Compared with the non-hypervascular group, the hypervascular group included higher proportions of patients with preoperatively diagnosed as HCC (27.7% vs. 5.7%, hypervascular vs. non-hypervascular groups, respectively, $p = 0.001$), those with previous history of HCC (14.9% vs. 3.4%), and those with viral hepatitis (29.8% vs. 14.8%). Lower levels of preoperative serum CA19-9 levels ($p < 0.001$) were found in the hypervascular group.

In the preoperative setting, implementation of lymphadenectomy in the hypervascular group was less frequent than in the

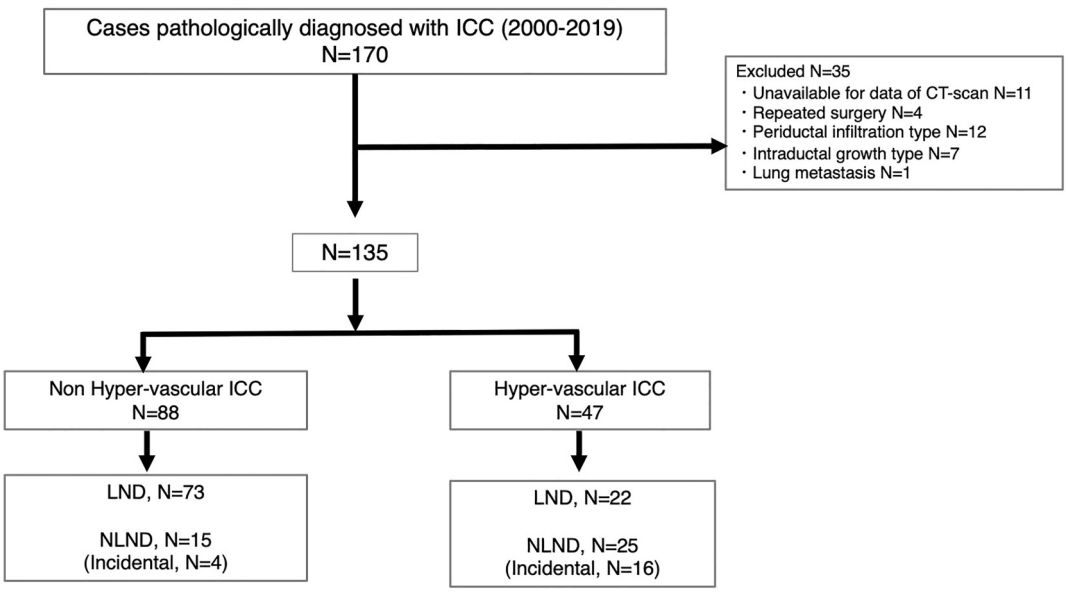


FIGURE 1 | Flow chart of the study.

TABLE 1 | Clinical variables and tumor characteristics in patients with ICC according to the CT-vascularity.

Variables	CT-vascularity		*p* value
	Non-hypervascular *N* = 88	Hypervascular *N* = 47	
Clinical findings			
Age, years, median (range)	68 (62–73.8)	70 (63–74)	0.330
Sex, male, *n* (%)	54 (61.4)	30 (63.8)	0.778
Preoperative diagnosis, *n* (%)			0.001*[a]
ICC	80 (90.9)	31 (66)	
HCC	5 (5.7)	13 (27.7)	
Meta	2 (2.3)	1 (2.1)	
Others	1 (1.1)	2 (4.3)	
HBV/HCV (+), *n* (%)	13 (14.8)	14 (29.8)	0.038*
History of HCC, *n* (%)	3 (3.4)	7 (14.9)	0.032*[a]
Child Pugh-grade B, *n* (%)	5 (5.7)	1 (2.1)	0.323[a]
CA19-9, U/mL, median (range)	67.8 (20.5–264.8)	26.6 (12.9–45.5)	< 0.001*
T-Bil, mg/dL, median (range)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.961
ALB, g/dL, median (range)	4.1 (3.8–4.3)	4.1 (3.8–4.3)	0.888
Surgical procedures			
Major LR, *n* (%)	75 (85.2)	31 (66)	0.009*
Laparoscopic LR	5 (5.7)	6 (12.8)	0.190[a]
Lymphadenectomy, *n* (%)	73 (83.0)	22 (46.8)	< 0.001*
Vascular reconstruction, *n* (%)	13 (14.8)	1 (2.1)	0.034*[a]
Biliary reconstruction, *n* (%)	24 (27.3)	2 (4.3)	0.001*
Postoperative findings			
Tumor size, cm, median (range)	4.2 (3.1–5.9)	3.5 (2.5–5.9)	0.297
Poorly differentiation, *n* (%)	16 (18.2)	9 (19.1)	0.890
MF + PI type, *n* (%)	12 (13.6)	0	0.008*[a]
LN metastasis, *n* (%)			< 0.001*
N0	39 (44.3)	21 (44.7)	
N1	35 (39.8)	1 (2.1)	
NX	14 (15.9)	25 (53.2)	
Para-aortic LN metastasis, *n* (%)			< 0.001*
Absent	66 (75.0)	22 (46.8)	
Present	8 (9.1)	0	
Unknown	14 (15.9)	25 (53.2)	
Microvascular invasion, *n* (%)	51 (58)	19 (40.4)	0.052
Major biliary invasion, *n* (%)	21 (23.9)	1 (2.1)	0.001*
Multiple tumors	20 (22.7)	10 (21.3)	0.847
Negative surgical margin, *n* (%)	73 (83.0)	41 (87.2)	0.513
Adjuvant chemotherapy, *n* (%)			0.352[a]
GEM	38 (43.2)	17 (36.2)	
S-1	10 (11.4)	2 (4.3)	
GEM + S-1	3 (3.4)	2 (4.3)	

Abbreviations: ALB, albumin; CA19-9, carbohydrate antigen 19-9; CT, computed tomography; GEM, gemcitabine; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma; LN, lymph node; LR, liver resection; Meta, metastatic liver cancer; MF, mass-forming; PI, periductal infiltrative; S-1, tegafur/gimeracil/oteracil; T-Bil, total bilirubin.

[a]Fisher exact test.

* $p < 0.05$ is a significant difference.

non-hypervascular group (46.8% vs. 83.0%). Intraoperative vascular reconstruction (2.1% vs. 14.8%), biliary reconstruction (4.3% vs. 27.3%), and major liver resection (66.0% vs. 85.2%) were performed less frequently in the hypervascular group than in the non-hypervascular group.

The postoperative results found that compared with the non-hypervascular group, the hypervascular group had less frequency of pathological MF + PI type (0% vs. 13.6%), and major biliary invasion (2.1% vs. 23.9%). Notably, the hypervascular group had significantly less frequency of pathological LN metastasis (2.1% vs. 39.8%), and para-aortic LN metastasis (0% vs. 9.1%)

3.2 | Long-Term Outcomes

Median follow-up times was 41.7 months. The median OS was 47.6 months, and the 1-, 3-, and 5-year survival rates were 84.4%, 56.1%, and 46.3%, respectively. Meanwhile, the median RFS was 16.0 months, and the corresponding 1-, 3-, and 5-year RFS rates were 53.9%, 30.7%, and 27.3%, respectively.

Patients in the hypervascular group had better OS and RFS compared with the non-hypervascular group (Figure 2A,B). The median OS and 1-, 3-, and 5-year survival rates of the hypervascular group and the non-hypervascular group were not reached, 97.9%, 87.1%, 79.5% and 28.1 months, 77.3%, 39.8%, 29.0%, respectively ($p < 0.001$). Meanwhile, the median RFS and 1-, 3-, and 5-year survival rates of the hypervascular group and the non-hypervascular group were 73.0 months, 72.1%, 54.6%, 54.6%, and 10.2 months, 44.3%, 18.2%, 13.2%, respectively ($p < 0.001$).

To further assess the prognostic independence of hypervascular ICC, the Cox regression analyses were performed (Table 2). Univariate and multivariate analyses showed that hypervascular ICC was identified as an independent prognostic factor for OS and RFS.

3.3 | Lymphadenectomy Was Not Associated With Benefits in Patients With Hypervascular ICC

The impact of lymphadenectomy on long-term outcomes in patients with hypervascular ICC was assessed. Of the 47 patients, 22 patients (46.8%) underwent lymphadenectomy (LND group) and the remaining 25 patients (53.2%) did not undergo lymphadenectomy (NLND group). Lymphadenectomy was incidentally omitted in the 16 patients (64.0%). Clinicopathological features are shown in Table S1. In this setting, the median OS was not reached and 152.4 months, in the LND and the NLND groups, respectively ($p = 0.819$). Regarding RFS, the median RFS was 73.0 and 127.8 months, respectively ($p = 0.912$). There was no significant difference in OS and RFS between the two groups (Figure 3). On multivariate analysis, tumor multiplicity was the only independent predictor of RFS (Table S2).

4 | Discussion

This study characterized the outcomes of hypervascular ICC quantified using routine CT images and evaluated the impact of lymphadenectomy for these patients at a Japanese hepatobiliary center. The hypervascular group displayed clinical features typically associated with HCC (i.e., viral hepatitis or history of HCC) and less aggressive tumor characteristics, particularly a lower incidence of LN metastasis. Importantly, hypervascular ICC demonstrated significantly better OS and RFS compared to non-hypervascular ICC, as demonstrated in univariate and multivariate analyses. Further, in the subgroup of patients with

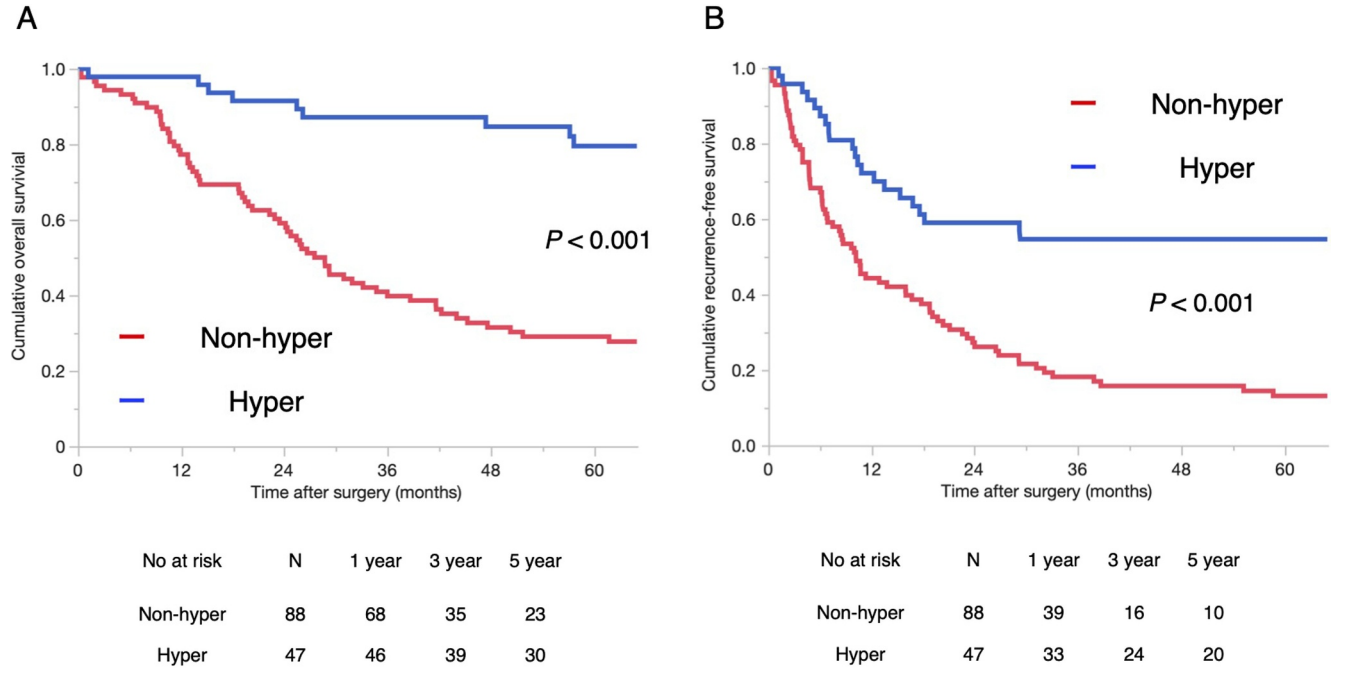
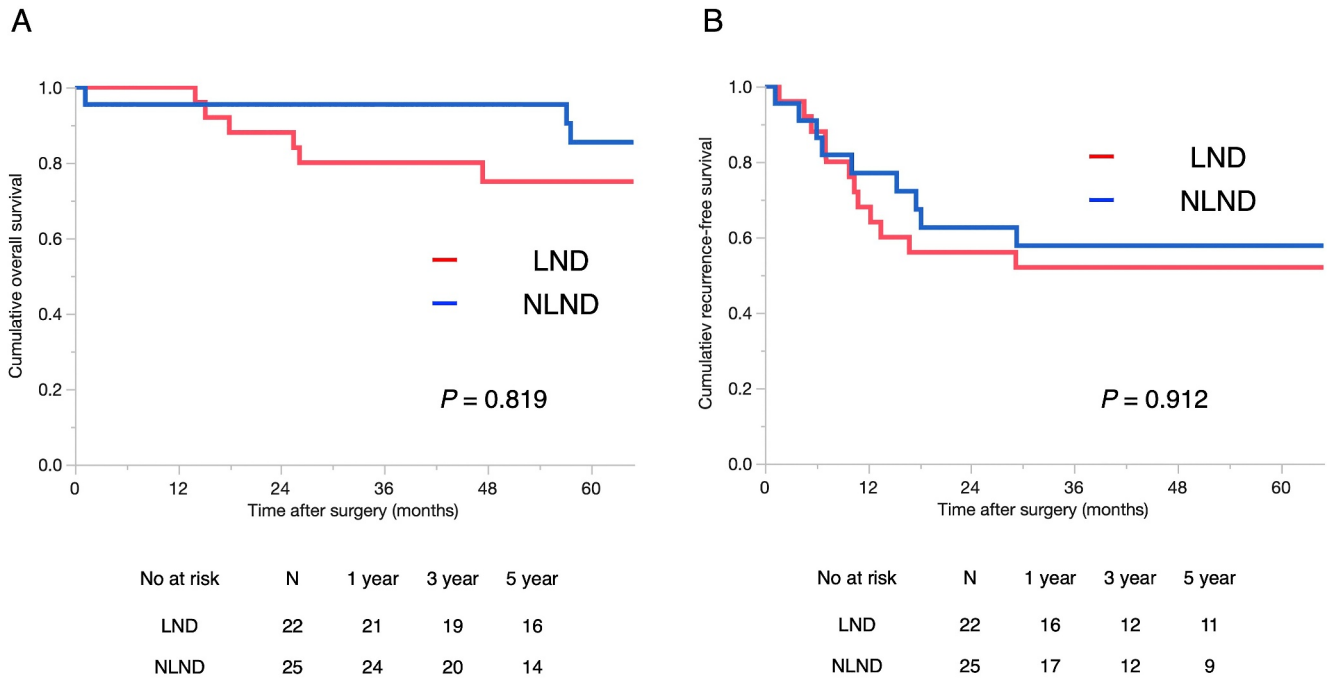


FIGURE 2 | Survival outcomes stratified by CT-vascularity in patients with ICC after surgery. (A) Overall survival; (B) recurrence-free survival.

TABLE 2 | Cox proportional hazard model of overall survival and recurrence-free survival in patients with ICC after liver resection.

	Overall survival						Recurrence-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age > 70 years	0.76	0.50–1.17	0.211				0.67	0.45–0.99	**0.044***	1.03	0.67–1.60	0.887
Male	0.92	0.60–1.41	0.701				1.03	0.69–1.53	0.889			
Tumor size > 3 cm	1.54	0.96–2.48	0.073				1.54	1.00–2.37	**0.049***	1.23	0.72–2.09	0.449
CA19-9 > 37 U/mL	2.18	1.42–3.36	**< 0.001***	1.60	1.01–2.55	**0.046***	1.82	1.22–2.72	**0.003***	1.35	0.88–2.08	0.166
Poor differentiation	1.73	1.04–2.86	**0.034***	1.19	0.69–2.06	0.530	2.11	1.31–3.41	**0.002***	1.72	1.03–2.87	**0.039***
LN metastasis			**< 0.001***			0.201			**< 0.001***			0.533
N0	1			1			1			1		
N1	2.73	1.69–4.41	**< 0.001***	1.50	0.90–2.49	0.121	2.41	1.52–3.81	**< 0.001***	1.26	0.76–2.10	0.373
NX	0.92	0.52–1.60	**0.754**	1.56	0.81–2.99	0.184	1	0.61–1.64	0.998	1.34	0.70–2.56	0.376
Microvascular invasion	1.80	1.18–2.74	**0.007***	1.32	0.82–2.12	0.251	1.52	1.03–2.25	**0.035***	1.12	0.73–1.73	0.598
Major biliary invasion	2.19	1.30–3.67	**0.003***	1.72	0.99–2.99	0.056	1.42	0.86–2.35	0.167			
Negative surgical margin	1.82	1.08–3.07	**0.024***	2.13	1.22–3.73	**0.008***	1.87	1.14–3.06	**0.013***	1.69	1.01–2.85	**0.048***
Multiple tumors	2.12	1.33–3.37	**0.002***	1.79	1.06–3.03	**0.028***	2.93	1.88–4.56	**< 0.001***	2.22	1.32–3.72	**0.002***
Hypervascular ICC	0.25	0.14–0.43	**< 0.001***	0.26	0.13–0.50	**< 0.001***	0.38	0.24–0.60	**< 0.001***	0.39	0.22–0.68	**0.001***

Abbreviations: CA19-9, carbohydrate antigen 19-9; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; LN, lymph node.
* $p < 0.05$ is a significant difference.



No at risk	N	1 year	3 year	5 year
LND	22	21	19	16
NLND	25	24	20	14

No at risk	N	1 year	3 year	5 year
LND	22	16	12	11
NLND	25	17	12	9

FIGURE 3 | Overall survival (A) and recurrence-free survival (B) between LND and NLND groups in patients with hypervascular ICC. LND, lymphadenectomy; NLND, non-lymphadenectomy.

hypervascular ICC, lymphadenectomy was not associated with benefit.

For ICC surgery, lymphadenectomy should be considered. However, the potential risks of complications associated with lymphadenectomy [7, 8] and its inadequacy in minimally invasive surgery [9, 10] suggest the need to identify candidates for whom lymphadenectomy can be omitted. Considering its role, the candidates for its omission may be patients with a low risk of LN metastasis. Hypervascular ICC has been identified as a subgroup with a low risk of LN metastasis, which is why we investigated the characteristics and outcomes of these patients. Additionally, hypervascular ICC is often misdiagnosed as HCC, resulting in the incidental omission of lymphadenectomy. This situation allowed us to assess the impact of lymphadenectomy on survival outcomes in hypervascular ICC, even in a single-center study with a consistent surgical policy.

Representatively, the vascular type of ICC was classified into the following three groups [13]: (i) hyper-enhancement, (ii) rim-enhancement, and (iii) hypo-enhancement types. Besides, a Japanese group proposed CT-vascularity to emphasize objectivity [15, 16]. While CT-vascularity ≥ 1 signifies arterial phase enhancement, our findings showed consistency between CT-vascularity results and radiologist-diagnosed hypervascular and hypovascular ICC (Figure S2). Meanwhile, the CT-vascularity of the rim-enhancement type was varied. The reason was that the tumor size in some cases was small and the enhancement pattern was atypical, which had a greater impact on visual judgment. Considering the validity and objectivity, the use of CT-vascularity would be preferred. Subsequently, the clinicopathological features of hypervascular ICC in this study, and survival outcomes were found to be consistent with previous studies [11–16] (e.g., clinical features typically associated with HCC and less aggressive tumor characteristics) as expected.

Recently increasing number of studies, including our conducted multicenter study [6, 23], have reported the possible benefit of lymphadenectomy for "node-negative" ICC, which should be discussed for the significance of lymphadenectomy and the potential proportions of LN metastasis in node-negative ICC ranged from 16.7% to 40.6% [6, 23–25]. On the contrary, lymphadenectomy was not associated with benefit in the hypervascular group. Besides the limited sample size, the most plausible reason was that the hypervascular group was inherently characterized by a relatively lower frequency of LN metastasis (i.e., 2.1% in Table 1) compared to the node-negative ICC, which might render lymphadenectomy less beneficial for the prognosis of this type of patient. A previous study that reported the unbeneficial effect of lymphadenectomy for ICC with the low risk of LN metastasis (i.e., 2.3%, CA 19-9 level of ≤ 120 U/mL, not an enlarged LN on computed tomography, and tumor not abutting the Glissonean pedicles) [26] might support our hypothesis. Overall, patients with hypervascular ICC did not benefit from lymphadenectomy, allowing for possible omission of lymphadenectomy in patients with hypervascular ICC.

Unfortunately, the analysis of clarifying the role of lymphadenectomy in non-hyper vascular ICC was inconclusive due to the limited sample size. Although the statistical difference was not reached, survival outcomes in patients with non-hypervascular ICC who did not undergo lymphadenectomy seemed to be poor (Figure S3). If this topic is evaluated by a much larger-sized study, a tailored strategy according to the CT-vascularity may be provided in the future.

The present study had some limitations, particularly the relatively small sample size due to the disease rarity and its single-center retrospective design. This limited sample size might have affected the statistical power of the analysis and the generalizability of the results. Future studies with larger, multi-center

cohorts are warranted to validate the results of this study. Nevertheless, this study was the first to demonstrate the limited impact of lymphadenectomy in hypervascular ICC, suggesting a rationale for its omission in these patients. We believe this study can contribute to the development of a new surgical strategy for ICC.

5 | Conclusion

Hypervascular ICC, quantified by the CT-vascularity, represents a favorable prognosis after surgical resection, and there is a possibility of omitting lymphadenectomy in this subgroup.

Author Contributions

Xuefeng Li: data curation, formal analysis, investigation, methodology, writing–original draft. **Tomoaki Yoh:** conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing–original draft, writing–review & editing. **Kotaro Shimada:** data curation, formal analysis, investigation, methodology, writing–original draft, writing–review & editing. **Yutaro Hori:** data curation, writing–review & editing. **Yukinori Koyama:** data curation, writing–review & editing. **Satoshi Ogiso:** data curation, writing–review & editing. **Takamichi Ishii:** data curation, writing–review & editing. **Hiroyoshi Isoda:** supervision, writing–review & editing. **Yuji Nakamoto:** supervision, writing–review & editing. **Etsuro Hatano:** project administration, supervision, writing–review & editing.

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Ethics Statement

The protocol was approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (approval code. R3809), and informed consent was considered to have been obtained from patients using an opt-out method.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.