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ORIGINAL ARTICLE

Defining Long-Term Survivors Following Resection of Intrahepatic Cholangiocarcinoma

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Abstract

Background Intrahepatic cholangiocarcinoma (ICC) is an aggressive primary tumor of the liver. While surgery remains the cornerstone of therapy, long-term survival following curative-intent resection is generally poor. The aim of the current study was to define the incidence of actual long-term survivors, as well as identify clinicopathological factors associated with long-term survival.

Methods Patients who underwent a curative-intent liver resection for ICC between 1990 and 2015 were identified using a multi-institutional database. Overall, 679 patients were alive with ≥ 5 years of follow-up or had died during follow-up. Prognostic factors among patients who were long-term survivors (LT) (overall survival (OS) ≥ 5) were compared with patients who were not non-long-term survivors (non-LT) (OS < 5).

Results Among the 1154 patients who underwent liver resection for ICC, 5- and 10-year OS were 39.6 and 20.3% while the actual LT survival rate was 13.3%. After excluding 475 patients who survived < 5 years, as well as patients were alive yet had < 5 years of follow-up, 153 patients (22.5%) who survived ≥ 5 years were included in the LT group, while 526 patients (77.5%) who died < 5 years from the date of surgery were included in the non-LT group. Factors associated with not surviving to 5 years

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included perineural invasion (OR 4.78, 95% CI, 1.92–11.8; $p = 0.001$), intrahepatic metastasis (OR 3.75, 95% CI, 0.85–16.6, $p = 0.082$), satellite lesions (OR 2.12, 95% CI, 1.15–3.90, $p = 0.016$), N1 status (OR 4.64, 95% CI, 1.77–12.2; $p = 0.002$), ICC > 5 cm (OR 2.40, 95% CI, 1.54–3.74, $p < 0.001$), and direct invasion of an adjacent organ (OR 3.98, 95% CI, 1.18–13.4, $p = 0.026$). However, a subset of patients (< 10%) who had these pathological characteristics were LT.

Conclusion While ICC is generally associated with a poor prognosis, some patients will be LT. In fact, even a subset of patients with traditional adverse prognostic factors survived long term.

Keywords Intrahepatic · Cholangiocarcinoma · Long-term · Survival

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer.[1–6] Long-term survival of patients with unresectable ICC is dismal, with only 5–10% of patients alive 5 years from the time of diagnosis.[7] While surgery remains the only hope for long-term cure for patients with resectable disease, 5-year overall survival (OS) remains poor even after hepatic resection (5-year OS, 25–30%). While several clinicopathological variables have been associated with prognosis including Cancer Antigen (CA) 19-9, tumor number and size, lymph node status, margin status, and vascular invasion, the incidence of long-term survivors after curative-intent surgery remains poorly defined. Traditionally, the American Joint Committee on Cancer (AJCC) staging manual has been the main means of stratifying patients with regard to prognosis[8]; however, new prognostic tools have also been accepted and utilized.[9] In particular, several studies have reported on nomograms based on patient and tumor-specific factors, as well as the impact of perioperative complications on long-term prognosis for patients with ICC undergoing surgery.[10–18]

Following resection of abdominal malignancies, most studies have examined short-term survival, while fewer studies have reported data specifically defining long-term survivors.[19] In one study of 618 patients who underwent resection for pancreatic adenocarcinoma, the authors reported an actual 5-year survival of only 12% following resection.[20] AJCC stage and negative surgical margins were predictive of long-term survival, while patient age, gender, and tumor location were not associated with actual 5-year survival. In a separate study, Zheng et al. reported on a large Western series of actual 10-year survivors following resection of hepatocellular carcinoma (HCC) and noted that surgical margin status was the main factor associated with long-term survival.[21] Despite these reports, no previous study has focused on actual long-term survivors following resection of ICC. As such, the objective of the current study was to define the incidence of actual long-term survivors following curative-intent resection of ICC using a large, international, multi-center cohort of patients. In addition, we sought to characterize the impact of clinicopathological factors on the likelihood of patients to survive long-term after surgical resection of ICC.

Materials and Methods

Patient Demographic and Clinical Data

Patients who underwent a liver resection for histologically confirmed ICC between 1990 and 2015 were identified from a multi-institutional database including 14 major hepatobiliary centers in the USA, Europe, Australia, and Asia (Johns Hopkins Hospital, Baltimore, MD, $n = 89$, 7.7%; Stanford University, Stanford, CA, $n = 45$, 3.9%; University of Virginia, Charlottesville, VA, $n = 22$, 1.9%; Emory University, Atlanta, GA, $n = 72$, 6.2%; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania, $n = 103$, 8.9%; Curry Cabral Hospital, Lisbon, Portugal, $n = 48$, 4.2%; Ospedale San Raffaele, Milan, Italy, $n = 88$, 7.6%; Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia, $n = 38$, 3.3%; Eastern Hepatobiliary Surgery Hospital, Shanghai, China, $n = 312$, 27.0%; Beaujon Hospital, Clichy, France, $n = 76$, 6.6%; University of Ottawa, Ottawa, Ontario, Canada, $n = 26$, 2.3%; Erasmus University Medical Centre, Rotterdam, Netherlands, $n = 51$, 4.4%; Yokohama City University School of Medicine, Yokohama, Japan, $n = 79$, 6.9%; University of Verona, School of Medicine, Verona, Italy, $n = 105$, 9.1%). Only patients who underwent curative intent surgery for non-metastatic ICC were included, while patients who underwent a palliative operation were excluded. In addition, patients who underwent only ablation or intra-arterial therapy (IAT) were excluded. The Institutional Review Board of each institution approved the study.

Standard patient demographic, clinicopathologic, tumor-specific, treatment-related data were collected, as previously reported.[18] Demographic and clinicopathologic data on age, gender, American Society of Anesthesiologists (ASA) classification, presence of cirrhosis, HBV or HCV infections, serum level of carcinoembryonic antigen (CEA), and CA 19-9 were collected. Treatment-related data included receipt of neoadjuvant chemotherapy, type of surgery, and receipt of adjuvant treatments. Of note, resection margin status was classified as microscopically negative (R0) or microscopically positive (R1). Patients who underwent non-radical resection

(macroscopically residual disease (R2)), as well as patients who underwent palliative surgery or received only non- surgical treatments (ablation or intra-arterial therapies) were excluded. Tumor-specific characteristics included tumor size and number, presence of intrahepatic metastasis (multiple hepatic lesions in separate segments) or satellite lesions (dominant mass with nodules in same segment),[22] liver capsule involvement, vascular/perineural/biliary invasion, and direct invasion of contiguous organs. Data on histological grade, morphological type, number of achieved, and metastatic lymph nodes were also collected. Tumor and lymph node stages were categorized according to the 8th edition of the AJCC.[8]

For the purpose of the study, patients who were alive yet whose follow-up time was less than 5 years were excluded. The analytic cohort was categorized into patients who survived at least 5 years after surgery (i.e., long-term survival group (LT)) vs. patients who died within 5 years from the date of surgery (i.e., non-long term survival group (non-LT)).

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQR) while categorical variables were reported as whole numbers and percentages. Overall survival (OS) was defined as the time interval between the date of surgery and the date of death. Time was censored at the date of last follow-up for living patients. OS estimates were calculated using the Kaplan-Meier method. Logistic regression models were used to evaluate associations between clinicopathological variables and long-term survival. The coefficients from the logistic regression models were subsequently reported as odds ratios (OR) with corresponding 95% confidence intervals (CI). All analyses were carried out with STATA version 12.0 (StataCorp, College Station, TX). All tests were two sided, and a p value < 0.05 was considered statistically significant.

Results

Among 1154 patients who underwent liver resection for ICC, overall actuarial survival at 5 and 10 years was 39.6 and 20.3%, respectively (Fig. 1). In the entire cohort, the incidence of actual survivors was 13.3% (n = 153) at 5 years, and among these patients, the incidence of actual survivors at 10 years was 10.4% (n = 16). Excluding 475 patients who were alive with a follow-up < 5 years, the analytic cohort consisted of 153 patients (22.5%) in the long-term survival group (LT) vs. 526 patients (77.5%) who died within 5 years of surgery in the non-long-term survival group (non-LT).

Many clinical and demographic factors among LT and non-LT patients were comparable (Table 1). For example, the proportion of men (non-LT, n = 788, 51.0% vs. LT, n = 306, 58.3%), median age (non-LT, 60 years, IQR, 45–69 vs. LT, 59 years, IQR, 49–66), as well as the incidence of cirrhosis (non-LT, n = 62, 14.5% vs. LT, n = 17, 14.2%), HBV (non-LT, n = 90, 21.5% vs. LT, n = 30, 25.6%), and HCV (non-LT, n = 16, 3.9% vs. LT, n = 5, 4.3%) were similar (all $p > 0.05$). In addition, utilization of preoperative chemotherapy was the same among non-LT (n = 7, 6.3%) and LT (n = 34, 8.9%) patients (p = 0.37). The use of adjuvant chemotherapy and radiotherapy also did not differ among non-LT and LT patients (adjuvant chemotherapy: non-LT group, n = 165, 33.3% vs. LT group, n = 52, 34.7%, p = 0.75) (adjuvant radiotherapy: non-LT: n = 30, 7.4% vs. LT, n = 7, 5.5%, p = 0.46).

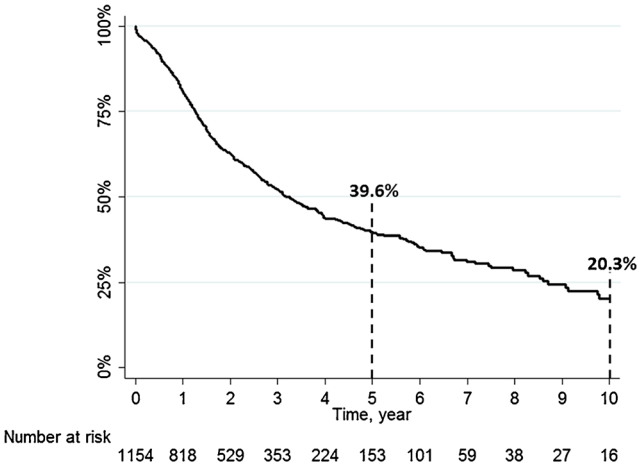

Fig. 1 Kaplan-Meier estimates of overall survival among the 1154 patients undergoing liver resection with curative intent for intrahepatic cholangiocarcinoma

A number of prognostic factors were, however, different among non-LT vs. LT patients. In particular, the incidence of periductal infiltrating/mass forming + periductal infiltrating (PI/MF + PI) tumor morphology and R1 surgical margin status was lower among LT patients compared with non-LT patients (PI/MF + PI: non-LT: n = 89, 17.9% vs. LT, n = 11, 7.1%, p = 0.002) (R1: non-LT, n = 83, 15.9% vs. LT, n = 11, 7.2%, p = 0.006). Moreover, the incidence of N1 disease and tumor size > 5 cm was also lower in the LT vs. non-LT group (N1: non-LT group, n = 123, 23.4% vs. LT group, n = 9, 5.9%, $p < 0.001$) (tumor size > 5 cm: non-LT group, n = 361, 68.6% vs. LT group, n = 75, 49.1%, $p < 0.001$). ICC involvement of adjacent organs was present in 48 (12.9%) non-LT patients compared with 3 (2.2%) LT patients (p = 0.003). In addition, the incidence of microvascular (microvascular invasion: non-LT group, n = 171, 33.3% vs. LT group, n = 34, 22.2%, p = 0.009) and perineural invasion (perineural invasion: non-LT group, n = 111, 23.2% vs. LT group, n = 12, 8.8%, $p < 0.001$) (Fig. 2a) were lower in the LT group. Median values of CA 19-9 and CEA were also lower in the LT group than in the non-LT group (CA 19-9: non-LT group, 84.2, IQR,

Table 1 Clinical and pathologic features of patients (n = 679)

	Non-LT N (%)	LT N (%)	p value
Patients	526 (77.5%)	153 (22.5%)	–
Age, median (IQR)	60 years (45–69)	59 years (49–66)	0.40
Gender			0.11
Female	219 (41.7%)	75 (49.0%)	
Male	307 (58.3%)	78 (51.0%)	
Cirrhosis			0.93
No	366 (85.5%)	103 (85.8%)	
Yes	62 (14.5%)	17 (14.2%)	
NA	98	33	
HBV infection			0.35
No	328 (78.5%)	87 (74.4%)	
Yes	90 (21.5%)	30 (25.6%)	
NA	108	36	
HCV infection			0.85
No	393 (96.1%)	111 (95.7%)	
Yes	16 (3.9%)	5 (4.3%)	
NA	117	37	
Neoadjuvant chemotherapy			0.37
No	347 (91.1%)	105 (93.7%)	
Yes	34 (8.9%)	7 (6.3%)	
NA	145	41	
Morphological type			0.002
MF, IG	408 (82.1%)	132 (92.9%)	
PI, MF + PI	89 (17.9%)	10 (7.1%)	
NA	29	11	
Margin status			0.006
R0	437 (84.0%)	142 (92.8%)	
R1	83 (15.9%)	11 (7.2%)	
NA	6	–	
Lymph node status			< 0.001
N0	119 (22.6%)	45 (29.4%)	
N1	123 (23.4%)	9 (5.9%)	
NX	284 (54.0%)	99 (64.7%)	
Tumor size			< 0.001
≤ 5 cm	165 (31.4%)	78 (50.9%)	
> 5 cm	361 (68.6%)	75 (49.1%)	
Liver capsule involvement			0.88
No	419 (79.7%)	121 (79.1%)	
Yes	107 (20.3%)	32 (20.9%)	
Direct invasion adjacent organs			0.003
No	478 (89.6%)	150 (98.0%)	
Yes	48 (10.4%)	3 (2.0%)	
Major vascular resection			0.55
No	458 (87.1%)	136 (88.9%)	
Yes	68 (12.9%)	17 (11.1%)	
Bile duct resection			< 0.001
No	358 (77.5%)	123 (91.8%)	
Yes	104 (22.5%)	11 (8.2%)	
NA	64	19	

Table 1 (continued)

	Non-LT N (%)	LT N (%)	*p* value
Grade			0.007
Well/moderate	377 (76.8%)	123 (87.2%)	
Poorly/undifferentiated	114 (23.2%)	18 (12.8%)	
NA	35	12	
Microvascular invasion			0.009
No	342 (66.7%)	119 (77.8%)	
Yes	171 (33.3%)	34 (22.2%)	
NA	13	–	
Perineural invasion			< 0.001
No	368 (76.8%)	125 (91.2%)	
Yes	111 (23.2%)	12 (8.8%)	
NA	47	16	
Satellite lesion			< 0.001
No	370 (70.9%)	135 (88.2%)	
Yes	152 (29.1%)	18 (11.8%)	
NA	4	–	
Intrahepatic metastasis			0.002
No	474 (90.6%)	150 (98.0%)	
Yes	49 (9.4%)	3 (2.0%)	
NA	3	–	
Ca 19–9, median (IQR)	84.2 (23.7–400.0)	25.5 (11.0–107.8)	< 0.001
CEA, median (IQR)	2.8 (1.6–5.4)	1.8 (1.0–3.2)	< 0.001
Adjuvant chemotherapy			0.75
No	331 (66.7%)	98 (65.3%)	
Yes	165 (33.3%)	52 (34.7%)	
NA	30	3	
Adjuvant radiotherapy			0.46
No	378 (92.6%)	121 (94.5%)	
Yes	30 (7.4%)	7 (5.5%)	
NA	118	25	

NA not available

23.7–400.0 vs. LT group, 25.5, IQR, 11.0–107.8, $p < 0.001$; CEA: non-LT group, 2.8, IQR, 1.6–5.4 vs. LT group, 1.8, IQR, 1.0–3.2, $p < 0.001$). More patients in the non-LT group had a poorly/undifferentiated tumor ($n = 114$, 23.3%) compared with LT patients ($n = 18$, 12.8%, $p = 0.007$; Table 1).

After controlling for competing risk factors on multivariable analysis, several factors remained strongly associated with LT (Table 2). For example, patients with direct invasion of adjacent organs had an almost fourfold decreased odds of surviving to 5 years compared with patients without direct invasion of adjacent organs (OR 3.98, 95% CI, 1.18–13.4, $p = 0.026$) (Fig. 2b). Patients with intrahepatic metastasis (OR 3.75, 95% CI, 0.85–16.6, $p = 0.082$) (Fig. 2c) and satellite lesions (OR 2.12, 95% CI, 1.15–3.90, $p = 0.016$) (Fig. 2d) were also less likely to be LT survivors. Patients with an ICC > 5 cm had an increased risk to be in the non-LT group than in the LT group (OR 2.40, 95% CI, 1.54–3.74, $p < 0.001$) (Fig. 2e). Accordingly, in the Kaplan-Meier analysis, 5- and 10-year OS was 32 and 16%, respectively, for patients with ICC ≥ 5 cm vs. 52 and 27% for patients with an ICC < 5 cm. Of note, N1 status (OR 4.64, 95% CI, 1.77–12.2; $p = 0.002$) and perineural invasion (OR 4.78, 95% CI, 1.92–11.8; $p = 0.001$) were the strongest independent predictors of poor prognosis and decreased likelihood of LT. In the LT group, while only three (2.0%) patients had intrahepatic metastasis and direct invasion of adjacent organs, 5% of patients in the LT group had satellite lesion ($n = 18$, 11.8%), perineural invasion ($n = 12$, 8.8%), N1 status ($n = 9$, 5.9%), and ICC ≥ 5 cm ($n = 75$, 49.1%).

In comparing LT vs. non-LT patients, the AJCC 8th edition T1b, T2, and T4 patients were under-represented in LT group vs. non-LT group (T1b: non-LT group, $n = 129$, 80.1% vs. LT group, $n = 32$, 19.9%; T2: non-LT group, $n = 205$, 84.4% vs. LT group, $n = 38$, 15.6%; T4: non-LT group, $n = 48$, 94.1% vs.

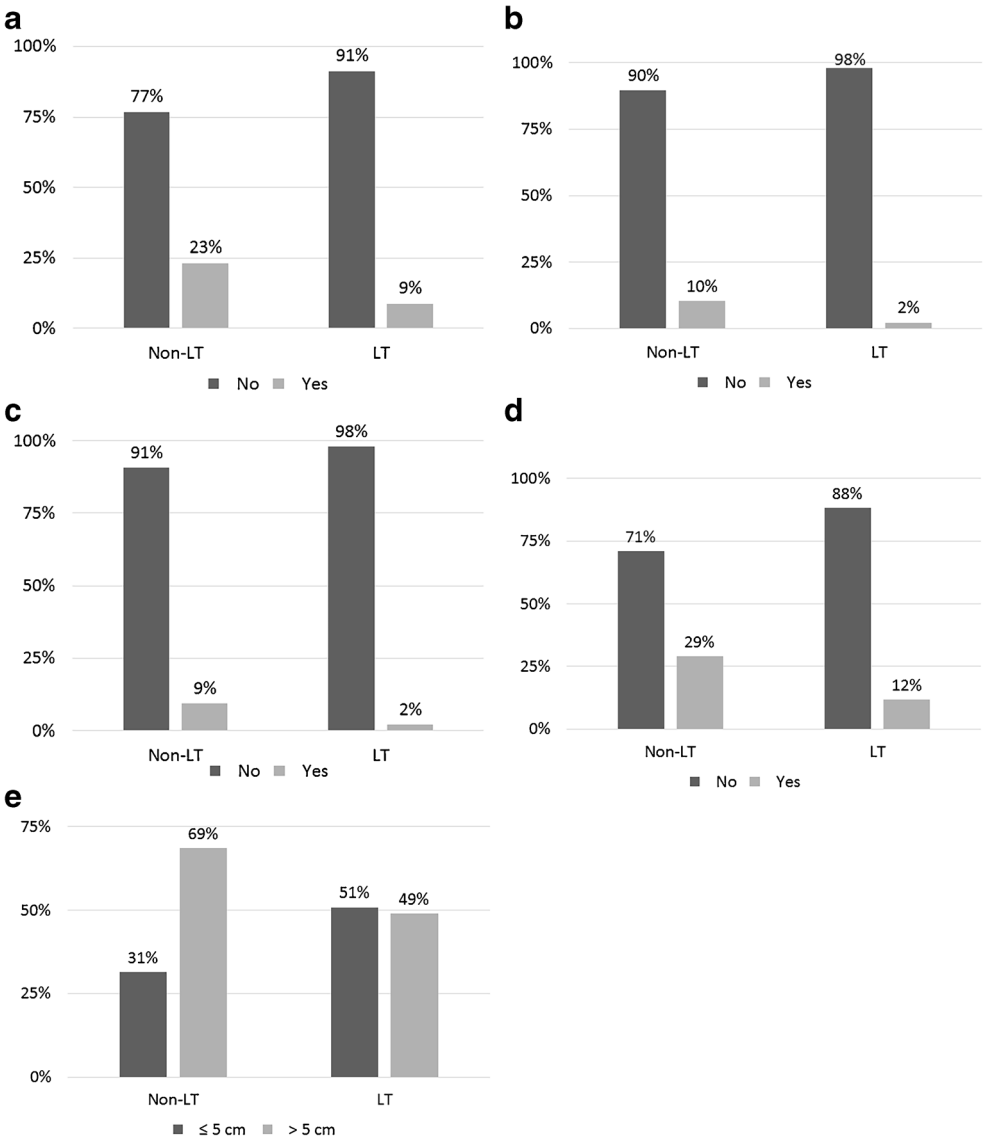

Fig. 2 Histogram showing the incidence of patients stratified by **a** perineural invasion, **b** invasion of adjacent organs, **c** intrahepatic metastasis, **d** satellite lesions, and **e** tumor size in the long-term vs. non-long-term groups

LT group, $n = 3$, 5.9%) (all $p < 0.05$). In contrast, more LT patients were noted to be AJCC T1a and T3 than in T1b and T2 (T1a: non-LT group, $n = 71$, 58.2% vs. LT group, $n = 51$, 41.8%; T3: non-LT group, $n = 73$, 71.6% vs. LT group, $n = 29$, 28.4%, $p < 0.001$) (Table 3). When nodal status was restricted to patients who had at least six LNs harvested as recommended by the AJCC, the proportion of LT survivors who were N0 or NX was 31% ($n = 16$) and 25.8% ($n = 128$), respectively, whereas only a minority of LT patients were N1 ($n = 9$, 6.8%) (Table 3). Only 158 (30.0% of 526 patients in the non-LT group) and 25 (16.3% of 153 patients in the LT group) patients in non-LT and LT groups, respectively, had an adequate nodal staging and were staged according to the AJCC 8th edition TNM staging system. The incidence of LT was 80% in stage Ia, 25% in stage Ib, 35% in stage II, 12% in stage III, and 7% in stage IV. In contrast, the incidence of non-LT was 93% in stage IIIb and decreased to only 20% in stage Ia (Table 3).

Table 2 Multivariable analysis

	OR	95% CI	*p* value
Intrahepatic metastasis	3.75	0.85–16.6	0.082
Direct invasion adjacent organs	3.98	1.18–13.4	0.026
Perineural invasion	4.78	1.92–11.8	0.001
Satellite lesion	2.12	1.15–3.90	0.016
Lymphnode status			
N0	–	–	–
N1	4.64	1.77–12.2	0.002
NX	1.28	0.76–2.15	0.36
Size > 5 cm	2.40	1.54–3.74	< 0.001

Table 3 Long-term survivors and AJCC staging system 8th edition

	Non-LT N (%)	LT N (%)	*p* value	OR	95% IC	*p* value
AJCC T stages			< 0.001			
T1a	71 (58.2%)	51 (41.8%)		–	–	–
T1b	129 (80.1%)	32 (19.9%)		2.89	1.71–4.91	< 0.001
T2	205 (84.4%)	38 (15.6%)		3.87	2.35–6.38	< 0.001
T3	73 (71.6%)	29 (28.4%)		1.81	1.03–3.17	0.038
T4	48 (94.1%)	3 (5.9%)		11.5	3.39–38.9	< 0.001
AJCC N stages			< 0.001			
N0	35 (68.6%)	16 (31.4%)		–	–	–
N1	123 (93.2%)	9 (6.8%)		6.25	2.54–15.3	< 0.001
NX	368 (74.2%)	128 (25.8%)		1.31	0.70–2.45	0.39
AJCC TNM stages			< 0.001			
Ia	1 (16.7%)	5 (83.3%)		–	–	–
Ib	8 (72.7%)	3 (27.3%)		12.0	0.79–180.9	0.07
II	17 (70.8%)	7 (29.2%)		7.42	0.69–79.9	0.09
IIIa	9 (90.0%)	1 (10.0%)		28.0	1.35–580.6	0.031
IIIb	123 (93.2%)	9 (6.8%)		54.7	5.51–541.7	0.001

Discussion

Although complete surgical resection remains the treatment of choice for patients with ICC, the prognosis of ICC remains unfavorable with 5-year survival ranging from 20 to 40%.[23] Several studies have identified clinicopathological factors associated with long-term outcomes of patients undergoing liver surgery for ICC, such as preoperative CA 19-9 levels, tumor number and size, lymph node status, margin status, as well as vascular invasion.[2, 13, 16, 24–30] Several predictive models have been applied to patients with ICC in order to better define prognosis.[9, 26, 31] The most commonly used staging system for ICC is the TNM classification system. In the recently released new 8th edition of the AJCC TNM manual, several new revisions were introduced into the staging for ICC.[8] Specifically, in the 8th edition, T1 disease has been revised to include tumor size (≤ 5 cm vs. > 5 cm); T2 now reflects an equivalent prognostic value of vascular invasion and multifocal disease; while T4 disease is defined as involving local extrahepatic structures by direct invasion. Hyder et al. reported a prognostic nomogram for resectable ICC based on the clinicopathologic data of 367 patients with ICC that included six factors, such as age, tumor size, number of lesions, nodal status, vascular invasion, and presence of cirrhosis.[9] Most of these past studies focused, however, on short-term prognosis within 5 years of surgery. To our knowledge, no past studies has specifically focused on the actual long-term survivors following curative-intent resection of ICC to identify clinicopathological factors associated with long-term survival. The current study is important because it is one of the first studies to examine the incidence of actual long-term survivors in a large, multi-center cohort of over 1000 patients undergoing surgery for ICC at 1 of 14 major hepatobiliary centers in the USA, Europe, Australia, and Asia, as well as measure the impact of clinicopathological factors on long-term survivors.

When analyzing the data, it was interesting to note that analysis of actual survivors provided additional information compared with simple, standard Kaplan-Meier survival estimates. In particular, while the calculated actuarial OS at 5 years was roughly 40%, there were only 153 (13%) actual long-term survivors among the 1154 patients following curative-intent surgery. In turn, data from the current study provide more accurate "actual" data on the long-term prognosis of patients undergoing curative intent surgery of ICC. While Kaplan-Meier analyses are helpful in estimating prognosis, this type of survival analysis may underestimate the effect of patients lost to follow-up and who are therefore censored in the analysis. Lost to follow-up may be particularly important among patients with ICC given the high risk of recurrence and death of disease in the first years following surgery for ICC.[32] As such, patients lost to follow-up are likely to adversely impact any estimation of prognosis and the Kaplan-Meier method may overestimate true survival.[14, 33] In turn, some groups, like our own, have proposed using nonmixture cure models as a means to better estimate the chance of statistical cure following surgical resection.[15, 34, 35] In fact, using a noncore statistical model, we had previously estimated that the overall probability of cure was approximately 10% for "all comer" patients undergoing hepatic resection for ICC. Interestingly, data from our previous statistical model (10%) very closely approximated the 13% incidence of actual long-term survivors reported in the current study.

Perhaps not surprisingly, LT patients had many more favorable prognostic factors compared with non-LT patients. In particular, patients who were in the LT group had a lower incidence of PI/MF + PI ICC vs. the non-LT group ($p = 0.002$). As our group recently reported, PI/MF + PI tumors were associated with more aggressive features than MF/IG ICC.[36] Specifically, patients with a PI/MF + PI tumor had a 5-year OS of 25.5% vs. 41.8% for patients with a MF/IG ICC ($p < 0.001$). Also, the incidence of tumors ≥ 5 cm was lower in the LT group, with over a twofold increased odds that patients with an ICC ≥ 5 cm were in the non-LT group (OR 2.40; $p < 0.001$). The correlation between tumor size and long-term outcome has been previously evaluated.[24] Hyder et al. reported that tumor size was a prognostic factor for survival after surgical resection for ICC and noted that the association of tumor size on survival plateaued at 7 cm.[9] The effect of tumor size on outcome has been correlated to the underlying presence of microscopic vascular invasion and higher tumor grade in larger ICC.[13] In a study by Spolverato et al., one third and one half of patients with tumors measuring 7 to 15 and ≥ 15 cm, respectively, had microscopic vascular invasion and one in three patients with tumors ≥ 15 cm had evidence of major vascular invasion.[13] Consistent with these previous findings, patients in the LT group were more likely to have well/moderately differentiated ICC and to have tumors with microvascular invasion. The importance of N status has also been reported in previous studies.[7, 10, 11, 37–44] In a recent meta-analysis, LN metastasis was associated with increased risk of death in pool data (HR 2.09),[7] and Kim et al. confirmed these findings reporting a similar relative risk of death associated with LN metastasis (HR 2.42; $p < 0.001$).[12] In the current study, lymph node metastasis (OR 4.64; $p = 0.002$) was one of the strongest independent predictors of poor prognosis and decreased chance of long-term survival. In fact, when the AJCC recommended cut-off of six LNs harvested was applied to identify N0 patients, the incidence of LTs in N0 stage increased to 31%, which was higher than the incidence of LTs in either the N1 and NX categories. Collectively, these data serve to emphasize both the prognostic value of N status and the importance of adequate nodal staging.

LT patients were more likely to have T1a-T1b-T3 tumors (i.e., solitary tumor measuring ≤ 5 cm (T1a); solitary tumor > 5 cm (T1b); tumor perforating the visceral peritoneum (T3)), rather than T2 tumors (i.e., solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion). These data suggest that perforation of the visceral peritoneum may not carry as poor a prognostic impact as vascular invasion. In fact, Spolverato et al. previously reported that, while T1b patients had a better 5-year OS (37.3%) than T2 patients (21.3%), T3 patients paradoxically had a better 5-year OS than either of these lower T categories (45.8%).[18] As such, an advanced T stage tumor may not preclude long-term survival. Moreover, while stage T2 includes both patients with intrahepatic metastases (multiple lesions in different segments) and satellite lesions (dominant mass with nodules in same segment), in the current analyses, these two distinct patterns of multifocal disease were associated with different chances of LT survival (intrahepatic metastasis: OR 3.75; satellite lesions: OR 2.12). Based on these results, stages T2 and T3 might need to be redefined to better stratify patient prognosis.

Another interesting finding of the current study was that traditional adverse prognostic factors did not categorically preclude LT survival. To this point, a subset of patients in the LT survival group were characterized by a number of traditionally poor prognostic factors including R1 disease (7%), T3 tumors (19%), moderate/poor tumor differentiation (13%), and N1 disease (6%). These data emphasize how prognostic factors cannot be utilized to rule out the possibility of LT survival even in patients with predicted poor outcomes. To this end, several groups have reported on using conditional survival estimates to provide quantitative information about the changing probability of survival over time among patients with cancer.[34, 35, 45, 46] Spolverato and colleagues reported that, while actuarial OS decreased over time from 39% at 3 years to 16% at 8 years, 3-year conditional increased over time among those patients who survived.[15] In fact, the 3-year conditional survival at 5 years—the probability of surviving to postoperative year 8 after having already survived to postoperative year 5—was 65% compared with an 8-year actuarial OS estimate of 16%. Taken together, while certain factors may be strongly associated with LT survival, data in the current study, as well as previous data, demonstrate that LT can occur even in a subset of patients with traditional adverse prognostic factors.

The current study had several limitations. The multi-center nature of the study also did not allow for standardization of operative or perioperative approach, especially in terms of performance and extent of lymphadenectomy, neoadjuvant and adjuvant chemotherapy, and follow-up. Although this is a possible limitation, it is also a strength of the study as it contributes to the generalizability of the data. Due to the retrospective nature of the study, selection bias should be taken into account when interpreting the results; however, such confounding was unlikely to impact the evaluation of the prognostic features of long-term survivors.

In conclusion, while ICC is generally associated with a poor prognosis, some patients can survive more than 5 years after surgery. The incidence of LT survivors following curative-intent surgery was low, as only one in ten patients actually survived past 5 years. Several pathological factors were associated with the likelihood of LT survivorship, yet LT survival did occur among a small subset of patients who had poor prognostic features. ICC is an aggressive disease with few LT survivors even after curative-intent surgery. Efforts should be aimed to better understand the pathogenesis

and molecular underpinnings of ICC in order to identify more effective systemic therapeutic agents. Only through the discovery and implementation of novel therapeutic approaches will we be able to improve the LT outcomes of patients with ICC.

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