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Role of Lymph Node Dissection in Small (≤ 3 cm) Intrahepatic Cholangiocarcinoma

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Abstract

Background and Aims The role of lymph node dissection (LND) in patients with small intrahepatic cholangiocarcinoma (ICC) is still under debate.

The aims of this study were to compare the lymph node (LN) status and its correlation with survival among patients with ICC stratified by tumor size.

Methods A retrospective analysis of a multi-institutional series of 259 patients undergoing curative-intent surgery was carried out. Patients were stratified into Small-ICC (≤ 3 cm) and Large-ICC (> 3 cm) based on tumor size.

Results There were 53 and 206 patients in Small-ICC and Large-ICC groups, respectively. The incidence of LND was 62% among Small-ICC patients and 78% among Large-ICC patients ($p = 0.016$). LN metastases were identified in 30.3% and 38.5% of Small-ICC and Large-ICC patients, respectively ($p = 0.37$). No differences in terms of number of harvested LN and LN metastases were identified comparing Small- and Large-ICC patients. The 5-year overall survival (OS) was 52.6% for Small-ICC and 36.2% for Large-ICC ($p = 0.024$). The 5-year OS according to the LN status (N0 vs N+) was 84.8% and 36.0% ($p = 0.032$) in Small-ICC, and 45.7% and 12.1% in Large-ICC ($p < 0.001$), respectively.

Conclusion While Small-ICC patients with no LN metastasis had a good long-term survival, the LN resulted in an important variable associated with survival also for patients in this group. Moreover, the incidence of LN metastasis did not differ when comparing Small-ICC and Large-ICC patients, suggesting that LND is mandatory in the surgical treatment of ICC regardless of tumor size.

Keywords Liver surgery · Cholangiocarcinoma · Lymph node dissection

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary tumor of the liver after hepatocellular carcinoma. In particular, ICC accounts for 8–10% of biliary tract cancers and 10–20% of all primary liver tumors.[1]

In the last decades, the incidence of ICC has increased worldwide. While the exact reason of this increased incidence has not been completely understood, it may be secondary to a higher prevalence of metabolic syndrome, viral hepatitis, and chemical exposure associated with an increased risk of developing ICC.[2,3]

Surgical resection with a R0 margin (complete removal of the tumor with no histological involvement of the margins) can offer the best chance of long-term survival among ICC patients, with a reported 5-year overall survival rate up to 48%.[4]

Lymph node (LN) metastasis is one of the major prognostic factors, with only less than 20% of patients with metastatic LN surviving 5 or more years after surgical resection.[5]

Tumor size has been associated with the prognosis of ICC patients in several series reported in the literature that have described good long-term results in terms of overall and disease-free survival with high chance of cure for patients with small-sized ICC.[6,7] In the literature, the incidence of small-sized ICC is very low and for this reason specific data on the impact of LN metastases and of LN dissection (LND) on the prognosis of these patients are still lacking.

The aims of the present study were to investigate the LN status and its association with prognosis in patients with ICC stratified by tumor size.

Patients and Methods

Patients

From January 1995 to December 2015, a total of 282 consecutive patients who underwent surgery for ICC at three hepatobiliary Italian tertiary referral centers (Division of General and Hepatobiliary Surgery, G.B. Rossi Hospital, University of Verona, Verona; Division of Hepatobiliary and General Surgery, Humanitas Clinical and Research Center, Humanitas University, Rozzano and Milan; Department of General and Emergency Surgery and Organ Transplantation, S. Orsola-Malpighi Hospital, University of Bologna, Bologna) were included in the present study. Among these patients, 13 patients did not undergo surgical resection (exploratory or palliative surgery) due to advanced disease. The remaining 269 patients underwent resection. Among the patients who underwent surgery, 10 (3.7%) had a residual macroscopic tumor (R2 resection) and were excluded. Thus, the remaining 259 patients who underwent curative resection were enrolled in this study.

While clinical data were retrieved from a prospectively maintained database, pathological data were retrospectively reviewed to classify patients based on tumor size. In particular, patients were dichotomized into Small-ICC defined as tumor size less than or equal to 3 cm and into Large-ICC defined as tumor size larger than 3 cm.

Data on tumor stages were collected according to the 8th edition of AJCC staging systems. Serum CA19-9 level greater than 55 U/mL was considered abnormally high. Data collection and analysis were performed according to the institutional guidelines and were conformed to the ethical standards of the World Medical Association (Declaration of Helsinki). The study was approved by each local ethical committee, and signed consent was obtained from all the subjects included in the study.

Statistical Analysis

Numerical variables were summarized using the mean and standard deviation or the median and interquartile range (IQR) as appropriate. Student's t test, chi-squared test, and Fisher test were used to compare means and proportions, respectively, between independent groups.

Overall survival (OS) was calculated from the date of surgery to the date of death from any cause or last follow-up. The median follow-up period for surviving patients was 38.6 months. Eight patients with 90-day postoperative mortality were excluded from the survival analysis. OS curves were estimated according to the Kaplan–Meier method and were compared using the log-rank test. Multivariable Cox model was used to estimate hazard ratios with 95% confidence intervals (95% CIs), adjusting for potential confounders. A $p \leq 0.05$ was considered statistically significant.

Results

Patient Characteristics

Clinical and pathological characteristics of the study population are summarized in Table 1.

Among the 259 patients included in the present study, 113 (43.6%) were ≥ 70 years old, 131 (50.5%) were male, and 53 (20.4%) patients presented a chronic liver disease. Mean and median tumor sizes were 6.2 (± 3.3) and 6.0 (3.7–8.0) cm, respectively. A total of 53 (20.4%) patients had a tumor smaller than or equal to 3 cm (Small-ICC) and 206 (79.6%) patients had a tumor larger than 3 cm (Large-ICC). Hepatic pedicle LND was performed on 194 (74.9%) patients. R0 resection was achieved in 185 (71.4%) patients. While the overall morbidity incidence was 31.6%, 90-day mortality incidence was 3.1% (8 patients).

Comparison of Clinical and Pathological Characteristics Between Small-ICC and Large-ICC

Characteristics of patients according to tumor size are summarized in Table 1. Small-ICC patients had lower serum Ca 19.9 levels (cutoff of 55 U/mL) compared with Large-ICC, 22.7% and 52.6%, respectively ($p = 0.010$). Moreover, Small-ICC patients had more frequently a single tumor than Large-ICC patients, 75.5% and 60.2%, respectively ($p = 0.040$). Major hepatectomies were performed on 24.5% of Small-ICC patients and on 69.9% of Large-ICC patients ($p < 0.001$).

Margin status was similar between the two groups; R0 resections resulted in 79.2% and in 69.4% of Small- and Large-ICC patients, respectively ($p = 0.16$). Postoperative short-term outcomes were similar between Small-ICC and Large-ICC groups: 90-day mortality rates were 1.9% and

Table 1 Patient characteristics according to tumor size: Small-ICC and Large-ICC

Characteristics		Total *n*, 259	Small-ICC *n*, 53	Large-ICC *n*, 206	Values
Age, *n* (%)	< 70 years	146 (56.4)	31 (58.5)	115 (55.8)	0.727
	≥ 70 years	113 (43.6)	22 (41.5)	91 (44.2)	
Gender, *n* (%)	Male	131 (50.6)	24 (45.3)	107 (51.9)	0.387
	Female	128 (49.4)	29 (54.7)	99 (48.1)	
Chronic liver disease, *n* (%)		53 (20.5)	15 (28.3)	38 (18.4)	0.113
Hepatitis viral infection, *n* (%)	HBV	13 (5.0)	5 (9.4)	8 (3.9)	0.099
	HCV	25 (9.7)	9 (17.0)	16 (7.8)	0.043
Serum Ca 19-9, *n* (%)	< 55 U/mL	135 (52.2)	41 (77.3)	97 (47.4)	0.010
	≥ 55 U/mL	124 (47.8)	12 (22.7)	109 (52.6)	
Tumor number, *n* (%)	Single	164 (63.3)	40 (75.5)	124 (60.2)	0.040
	Multiple	95 (36.7)	13 (24.5)	82 (39.8)	
Major hepatectomies, *n* (%)		157 (60.6)	13 (24.5)	144 (69.9)	<0.001
Lymph node dissection, *n* (%)		194 (74.9)	33 (62.3)	161 (78.2)	0.017
Radicality, *n* (%)	R0	185 (71.4)	42 (79.2)	143 (69.4)	0.158
	R1	74 (28.6)	11 (20.8)	63 (30.6)	
Vascular invasion, *n* (%)		94 (36.3)	12 (22.6)	82 (39.8)	0.020
Biliary invasion, *n* (%)		27 (10.4)	5 (9.4)	22 (10.7)	0.791
Perineural invasion, *n* (%)		145 (64.7)	25 (56.8)	120 (66.7)	0.220
Stage T, *n* (%)					< 0.001
T1		66 (25.4)	22 (41.5)	44 (21.3)	
T2		117 (45.2)	24 (45.3)	93 (45.2)	
T3		62 (23.9)	6 (11.3)	56 (27.2)	
T4		14 (5.4)	1 (1.9)	13 (6.3)	
Adjuvant chemotherapy, *n* (%)		106 (42.4)	13 (25.0)	93 (47.0)	0.004
Postoperative 90-day mortality, *n* (%)		8 (3.1)	1 (1.9)	7 (3.4)	0.571
Postoperative morbidity, *n* (%)		60 (31.6)	11 (26.8)	49 (32.9)	0.460

3.4% ($p = 0.57$), while morbidity rates were 26.8% and 32.9% for Small- and Large-ICC patients, respectively ($p = 0.46$).

Only 22.6% of Small-ICC patients had vascular invasion compared with 39.8% of Large-ICC patients ($p = 0.020$). Conversely, incidence of biliary and perineural invasion was similar between the two groups ($p = 0.79$ and $p = 0.22$, respectively).

Comparison of Lymph Node Dissection Between Small-ICC and Large-ICC

Hepatic pedicle LND was performed in 62.3% of Small-ICC and in 78.2% of Large-ICC ($p = 0.017$). Table 2 reports the comparison between the characteristics of patients in Small- and Large-ICC groups.

Among patients who underwent LND, mean and median numbers of harvested and positive LNs were similar between Small-ICC and Large-ICC ($p = 0.23$ and $p = 0.95$, respectively). Even though the incidence of metastatic LNs was associated with tumor size increasing from 30.3% among Small-ICC patients to 38.5% among Large-ICC patients, this difference was not statistically significant ($p = 0.37$).

Survival Analysis

The 5-year OS rate and median OS of the entire cohort were 40.6% and 45.9 months, respectively.

OS rate was significantly higher in Small-ICC patients compared to Large-ICC patients, with a 5-year OS of 52.7% and 36.2%, respectively ($p = 0.024$) (Fig. 1).

The number of patients with small ICC who required major resection for centrally located tumors was 13 (24.5%) compared to 53 (75.5%) submitted to minor resection for peripheral tumors. The frequency of nodal metastases for centrally located tumors was 36.4% compared to 27.3% for peripheral tumors; this difference was not statistically significant ($p = 0.440$). The median survival for patients submitted to minor and major resections were 68 and 59 months, respectively; the difference did not reach statistical significance ($p = 0.311$).

The results of the univariate and multivariable analyses investigating the factors associated with survival among Small- and Large-ICC patients are reported in Table 3.

Based on the univariate analysis, Ca 19-9 level (≥ 55 U/mL), tumor number (single vs multiple), surgical margin, AJCC 8th ed. T stages, and LN status were identified as prognostic factors

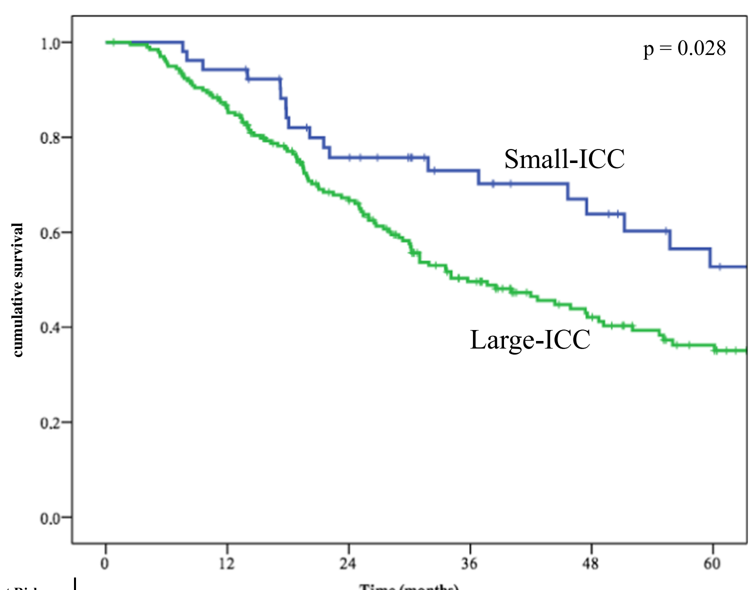
Table 2 Comparison of lymph node dissection data between Small-ICC and Large-ICC

Lymph node dissection		Small-ICC n, 33	Large-ICC n, 161	Values
LN status, n (%)	N0	23 (69.7%)	99 (61.5%)	0.374
	N+	10 (30.3%)	62 (28.5%)	
Number of LNs retrieved				
Mean (SD)		5.2 (±3.7)	6.4 (±5.4)	0.230
Median (IQR)		4.0 (2.0–8.0)	5.0 (2.0–9-0)	
Number of LNs retrieved, n (%)	1–2	10 (30.3)	42 (26.1)	0.869
	3–5	9 (27.3)	49 (30.4)	
	≥ 6	14 (42.4)	70 (43.5)	
Lymph node status, n (%)	N0	23 (69.7)	99 (61.5)	0.374
	N+	10 (30.3)	62 (38.5)	
Number of positive LNs				
Mean (SD)		3.1 (±1.8)	3.0 (±3.4)	0.947
Median (IQR)		3.0 (2.0–4.0)	2.0 (1.0–3.25)	
Number of positive lymph nodes, n (%)	1–3	7 (70)	46 (74)	0.639
	> 3	3 (30)	16 (26)	

for OS among Large-ICC patients. Figure 2 a shows the survival curves for Large-ICC patients according to LN Status (N0, N+, and NX). The 5-year OS was 45.7%, 15.1%, and 42.8% for N0, N1, and NX patients, respectively ($p < 0.001$). Based on the multivariable analysis, Ca 19-9 ≥ 55 U/mL (HR 2.07, 95% CI 1.08–3.98, $p = 0.029$), tumor number (single vs multiple) (HR 2.76, 95% CI 1.48–5.14, $p = 0.001$), surgical margin (HR 1.63, 95% CI 1.02–2.95, $p = 0.047$), and LN status (HR 2.23, 95% CI 1.23–4.05, $p = 0.009$) were confirmed to be independent prognostic factors for OS in Large-ICC.

Based on the univariate analysis, tumor number (single vs multiple), surgical margin, and LN status were identified as prognostic factors for OS in Small-ICC patients. Figure 2 b shows the survival curves of Small-ICC patients stratified by LN status (N0, N+, and NX). The 5-year OS was 84.8%, 36.0%, and 46.0% for N0, N1, and NX patients, respectively ($p = 0.032$). In the multivariable analysis, only surgical margins (HR 7.87, 95% CI 1.64–37.8, $p = 0.010$) and LN status (HR 6.62, 95% CI 1.40–31.4, $p = 0.017$) were confirmed to be the independent prognostic factors for OS in Small-ICC. Figures S1 and S2 show the comparison between Large-ICC and Small-ICC patients stratified by the LN status (N0, N+, and NX).

According to LN status, 49.1%, 54.2%, and 10.7% of N0, N1, and NX patients received adjuvant chemotherapy,



Patients at Risk						
Small-ICC	52	49	36	26	20	14
Large-ICC	199	164	113	71	48	32

Fig. 1 Overall survival for patients submitted to surgery for Small-ICC and Large-ICC ($p = 0.028$)

Table 3 Univariate and multivariate analyses for the factors related with survival for Small-ICC and Large-ICC

Clinicopathological features		Large-ICC					Small-ICC				
		Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
		5-year OS (%)	*p* values	HR	95% C.I.	*p* values	5-year OS (%)	*p* values	HR	95% C.I.	*p* values
Age (years)	< 70	39.2	0.295				61.3	0.237			
	≥ 70	33.0					36.1				
Ca 19–9 (U/mL)	< 55	43.9	< 0.001	2.070	1.077–3.981	0.029	72.5	0.985			
	≥ 55	24.4					80.0				
Tumor number	Single	45.9	< 0.001	2.763	1.484–5.142	0.001	57.2	0.043	0.459	0.041–5.167	0.528
	Multiple	22.7					38.9				
Type of hepatectomy	Minor	37.8	0.258				50.3	0.243			
	Major	35.6					59.2				
Radicality	R0	47.2	0.023	1.628	1.020–2.945	0.047	55.9	0.021	7.874	1.640–37.800	0.010
	R1	34.1					36.4				
Vascular invasion	No	41.2	0.040	1.123	0.625–2.019	0.698	54.2	0.191			
	Yes	28.4					48.6				
Biliary invasion	No	33.9	0.409				50.7	0.596			
	Yes	53.2					60.0				
Perineural invasion	No	32.7	0.739				60.9	0.369			
	Yes	35.8					48.9				
AJCC 8th T stage	T1–2	41.1	0.033	1.133	0.617–2.082	0.687	49.7	0.823			
	T3–4	25.6					65.7				
Lymph node status	N0	45.7	< 0.001	2.226	1.225–4.045	0.009	84.8	0.032	6.624	1.396–31.441	0.017
	N+	12.1					36.0				
Adjuvant ChT	No	35.6	0.796				50.0	0.377			
	Yes	41.2					61.9				

respectively. While median OS for patients who had adjuvant chemotherapy was 84, 28, and 66 months for N0, N1, and NX patients compared to 55, 19, and 45 months for N0, N1, and NX patients who did not have adjuvant chemotherapy, these differences were not statistically significant (all $p > 0.45$).

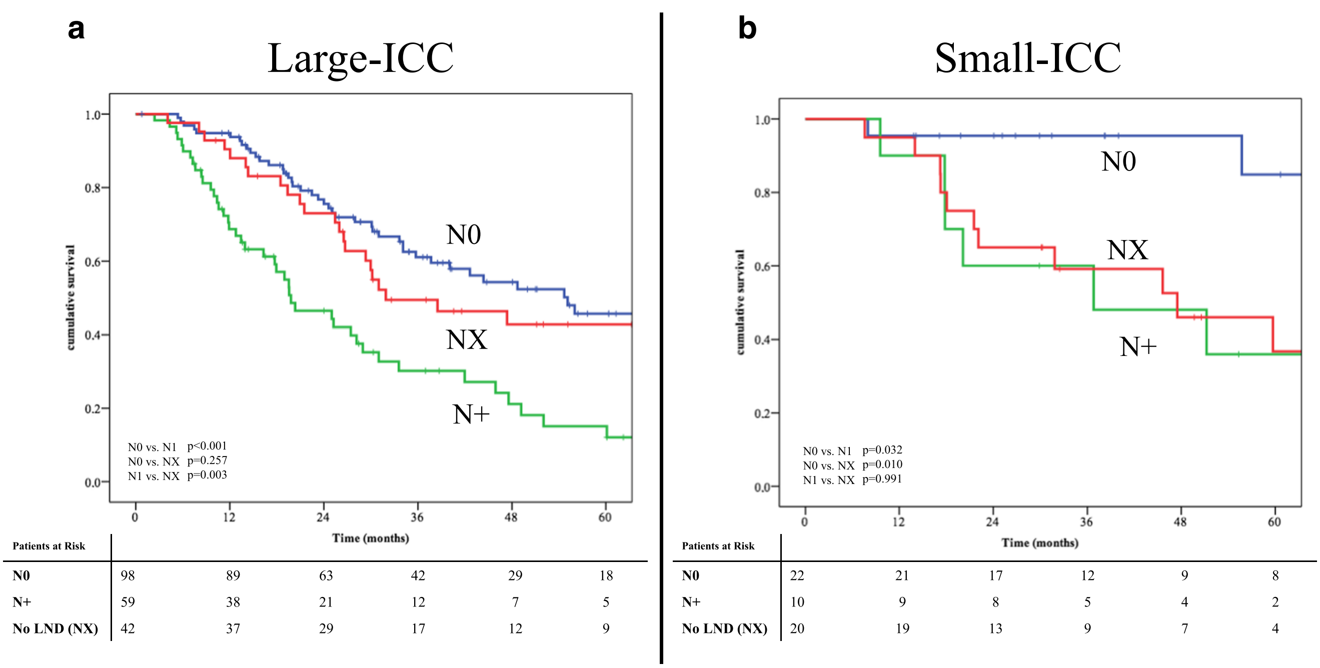


Fig. 2 Overall survival for patients submitted to surgery according to lymph node status in (**a**) and (**b**)

Discussion

This large multi-institutional study investigated the factors associated with the prognosis of ICC patients stratified by tumor size. In particular, the incidences of LND and LN metastases were compared among patients in Small- (≤ 3 cm) and Large-ICC (> 3 cm) groups analyzing their impact on patient survival. Of note, while the clinical and pathological characteristics of Small- and Large-ICC resulted in significant differences, the incidence of LN metastases was comparable among the two groups. Moreover, 5-year OS survival for Small-ICC patients was greater than 80% in the subgroup of N0 patients, confirming the good long-term results of the curative-intent surgery for these patients. Interestingly, in both univariate and multivariable analyses, LN status resulted as one of the most important factors associated with patients' long-term survival.

Tumor size is one of the well-known prognostic factors for survival of ICC patients and several studies have demonstrated its relationship with other prognostic factors. Ribero et al.[8] in an Italian multi-institutional study reported that larger ICCs had an increased incidence of LN metastasis, vascular invasion, multinodular disease, and high tumor grading. Mavros et al.[9] in a review and meta-analysis reported a 10% increased risk of death (HR, 1.09) for each centimeter of increment in tumor size.

In the literature, only few papers have focused on the clinicopathological characteristics and prognostic factors of Small-ICC patients. Sakamoto et al.[10] in a Japanese nationwide multi-institutional study identified 27 patients with tumors smaller than or equal to 2 cm. Among these patients, 5-year OS was 82% and incidences of lymph node metastases, biliary invasion, and vascular invasion were 25%, 35%, and 25%, respectively. More recently, a report on the outcomes of liver transplantations for early ICC patients demonstrated a 5-year OS of 65% for patients with ICC smaller than 2 cm, suggesting that liver transplant might be a curative-intent treatment for these patients, especially for patients with an incidentally discovered disease.[11]

Of note, these data are comparable with those reported in our study. In fact, for N0 patients with ICC smaller than or equal to 3 cm, 5-year OS was 84.8%.

The choice of the 3-cm cutoff value in our study was made according the analysis of data present in literature. In Sapisochin et al.[11] the authors analyzed the prognosis of early (≤ 2 cm) and intermediate (single ≤ 3 cm) ICC compared to advanced ICC (> 3 cm) after liver transplantation. Specifically, these authors demonstrated a clear survival benefit in patients with ICC smaller than or equal to 3 cm compared to more advanced ICC; moreover, the differences between survival rates for ICC smaller than 2 or 3 cm were very similar. Although these data cannot provide any pathogenetic or biological explanation for different behaviors according to tumor size, clinical outcomes for tumors smaller than 3 cm seem to be very similar. Moreover, in our multi-institutional database, the number of patients with tumors smaller than or equal to 2 cm was very small (13 patients, 5%) compared to 53 patients (20%) for the 3-cm cutoff, demonstrating the low frequency of small-sized ICC in surgical series.

The role of LND is still debated in the literature with LND rate ranging from 27 to 100% of patients in the series reported in the literature.[12] A recent study based on the National Cancer Database pointed out that 42% patients who underwent surgery for ICC did not undergo LND.[13] Moreover, a recent multi-institutional study confirmed that, among ICC patients, the disease-specific survival (DSS) of N0 patients was significantly higher compared to patients who did not undergo LND (NX) with a DSS at 18 months of 70.2% and 60.6%, respectively.[14] Moreover, the number of harvested LN has been associated with the survival of N0 patients suggesting that an inadequate LN staging might result in the presence of occult LN metastases.[15]

The incidence of LN metastases reported in the literature varies from 35 to 45% among ICC patients while there are no specific data about the incidence of LN metastases among Small-ICC patients.[16–18] The relationship between tumor stage and incidence of LN metastases has not been clearly demonstrated even though a recent multi-institutional study reported a significant incidence of LN metastasis also among patients with early-stage ICC. Specifically, more than 20% of patients in T1a/T1b stages and 40% of patients in T2 stages had lymph node metastases.[19]

Lymph node metastasis is one of the most important factors associated with patient survival. The prognosis of ICC patients with LN metastasis is dismal with 5-year OS ranging from 0 to 10%.[20] Moreover, Nakagawa et al.[21] reported that patient survival might be associated with the number of positive LN, with a 3-year OS of 62, 50, and 0% for patients with 0, 1–2, and ≥ 3 positive LN, respectively ($p < 0.05$). Interestingly, in the present study, the incidence of LN metastases was not significantly different among patients stratified by tumor size, suggesting that also Small-ICC patients can have a significant incidence of LN metastasis. In the literature, important prognostic factors associated with a poor prognosis of ICC patients undergoing curative-intent surgery include LN metastasis, microvascular invasion, positive surgical margins, multifocality, and poorly differentiated tumors.[9,22] In particular, Guglielmi et al.[23] reported that macroscopic gross appearance of the tumor, LN metastases, macroscopic vascular invasion, and positive resection margins were independent prognostic factors for OS of patients with ICC. Different prognostic nomograms have been developed in recent years to define survival after curative-intent surgery for ICC. In 2013, Wang et al.[24] proposed a nomogram including serum carcinoembryonic antigen, CA 19-9, tumor size and number, vascular invasion, LN metastasis, direct invasion of adjacent organs, and local extrahepatic metastasis to predict patient survival, reporting a C-index for the nomogram of 0.74. Conversely, no paper investigated the prognostic factors for patients with Small-ICC. According to Sakamoto et al.[10]

who described vascular invasion as one of the most important prognostic factors for ICC, in their analysis, the 5-year OS for Small-ICC patients without vascular invasion was about 100%.

Interestingly, there were significant differences in terms of prognostic factors associated with a poor prognosis comparing the Small- and Large-ICC groups. In fact, while LN metastases were associated with patient prognosis for both Small- and Large-ICC patients, only few other factors were independent predictors of survival for Small-ICC patients. This result seems to emphasize the importance of LN status as the main pathological factor associated with the prognosis of Small-ICC patients.

Several limitations might be considered when interpreting the results of this study including the multi-institutional, retrospective design and the long inclusion period. However, the long inclusion time and multi-institutional design allowed obtaining a larger cohort of patients with longer follow-up periods that might be crucial for a more precise evaluation of factors related with survival. While the small number of patients with ICC < 3 cm might limit the reproducibility of our result, the rarity of the disease and the lack of information about this specific subset of patients must be considered to evaluate the significance and the reproducibility of our result.

Conclusions

This multi-institutional, retrospective study identified a subset of patients with ICC characterized by a small tumor size (ICC < 3 cm, Small-ICC) who demonstrated good long-term survival after curative-intent surgery. Moreover, our results underlined the importance of lymph node dissection for patients with ICC that resulted in vital importance for an optimal staging also for Small-ICC patients considering that the incidence of LN metastasis was not associated with the tumor size. Regardless of the tumor size, LN status was the most important factor associated with patient prognosis confirming that lymph node dissection is mandatory in the surgical treatment of ICC.

Compliance with Ethical Standards

Data collection and analysis were performed according to the institutional guidelines and were conformed to the ethical standards of the World Medical Association (Declaration of Helsinki). The study was approved by each local ethical committee, and signed consent was obtained from all the subjects included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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