Surgical Management of Intrahepatic Cholangiocarcinoma in Patients with Cirrhosis: Impact of Lymphadenectomy on Peri-Operative Outcomes

Fabio Bagante¹ · Gaya Spolverato¹ · Matthew Weiss² · Sorin Alexandrescu³ · Hugo P. Marques⁴ · Luca Aldrighetti⁵ · Shishir K. Maithel⁶ · Carlo Pulitano⁷ · Todd W. Bauer⁸ · Feng Shen⁹ · George A. Poultsides¹⁰ · Olivier Soubrane¹¹ · Guillaume Martel¹² · B. Groot Koerkamp¹³ · Alfredo Guglielmi¹ · Endo Itaru¹⁴ · Andrea Ruzzenente¹ · Timothy M. Pawlik¹⁵

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Abstract

Background The consequences of lymphadenectomy (LND) on cirrhotic patients undergoing hepatectomy for intrahepatic cholangiocarcinoma (ICC) have not been investigated. We sought to analyze the impact of LND on morbidity among patients undergoing resection for ICC.

Methods A total of 1005 patients who underwent hepatectomy for ICC at one of the 14 participating institutions between 1990 and 2015 were identified. A propensity score match analysis was performed to reduce confounding biases between cirrhosis and non-cirrhosis groups.

Results Cirrhosis was diagnosed in 118 (11.7%) patients. Among non-cirrhotic patients, 63% underwent major liver resection versus only 20% among patients with cirrhosis ($p < 0.001$). LND was also less common among cirrhotic versus non-cirrhotic patients (19 vs. 50%, $p < 0.001$). The incidence of complications was 41 and 30% among patients who did not and did have cirrhosis, respectively ($p = 0.022$). The propensity-matched cohort included 150 patients. The incidence of complications was 71% among patients who underwent lymphadenectomy versus 23% among patients who did not undergo lymphadenectomy (OR 8.39) ($p < 0.001$). In the propensity-matched analysis, the median HLN was comparable among patients independent of cirrhosis status (median HLN: non-cirrhosis, 2.5 vs. cirrhosis, 2) ($p = 0.95$). While lymphadenectomy was associated with a higher risk of infections (non-cirrhosis, 0% vs. cirrhosis, 21%, $p < 0.001$) among patients with cirrhosis, infections were not associated with lymphadenectomy among non-cirrhotic patients ($p = 0.19$).

Conclusion Lymphadenectomy was associated with an increased risk of complications among patients with cirrhosis undergoing surgery for ICC. The benefit of lymphadenectomy in cirrhotic patients should be considered in light of the higher risk of postoperative complications compared with non-cirrhotic patients.

Introduction

A variety of liver diseases including intrahepatic lithiasis, primary sclerosing cholangitis, congenital abnormalities of the bile ducts, and liver fluke infection can induce a state of

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Fabio Bagante and Gaya Spolverato have contributed equally to this manuscript.

✉ Timothy M. Pawlik
tim.pawlik@osumc.edu

¹ Department of Surgery, University of Verona, Verona, Italy

² Department of Surgery, Johns Hopkins Hospital, Baltimore, MD, USA

³ Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania

⁴ Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal

⁵ Department of Surgery, Ospedale San Raffaele, Milan, Italy

chronic biliary inflammation resulting in severe fibrosis and cirrhosis of the underlying liver parenchyma [1–3]. Several studies have identified cirrhosis as a risk factor for the development of intrahepatic cholangiocarcinoma (ICC) [1, 2, 4–6]. In fact, a strong association between HCV-related cirrhosis and ICC [7, 8] and a weaker but consistent association between HBV-related cirrhosis and ICC have been identified [9]. Furthermore, cirrhosis associated with metabolic syndrome, steatohepatitis, and non-alcoholic fatty liver disease (NAFLD) has been linked to an increased risk of ICC [10, 11]. A population-based analysis using the Surveillance, Epidemiology, and End Results (SEER) database confirmed a strong association between cirrhosis and ICC [12].

Recently, the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual emphasized the importance of adequate nodal staging for ICC [13]. The manual called for a minimum of six harvested lymph nodes (HLN) for adequate nodal staging. The potential implications of performing lymphadenectomy among patients with ICC and cirrhosis have not been investigated. This topic is of particular importance because the subset of patients with cirrhosis may be at increased risk of morbidity [14]. For example, Lee et al. [15] reported that patients with cirrhosis who underwent gastrectomy and a D2 lymphadenectomy for gastric cancer had a higher incidence of postoperative complications of up to 40%. In a separate study, Tachibana et al. [16] reported that the incidence of postoperative complication was as high as 80% among patients with cirrhosis who underwent esophagectomy combined with an extended lymphadenectomy.

While the impact of cirrhosis on morbidity related to hepatectomy has been well defined [17], the possible increase in morbidity related to lymphadenectomy among patients with ICC and cirrhosis has not been examined. Therefore, the objective of the current study was to define the impact of cirrhosis on lymphadenectomy utilization relative to short-term outcomes following surgery for ICC using a large multi-institutional international dataset.

Patients and methods

Study population and data collection

Patients who underwent hepatectomy for ICC at one of 14 hepatobiliary centers between 1990 and 2015 were identified (Supplementary Methods). Only patients who underwent curative-intent hepatectomy for ICC without extrahepatic metastasis were included. Patients who underwent only non-surgical treatments such as percutaneous ablation or intra-arterial therapy were excluded. Standard patient demographic and clinicopathological characteristics were collected including age, gender, American Society of Anesthesiologist (ASA) class, serum level of CA19-9, morphological type, number of ICC, tumor size, invasion of adjacent organs, liver capsule involvement, margin status, tumor grade, major vascular invasion, lymphovascular invasion, perineural invasion, and lymph-nodal status were collected. The diagnosis of cirrhosis was histologically confirmed. Treatment-related data such as type and extent of hepatectomy, lymphadenectomy, receipt of neoadjuvant, and adjuvant chemotherapy were also recorded. Tumor stage was categorized according to the 8th edition of the American Joint Committee on Cancer (AJCC) [13].

Statistical analysis

Continue variables were described as medians with interquartile range (IQR), and categorical variables were recorded as totals and frequencies. Univariable comparisons were assessed using Chi-squared test or Fisher's exact test as appropriate. To account for any potential residual confounders regarding the effect of cirrhosis on postoperative complications, propensity scores matching was performed (Supplementary Methods). The degrees of covariate imbalance in unmatched and matched samples were measured using the standardized differences as proposed by Austin et al. [18]. A *p* value of <0.10 (two-tailed) was considered statistically significant. All analyses were performed using Stata version 12.0 (StataCorp LP, College Station, TX, USA) or R software for statistical computing,

⁶ Department of Surgery, Emory University, Atlanta, GA, USA

⁷ Department of Surgery, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia

⁸ Department of Surgery, University of Virginia, Charlottesville, VA, USA

⁹ Department of Surgery, Eastern Hepatobiliary Surgery Hospital, Shanghai, China

¹⁰ Department of Surgery, Stanford University, Stanford, CA, USA

¹¹ Department of Hepatobiliopancreatic Surgery and Liver Transplantation, AP-HP, Beaujon Hospital, Clichy, France

¹² Division of General Surgery, Department of Surgery, University of Ottawa, Ottawa, ON, Canada

¹³ Department of Surgery, Erasmus University Medical Centre, Rotterdam, Netherlands

¹⁴ Gastroenterological Surgery Division, Yokohama City University School of Medicine, Yokohama, Japan

¹⁵ Department of Surgery, The Urban Meyer III and Shelley Meyer Chair in Cancer Research, The Ohio State University Wexner Medical Center, 395 W. 12th Ave., Suite 670, Columbus, OH 43210, USA

v. 3.0.2 34, with the additional packages: Hmisc and Matching.

Results

Baseline characteristics of patients in non-cirrhosis and cirrhosis groups

A total of 1005 patients underwent hepatectomy for ICC. Cirrhosis was present in 118 (11.7%) patients, while 887 (88.3%) patients did not have cirrhosis (Table 1). All patients who had cirrhosis were Child–Pugh Class A and well compensated. Several clinical characteristics were different between the cirrhotic versus non-cirrhotic groups (Supplementary Materials). At the time of surgery, patients who did not have cirrhosis ($n = 494$, 63.2%) more often underwent a major hepatectomy compared with cirrhotic patients (20.4%, $n = 22$) ($p < 0.001$). In addition, compared with patients who had cirrhosis, patients who did not have cirrhosis were more likely to have undergone a concomitant bile-duct resection (non-cirrhosis, $n = 155$, 19.8% vs. cirrhosis, $n = 3$, 2.8%; $p < 0.001$). Of note, while roughly half of patients without cirrhosis underwent a lymphadenectomy ($n = 445$, 50.2%), less than 1 in 5 patients who had cirrhosis had any lymph nodes harvested at the time of surgery ($n = 23$, 19.5%) ($p < 0.001$). On pathological assessment, the median HLN was 3 (IQR, 1–6) among patients with cirrhosis compared with 4 (IQR, 2–8) among patients who did not have cirrhosis ($p = 0.12$). The median number of metastatic lymph nodes (MLN) was no different among patients who did ($n = 1$, IQR, 1–3) and did not ($n = 1$, IQR, 1–5) have cirrhosis ($p = 0.51$). On pathological assessment, there was also no difference in the proportion of patients who had R1 surgical margin (R1 margin: non-cirrhosis, $n = 123$, 14.1% vs. cirrhosis, $n = 10$, 8.5%) ($p = 0.11$).

Following surgery, a total of 395 patients experienced a complication for an overall morbidity rate of 39.3%. The incidence of any complication was slightly higher among patients who did not have cirrhosis ($n = 360$, 40.6%) compared with patients who had cirrhosis ($n = 35$, 29.7%) ($p = 0.022$). Particularly, the incidences of renal failure, pleural effusion, posthepatectomy liver failure (PHLF), hemorrhages, wound infections, respiratory, and cardiovascular complications were not different comparing non-cirrhosis and cirrhosis groups (all $p > 0.1$). In contrast, patients with cirrhosis group had a lower incidence of bile leakage and infections after surgery compared with non-cirrhotic patients (bile leakage: non-cirrhosis, $n = 59$, 6.6% vs. cirrhosis, $n = 3$, 2.5%, $p = 0.08$; infections: non-cirrhosis, $n = 86$, 9.7% vs. cirrhosis, $n = 4$, 3.4%, $p = 0.024$; Table 2). Interestingly, there was no difference

Table 1 Clinical and pathological features of the entire study cohort ($n = 1005$)

Variables	Non-cirrhosis <i>N</i> (%)	Cirrhosis <i>N</i> (%)	<i>p</i> value
Patients	887 (88.3%)	118 (11.7%)	–
Age, median (IQR)	62 years (53–70)	56 years (46–65)	<0.001
Gender			<0.001
Female	420 (47.4%)	22 (18.6%)	
Male	467 (52.6%)	96 (81.4%)	
ASA			0.013
≤ 2	534 (60.2%)	85 (72.0%)	
> 2	353 (39.8%)	33 (28.0%)	
Neoadjuvant chemotherapy			0.14
No	707 (90.6%)	97 (95.1%)	
Yes	73 (9.4%)	5 (4.9%)	
Morphological type			0.67
MF, IG	677 (83.1%)	94 (84.7%)	
PI, MF + PI	138 (16.9%)	17 (15.3%)	
Type of resections			<0.001
Wedge resection	116 (14.9%)	35 (32.4%)	
Minor resection	171 (21.9%)	51 (47.2%)	
Major resection	494 (63.2%)	22 (20.4%)	
Margin status			0.11
R0	749 (85.9%)	108 (91.5%)	
R1	123 (14.1%)	10 (8.5%)	
Lymph-node status			<0.001
Negative	273 (30.8%)	11 (9.3%)	
Metastatic	172 (19.4%)	12 (10.2%)	
Not harvested	442 (49.8%)	95 (80.5%)	
Tumor size			<0.001
≤ 5 cm	345 (38.9%)	70 (59.3%)	
> 5 cm	542 (61.1%)	48 (40.7%)	
Liver capsule involvement			0.59
No	758 (85.5%)	103 (87.3%)	
Yes	129 (14.5%)	15 (12.7%)	
Direct invasion adjacent organs			0.094
No	748 (95.8%)	107 (99.1%)	
Yes	33 (4.2%)	1 (0.9%)	
Major vascular resection			0.083
No	633 (80.9%)	94 (87.9%)	
Yes	149 (19.1%)	13 (12.2%)	
Bile-duct resection			<0.001
No	628 (80.2%)	105 (97.2%)	
Yes	155 (19.8%)	3 (2.8%)	
Grade			0.67
Well/moderate	677 (83.1%)	94 (84.7%)	
Poorly/undifferentiated	138 (16.9%)	17 (15.3%)	
Microvascular invasion			0.041
No	549 (63.6%)	85 (73.3%)	

Table 1 continued

Variables	Non-cirrhosis <i>N</i> (%)	Cirrhosis <i>N</i> (%)	<i>p</i> value
Yes	314 (36.4%)	31 (26.7%)	0.002
Perineural invasion			
No	570 (74.7%)	98 (88.3%)	0.99
Yes	193 (25.3%)	13 (11.7%)	
Multi-focal			0.18
No	744 (83.9%)	99 (83.9%)	
Yes	143 (16.1%)	19 (16.1%)	0.79
Ca 19–9, median (IQR)	52 (17–232)	31 (17–65)	
CEA, median (IQR)	2.4 (1.4–4.4)	2.4 (1.6–3.9)	0.022
Complication			
No	527 (59.4%)	83 (70.3%)	0.48
Yes	360 (40.6%)	35 (29.7%)	
Clavien–Dindo grade of complication*			0.12
1–2	204 (56.7%)	22 (62.7%)	
≥3	156 (43.3%)	13 (37.1%)	0.19
Length of stay, median (IQR)	13 (8–18)	14 (11–20)	
Overall survival, 5 year (95% CI)	40.9% (36.4–45.3)	39.0% (28.7–49.2)	

*N = 395 patients who had postoperative complications

NA not available, *CI* confidence interval

in the grade of complication (Clavien–Dindo grade > 3: non-cirrhosis, *n* = 156, 43.3% vs. cirrhosis, *n* = 13, 37.1%) or length of stay (non-cirrhosis, 13 days vs. cirrhosis, 14 days) (both *p* > 0.1).

Among the subset of patients who underwent a lymphadenectomy (*n* = 468, 46.6%), the incidence of postoperative complications was comparable among patients who did (56.5%) and did not (42.9%) have cirrhosis (*p* = 0.21). In addition, among only patients who had cirrhosis, lymphadenectomy was associated with risk of complications (OR 4.31, 95% 1.66–11.2) (*p* = 0.003). Among patients who did not have cirrhosis, there was an increased risk of infections among patients who underwent lymphadenectomy compared with patients who did not (infections: no lymphadenectomy, *n* = 26, 5.9% vs. lymphadenectomy, *n* = 60, 13.5%) (*p* < 0.001); several specific complications were associated with lymphadenectomy when performed among cirrhotic patients (Table 3). Particularly, among patients with cirrhosis, lymphadenectomy was associated with higher risk of superficial wound infections (non-cirrhosis, *n* = 1, 1.0% vs. cirrhosis, *n* = 2, 8.7%, *p* = 0.037) and surgical site infections (non-cirrhosis, *n* = 0, 0% vs. cirrhosis, *n* = 4, 17.4%, *p* < 0.001).

Table 2 Type of complications in non-cirrhosis and cirrhosis groups (*n* = 1005)

Variables	Non-cirrhosis <i>N</i> (%)	Cirrhosis <i>N</i> (%)	<i>p</i> value
Patients	887 (88.3%)	118 (11.7%)	–
Respiratory complications			0.25
No	848 (95.6%)	110 (93.2%)	0.56
Yes	39 (4.4%)	8 (6.8%)	
Cardiovascular complications			0.77
No	865 (97.5%)	114 (96.6%)	0.79
Yes	22 (2.5%)	4 (3.4%)	
Renal failure			0.75
No	875 (98.7%)	116 (98.3%)	0.19
Yes	12 (1.3%)	2 (1.7%)	
Pleura effusion			0.08
No	813 (91.7%)	109 (92.4%)	0.97
Yes	74 (8.3%)	9 (7.6%)	
Posthepatectomy liver failure			0.024
No	868 (97.9%)	116 (98.3%)	0.97
Yes	19 (2.1%)	2 (1.7%)	
Hemorrhage			0.08
No	867 (97.8%)	113 (95.8%)	0.97
Yes	20 (2.2%)	5 (4.2%)	
Bile leakage			0.024
No	828 (93.4%)	115 (97.5%)	0.024
Yes	59 (6.6%)	3 (2.5%)	
Wound infection			0.024
No	865 (97.5%)	115 (97.5%)	0.024
Yes	22 (2.5%)	3 (2.5%)	
Infections			0.024
No	801 (90.3%)	114 (96.6%)	0.024
Yes	86 (9.7%)	4 (3.4%)	

Propensity score matching analysis

A propensity score matching was performed to minimize confounding and create more comparable cohorts (*n* = 150) among patients who did and did not have cirrhosis (Table 4). After propensity matching, demographic and clinicopathological characteristics among the cirrhotic and non-cirrhotic patients were comparable (Table 4). On propensity-matched analysis, the incidence of postoperative complications was 32.0% (*n* = 24) in both cohorts of patients (*p* > 0.99; Table 4). Interestingly, among the 24 patients who did not have cirrhosis yet had a complication, 1 (4.2% of 24) patient had a severe complication (Clavien–Dindo grade of complication ≥ 3) versus 5 (20.8% of 24) patients in the cirrhosis group (*p* = 0.08). Among patients who did not have cirrhosis, the incidence of complications

Table 3 Type of complications in non-cirrhosis and cirrhosis groups for patients who underwent and did not undergo lymphadenectomy ($n = 1005$)

	Non-cirrhosis <i>N</i> (%)		<i>p</i> value	Cirrhosis <i>N</i> (%)		<i>p</i> value
	No Lymphad.	Lymphad		No Lymphad.	Lymphad	
Patients	442 (49.8%)	445 (50.2%)	–	95 (80.5%)	23 (19.5%)	–
Respiratory complications			0.64			<0.00
No	424 (95.9%)	424 (95.3%)		93 (97.9%)	17 (73.9%)	1
Yes	18 (4.1%)	21 (4.7%)		2 (2.1%)	6 (26.1%)	
Cardiovascular complications			0.68			0.00
No	432 (97.7%)	433 (97.3%)		94 (99.0%)	20 (86.9%)	4
Yes	10 (2.3%)	12 (2.7%)		1 (1.0%)	3 (13.0%)	
Renal failure			0.57			0.48
No	437 (98.9%)	438 (98.4%)		93 (97.9%)	23 (100%)	
Yes	5 (1.1%)	7 (1.6%)		2 (2.1%)	–	
Pleura effusion						
No	387 (87.6%)	426 (95.7%)		89 (93.7%)	20 (86.9%)	
Yes	55 (12.4%)	19 (4.3%)	<0.001	6 (6.3%)	3 (13.0%)	0.28
Posthepatectomy liver failure			0.81			0.00
No	432 (97.7%)	436 (98.0%)		95 (100%)	21 (91.3%)	4
Yes	10 (2.3%)	9 (2.0%)		–	2 (8.7%)	
Hemorrhage			0.66			0.24
No	433 (98.0%)	434 (97.5%)		92 (96.8%)	21 (91.3%)	
Yes	9 (2.0%)	11 (2.5%)		3 (3.2%)	2 (8.7%)	
Bile leakage			0.24			0.037
No	417 (94.3%)	411 (92.4%)		94 (99.0%)	21 (91.3%)	
Yes	25 (5.7%)	34 (7.6%)		1 (1.0%)	2 (8.7%)	
Wound infection			0.99			0.037
No	431 (97.5%)	434 (97.5%)		94 (99.0%)	21 (91.3%)	
Yes	11 (2.5%)	11 (2.5%)		1 (1.0%)	2 (8.7%)	
Infections			<0.00			<0.00
No	416 (94.1%)	385 (86.5%)	1	95 (100%)	19 (82.6%)	1
Yes	26 (5.9%)	60 (13.5%)		–	4 (17.4%)	

was 42.9% ($N = 6$) among patients who underwent lymphadenectomy versus 29.5% ($N = 18$) among patients who did not undergo lymphadenectomy ($p = 0.33$; Fig. 1a). In contrast, the incidence of complication was 71.4% ($N = 10$) among patients who underwent lymphadenectomy versus 22.9% ($N = 14$) among patients who did not undergo lymphadenectomy (OR 8.39, 95% CI 2.3–30.9) ($p < 0.001$; Fig. 1b). In the propensity-matched analysis, the median HLN was comparable among patients independent of cirrhosis status ($p = 0.95$; Fig. 2a) and was not associated with the occurrence of complications ($p = 0.68$; Fig. 2b). While lymphadenectomy was associated with a higher risk of infections (non-cirrhosis, $n = 0$, 0% vs. cirrhosis, $n = 3$, 21.4%, $p < 0.001$) among patients with cirrhosis, infections were not associated with

lymphadenectomy among patients who did not have cirrhosis ($p = 0.19$) (Supplementary Tables 1S and 2S).

Discussion

Cirrhosis can be a common finding among patients with liver malignancies. While the association of cirrhosis with HCC is well established [19], more recent data have established that cirrhosis can also significantly increase the risk of ICC [8–10]. In turn, cirrhosis can have important implications in the peri-operative management of patients undergoing liver surgery increasing the risk of morbidity and mortality associated with liver resection [17]. Since lymphadenectomy is not commonly performed for HCC, the potential incremental risk of lymph-node dissection in

Table 4 Clinical and pathological features of patients after propensity score matching analysis ($n = 150$)

Variables	Non-cirrhosis <i>N</i> (%)	Cirrhosis <i>N</i> (%)	<i>p</i> value
Patients	75 (50.0%)	75 (50.0%)	–
Age, median (IQR)	57 years (48–64)	54 years (46–66)	0.72
Gender			0.57
Female	20 (26.7%)	17 (22.7%)	
Male	55 (73.3%)	58 (77.3%)	
ASA			0.55
≤ 2	61 (81.3%)	58 (77.3%)	
> 2	14 (18.7%)	17 (22.7%)	
Neoadjuvant chemotherapy			0.30
No	69 (98.6%)	66 (95.6%)	
Yes	1 (1.4%)	3 (4.4%)	
Morphological type			0.98
MF, IG	70 (95.9%)	71 (95.9%)	
PI, MF + PI	3 (4.1%)	3 (4.1%)	
Type of resections			0.97
Wedge resection	23 (32.4%)	23 (32.4%)	
Minor resection	32 (45.1%)	33 (46.5%)	
Major resection	16 (22.5%)	15 (21.1%)	
Margin status			0.47
R0	70 (93.3%)	72 (96.0%)	
R1	5 (6.7%)	3 (4.0%)	
Lymph-node status			0.93
Negative	9 (12.0%)	8 (10.7%)	
Metastatic	5 (6.7%)	6 (8.0%)	
Not harvested	61 (81.3%)	61 (81.3%)	
Tumor size			0.86
≤ 5 cm	51 (68.0%)	50 (66.7%)	
> 5 cm	24 (32.0%)	25 (33.3%)	
Liver capsule involvement			0.55
No	68 (90.7%)	70 (93.3%)	
Yes	7 (9.3%)	5 (6.7%)	
Direct invasion adjacent organs			> 0.99
No	70 (98.6%)	70 (98.6%)	
Yes	1 (1.4%)	1 (1.4%)	
Major vascular resection			0.31
No	69 (92.0%)	71 (95.9%)	
Yes	6 (8.0%)	3 (4.1%)	
Bile-duct resection			0.56
No	69 (97.2%)	70 (98.6%)	
Yes	2 (2.8%)	1 (1.4%)	
Grade			0.51
Well/moderate	67 (93.1%)	63 (90.0%)	
Poorly/undifferentiated	5 (6.9%)	7 (10.0%)	
Microvascular invasion			0.82
No	62 (83.8%)	63 (85.1%)	
Yes	12 (16.2%)	11 (14.9%)	
Perineural invasion			0.15
No	63 (87.5%)	68 (94.4%)	

Table 4 continued

Variables	Non-cirrhosis N (%)	Cirrhosis N (%)	p value
Yes	9 (12.5%)	4 (5.6%)	0.56
Multi-focal			
No	67 (89.3%)	69 (92.0%)	0.27
Yes	8 (10.7%)	6 (8.0%)	
Ca 19–9, median (IQR)	30 (12–77)	33 (17–66)	0.40
CEA, median (IQR)	2.4 (1.6–3.4)	2.3 (1.6–3.7)	>0.99
Complication			0.08
No	51 (68.0%)	51 (68.0%)	
Yes	24 (32.0%)	24 (32.0%)	0.034
Clavien–Dindo grade of complication*			
1–2	23 (95.8%)	19 (79.2%)	0.39
≥3	1 (4.2%)	5 (20.8%)	
Length of stay, median (IQR)	14 (10–17)	14 (11–20)	
Overall survival, 5 year (95% CI)	50.0% (35.0–63.3)	48.7% (35.8–60.5)	

*N = 48 patients who had postoperative complications

NA not available, CI confidence interval

the setting of cirrhosis and HCC has not been clinically relevant. The topic of lymphadenectomy is much more relevant among ICC patients as the 8th edition of the AJCC staging system now recommends that surgeons perform a lymphadenectomy [13]. The current study was important because it specifically examined peri-operative outcomes of that subset of ICC patients who had concomitant cirrhosis. While the incidence of any complication was not higher among patients who had cirrhosis, this group of patients was more likely to undergo a minor versus major hepatectomy. Interestingly, while roughly half of patients without cirrhosis underwent a lymphadenectomy, only about 20% of patients with cirrhosis had any LNH at the time of surgery. When lymph nodes were indeed evaluated,

however, the incidence of MLN was comparable among patients who did and did not have cirrhosis. On propensity score matching analysis, lymphadenectomy was associated with an increased risk of morbidity among patients with cirrhosis compared with patients who did not have cirrhosis. To our knowledge, these data are the first to examine specifically the topic of lymphadenectomy for ICC among patients with cirrhosis.

A recent population-based study using the National Health and Nutrition Survey data estimated that the prevalence of cirrhosis was approximately 0.27% in the USA [20]. The authors also noted that male sex and older age were independently associated with the risk of cirrhosis [20]. In the current study, we noted that the incidence of

Fig. 2 **a** Number of lymph node harvested among patients with no cirrhosis ($n = 75$) versus patients with cirrhosis ($n = 75$) in the propensity-matched cohort. **b** Number of lymph node harvested among patients who had no complications ($n = 102$) versus patients who experience at least one complication ($n = 48$)

cirrhosis among ICC patients was higher among men, yet the median age of patients with ICC and cirrhosis was younger than non-cirrhotic patients. Cirrhosis is an important risk factor for ICC, as several studies have reported a strong association between cirrhosis and ICC [21–23]. Several studies from Eastern countries have noted an incidence of cirrhosis as high as 20–25% among patients with ICC [24, 25]. Conversely, in most Western series, the incidence of cirrhosis has been somewhat lower at about 10% [26–28]. In the current study, roughly 1 in 10 patients who had ICC also had pathological evidence of underlying cirrhosis. Differences in the reported incidences of cirrhosis are undoubtedly multi-factorial and may be related to regional epidemiological differences in terms of incidence of environmental risk factors (e.g., hepatitis, obesity, and hepatolithiasis). The “intermediate” incidence of cirrhosis reported in the current study likely reflects the multinational character of our database. In fact, in our study cohort, the incidence of cirrhotic patients was 2.9% among centers in the USA versus 9.5% among European centers and 19.2% among Eastern centers ($p < 0.001$).

Perhaps not surprisingly, there were several differences in the baseline clinicopathological and surgical characteristics among cirrhotic versus non-cirrhotic patients. For example, the size of ICC tumors was smaller among patients with cirrhosis. Patients who had cirrhosis underwent fewer major hepatectomies, as well as were less likely to have a concomitant major vascular ($\Delta = -7\%$) or bile-duct ($\Delta = -17\%$) resection. In addition, patients with cirrhosis were also less likely to undergo lymphadenectomy ($\Delta = -30\%$). Previous data from our own group had noted that utilization of lymphadenectomy among patients with ICC varied considerably [29–31]. In fact, the odds of performing a lymphadenectomy has increase over time as

more and more surgeons have accepted the importance of nodal staging for ICC [32]. Furthermore, surgeons are more prone to perform a lymphadenectomy among patients with more advanced T-stage disease [32]. The current study expands on this previous work as it noted that the presence of cirrhosis also significantly influenced the surgical decision to perform a lymphadenectomy. In fact, patients with cirrhosis were about a third less likely to have a lymph node evaluated. These data are important especially in light of the finding that when lymphadenectomy was performed, the chance of finding metastatic disease in the nodal basin was comparable among cirrhotic and non-cirrhotic patients.

Given the varied baseline clinical and surgical details among cirrhotic and non-cirrhotic patients, a propensity score match analysis was performed to obtain a more comparable cohort of patients. Among the 150 propensity-matched patients, the overall incidence of morbidity was comparable among cirrhotic and non-cirrhotic patients ($\approx 30\%$). Of note, the incidence of severe complication (Clavien–Dindo grade ≥ 3) was, however, fivefold higher among patients with cirrhosis compared with non-cirrhotic patients (non-cirrhosis 4.2% vs. cirrhosis 20.8%). Interestingly, among non-cirrhotic patients, there was no difference in the risk of morbidity among patients with or without lymphadenectomy. In contrast, among patients who had cirrhosis, the risk of a complication was roughly threefold higher among patients who had a lymphadenectomy (71%) compared with patients who did not have a lymphadenectomy (23%) ($p < 0.001$). These data are consistent with findings from previous studies that have evaluated lymphadenectomy and cirrhosis for other malignancies [14–16]. In one study that examined patients with gastric cancer, the authors reported that lymphadenectomy in the presence of cirrhosis was associated

with a great risk of complications including infection and ascites [15]. Interestingly, in the current study we similarly noted that lymphadenectomy in the setting of cirrhosis was associated with a higher risk of infection, yet not ascites. As such, the data would collectively suggest that the benefit of lymphadenectomy in cirrhotic patients should be considered relative to the somewhat higher morbidity.

Several limitations should be considered when interpreting the results. Given the retrospective design and the multicenter nature of the study, selection bias was possible. Undoubtedly, there were some patients with cirrhosis who were not offered surgery due to the poor underlying quality of their non-tumorous hepatic parenchyma. In addition, only Child–Pugh Class A patients were included in the current study and therefore the results should not be extrapolated to patients with more advanced cirrhosis. The study cohort also included patients who underwent liver surgery at one of fourteen hepatobiliary centers in the USA, Europe, Australia, and Asia. The results from the current study may therefore not be generalizable to non-academic, community centers or lower volume hepatobiliary centers.

In conclusion, the incidence of cirrhosis among ICC patients undergoing surgical management was 12%. The incidence of cirrhosis varied somewhat by center and geographic region. Patients who had cirrhosis were less likely to undergo a major hepatectomy and were about one-third less likely to undergo lymphadenectomy at the time of surgery. The incidence of MLN was comparable among cirrhotic and non-cirrhotic patients when lymph-node evaluation was performed. On propensity matching, even after controlling for competing risk factors, patients with cirrhosis had a higher likelihood of complications when a lymphadenectomy was performed. As such, the AJCC 8th edition recommendation to perform an extended lymph-node harvest should be considered in light of these data when operating on patients with ICC and cirrhosis.

References

- Plentz RR, Malek NP (2015) Clinical presentation, risk factors and staging systems of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* 29:245–252
- Shin HR, Oh JK, Masuyer E et al (2010) Epidemiology of cholangiocarcinoma: an update focusing on risk factors. *Cancer Sci* 101:579–585
- Chan-On W, Kuwahara K, Kobayashi N et al (2009) Cholangiocarcinomas associated with long-term inflammation express the activation-induced cytidine deaminase and germinal center-associated nuclear protein involved in immunoglobulin V-region diversification. *Int J Oncol* 35:287–295
- Goral V (2017) Cholangiocarcinoma: new insights. *Asian Pac J Cancer Prev* 18:1469–1473
- Thinkhamrop K, Khuntikeo N, Phonjitt P et al (2015) Association between diabetes mellitus and fatty liver based on ultrasonography screening in the world's highest cholangiocarcinoma incidence region, Northeast Thailand. *Asian Pac J Cancer Prev* 16:3931–3936
- Zhang H, Yang T, Wu M et al (2016) Intrahepatic cholangiocarcinoma: epidemiology, risk factors, diagnosis and surgical management. *Cancer Lett* 379:198–205
- Welzel TM, Graubard BI, El-Serag HB et al (2007) Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin Gastroenterol Hepatol* 5:1221–1228
- Shaib YH, Davila JA, McGlynn K et al (2004) Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol* 40:472–477
- Peng NF, Li LQ, Qin X et al (2011) Evaluation of risk factors and clinicopathologic features for intrahepatic cholangiocarcinoma in Southern China: a possible role of hepatitis B virus. *Ann Surg Oncol* 18:1258–1266
- Michelotti GA, Machado MV, Diehl AM (2013) NAFLD NASH and liver cancer. *Nat Rev Gastroenterol Hepatol* 10:656–665
- Cauchy F, Fuks D, Zarzavadjian Le Bian A et al (2014) Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery: the new scourges? *World J Hepatol* 6:306–314
- Shaib YH, El-Serag HB, Davila JA et al (2005) Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology* 128:620–626
- Amin MB, American Joint Committee on Cancer (2017) *AJCC cancer staging manual* Chicago, American Joint Committee on Cancer, Springer
- Bagante F, Spolverato G, Weiss M et al. (2018) Assessment of the lymph node status in patients undergoing liver resection for intrahepatic cholangiocarcinoma: the new eighth edition AJCC staging system. *J Gastrointest Surg* 22(1):52–59
- Lee JH, Kim J, Cheong JH et al (2005) Gastric cancer surgery in cirrhotic patients: result of gastrectomy with D2 lymph node dissection. *World J Gastroenterol* 11:4623–4627
- Tachibana M, Kotoh T, Kinugasa S et al (2000) Esophageal cancer with cirrhosis of the liver: results of esophagectomy in 18 consecutive patients. *Ann Surg Oncol* 7:758–763
- Hackl C, Schlitt HJ, Renner P et al (2016) Liver surgery in cirrhosis and portal hypertension. *World J Gastroenterol* 22:2725–2735
- Austin PC, Grootendorst P, Anderson GM (2007) A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 26:734–753
- El-Serag HB (2011) Hepatocellular carcinoma. *N Engl J Med* 365:1118–1127
- Scaglione S, Kliethermes S, Cao G et al (2015) The epidemiology of cirrhosis in the United States: a population-based study. *J Clin Gastroenterol* 49:690–696
- Affo S, Yu LX, Schwabe RF (2017) The role of cancer-associated fibroblasts and fibrosis in liver cancer. *Annu Rev Pathol* 12:153–186
- Vijgen S, Terris B, Rubbia-Brandt L (2017) Pathology of intrahepatic cholangiocarcinoma. *Hepatobiliary Surg Nutr* 6:22–34
- Tyson GL, El-Serag HB (2011) Risk factors for cholangiocarcinoma. *Hepatology* 54:173–184
- Jeong S, Cheng Q, Huang L et al (2017) Risk stratification system to predict recurrence of intrahepatic cholangiocarcinoma after hepatic resection. *BMC Cancer* 17:464
- Wang Y, Li J, Xia Y et al (2013) Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol* 31:1188–1195
- Ali SM, Clark CJ, Mounajjed T et al (2015) Model to predict survival after surgical resection of intrahepatic cholangiocarcinoma: the Mayo Clinic experience. *HPB (Oxford)* 17:244–250

27. Doussot A, Lim C, Gomez Gavara C et al (2016) Multicentre study of the impact of morbidity on long-term survival following hepatectomy for intrahepatic cholangiocarcinoma. *Br J Surg* 103:1887–1894
28. Doussot A, Gonen M, Wiggers JK et al (2016) Recurrence patterns and disease-free survival after resection of intrahepatic cholangiocarcinoma: preoperative and postoperative prognostic models. *J Am Coll Surg* 223:493–505
29. Kim Y, Moris DP, Zhang XF et al. (2017) Evaluation of the 8th edition American Joint Commission on Cancer (AJCC) staging system for patients with intrahepatic cholangiocarcinoma: a surveillance, epidemiology, and end results (SEER) analysis. *J Surg Oncol* 116(6):643–650
30. Bagante F, Gani F, Spolverato G et al (2015) Intrahepatic cholangiocarcinoma: prognosis of patients who did not undergo lymphadenectomy. *J Am Coll Surg* 221:e1031–e1034
31. Kim Y, Spolverato G, Amini N et al (2015) Surgical management of intrahepatic cholangiocarcinoma: defining an optimal prognostic lymph node stratification schema. *Ann Surg Oncol* 22:2772–2778
32. Zhang XF, Chakedis J, Bagante F et al (accepted) Trends in utilization of lymphadenectomy in curative-intent surgery for intrahepatic cholangiocarcinoma. *Brit J Surg*