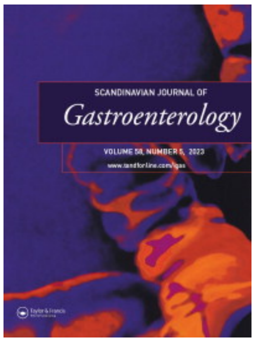

Scandinavian Journal of Gastroenterology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/igas20

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To cite this article: Mushegh A. Sahakyan, Davit L. Aghayan, Bjørn Edwin, Ruslan Alikhanov, Natalia Britskaia, Kristoffer Watten Brudvik, Mathieu D'Hondt, Celine De Meyere, Mikhail Efanov, Åsmund A. Fretland, Rune Hoff, Warsan Ismail, Arpad Ivanecz, Airazat M. Kazaryan, Kristoffer Lassen, Tomislav Magdalenić, Isabelle Parmentier, Bård Ingvald Røsok, Olaug Villanger & Sheraz Yaqub (2023) Laparoscopic versus open liver resection for intrahepatic cholangiocarcinoma: a multicenter propensity score-matched study, Scandinavian Journal of Gastroenterology, 58:5, 489-496, DOI: 10.1080/00365521.2022.2143724

To link to this article: https://doi.org/10.1080/00365521.2022.2143724

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
2023, VOL. 58, NO. 5, 489–496
https://doi.org/10.1080/00365521.2022.2143724

ORIGINAL ARTICLE

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Laparoscopic versus open liver resection for intrahepatic cholangiocarcinoma: a multicenter propensity score-matched study

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ABSTRACT

Background: The role of laparoscopy in the treatment of intrahepatic cholangiocarcinoma (ICC) remains unclear. This multicenter study examined the outcomes of laparoscopic liver resection for ICC.
Methods: Patients with ICC who had undergone laparoscopic or open liver resection between 2012 and 2019 at four European expert centers were included in the study. Laparoscopic and open approaches were compared in terms of surgical and oncological outcomes. Propensity score matching was used for minimizing treatment selection bias and adjusting for confounders (age, ASA grade, tumor size, location, number of tumors and underlying liver disease).
Results: Of 136 patients, 50 (36.7%) underwent laparoscopic resection, whereas 86 (63.3%) had open surgery. Median tumor size was larger (73.6 vs 55.1 mm, $p = 0.01$) and the incidence of bi-lobar tumors was higher (36.6 vs 6%, $p < 0.01$) in patients undergoing open surgery. After propensity score matching baseline characteristics were comparable although open surgery was associated with a larger fraction of major liver resections (74 vs 38%, $p < 0.01$), lymphadenectomy (60 vs 20%, $p < 0.01$) and longer operative time (294 vs 209 min, $p < 0.01$). Tumor characteristics were similar. Laparoscopic resection resulted in less complications (30 vs 52%, $p = 0.025$), fewer reoperations (4 vs 16%, $p = 0.046$) and shorter hospital stay (5 vs 8 days, $p < 0.01$). No differences were found in terms of recurrence, recurrence-free and overall survival.
Conclusion: Laparoscopic resection seems to be associated with improved short-term and with similar long-term outcomes compared with open surgery in patients with ICC. However, possible selection criteria for laparoscopic surgery are yet to be defined.

ARTICLE HISTORY
Received 8 August 2022
Revised 14 October 2022
Accepted 30 October 2022

KEYWORDS
Laparoscopy; cholangiocarcinoma; complications; recurrence; survival

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer. Due to its aggressive nature and late onset of symptoms most patients are diagnosed with an advanced disease associated with a dismal prognosis [1–3]. Liver resection is the only potentially curative treatment in ICC with 5-year overall survival of 20–40% [4–6].

In specialized centers, laparoscopic liver resection is increasingly replacing open liver resection in the management of colorectal liver metastases and hepatocellular carcinoma providing considerable benefits in surgical outcomes [7–9]. At the same time, the role of laparoscopy in the treatment of ICC remains unclear. While the available evidence is mostly based on single-center series, a few registry-based studies comparing laparoscopic and open liver resections for ICC have recently emerged [10,11]. These include data pooled from multiple centers with pronounced differences in annual caseload and surgical expertise. Given the heterogeneity of such data and the relatively scarce number of resected ICC, studies from expert centers performing both

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/00365521.2022.2143724.

laparoscopic and open liver resection are needed to strengthen the knowledge on this topic.

This multicenter study aimed to examine the results of laparoscopic liver resection in patients with ICC. Surgical and oncological outcomes were compared to those of open liver resection.

Materials and methods

Study design and data

This multicenter cohort study was conducted by four European expert centers in liver surgery. These were Oslo University Hospital (Oslo, Norway), Groeninge Hospital (Kortrijk, Belgium), University Medical Centre Maribor (Maribor, Slovenia) and Moscow Clinical Scientific Center (Moscow, Russia). Data were collected from the prospectively maintained databases or electronic/paper-based hospital records. Included variables were patient characteristics (age, gender, body mass index), medical history, laboratory findings, intra- and postoperative results, pathology data, as well as the long-term oncologic outcomes (recurrence, recurrence-free and overall survival). This study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. The study was approved by the local hospital review boards according to the guidelines of the regional ethics committees.

All patients with ICC who had undergone liver resection by open or laparoscopic approach at the participating centers between January 1, 2012, and December 31, 2019, were included. The two approaches were compared by perioperative and oncologic outcomes. The latter include both pathology findings and long-term oncologic results. The two cohorts were matched for potential confounders. These were patient age, the American Society of Anesthesiologists (ASA) grade, tumor size, location, number of tumors and underlying liver disease.

Patients with perihilar and distal cholangiocarcinoma, and gallbladder cancer were excluded. Patients with ICC who had undergone procedures other than liver resection (like diagnostic laparoscopy or biopsy) were also excluded from the study. Finally, cases with missing data on baseline and perioperative parameters were left out ($n = 7$). Patients who had died within 90-days of surgery were excluded from the long-term oncologic outcome analyses.

Patient management and procedures

All patients were evaluated by the multidisciplinary teams at the participating centers before being referred to surgery. Contraindications for surgery included diffuse satellite lesions precluding adequate future liver remnant, unresectable tumors due to the involvement of the portal bifurcation, as well as presence of positive distant lymph nodes and/or non-hepatic metastatic disease on preoperative imaging. The choice of surgical approach (open or laparoscopic) differed from center to center depending on surgeon expertise, tumor location (central location, proximity to the major vascular structures), and the indication for vascular and/or biliary reconstruction.

There were no uniform indications for neoadjuvant chemotherapy in the participating centers. These included primary unresectable ICC, tumor adherence to the major vessels, presence of satellite lesions. Approximately 9% of patients included in this study underwent neoadjuvant chemotherapy prior to liver resection.

Definitions

Minor and major hepatectomy were defined as resections of <3 and ≥ 3 consecutive liver segments, respectively. The Southampton difficulty scoring system was used to grade the complexity of surgical procedures [13]. Operative time was estimated from skin incision to its closure. Intraoperative blood loss was not reported as the weight of the surgical swabs used in open surgery were not routinely registered at all participating centers. Conversion included all cases of laparotomy during laparoscopic liver resection not related to the specimen extraction. Postoperative complications were defined and graded according to Clavien and Dindo [14]. Clavien-Dindo grade $\geq$ IIIa complications were considered as severe. For comprehensive and accurate measurement of complications the Comprehensive Complication Index (CCI) was used [15]. Mortality was defined as any death within 90-days of surgery.

Tumor size was estimated based on its largest diameter reported by the pathologist. R1 resection was defined as <1 mm distance between the resection margin and tumor. TNM stage of the disease was determined by using the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system for ICC [16,17].

Recurrence was defined as radiological evidence of intra-abdominal soft tissue suspicious of malignancy at the surgical site and/or distant metastases. The former was classified as intrahepatic, extrahepatic or both. Patients without recurrence were censored at the last follow-up. Recurrence-free survival was defined as the time from surgery to first recurrence or the date of censoring. The time between surgery and death or censoring date was defined as overall survival.

Statistics

Median (range) and mean (± standard deviation) values were used for reporting continuous variables, while frequencies (percentages) were used for categorical variables. Two-sample Student's t-test and Man-Whitney *U* test were applied for normally and non-normally distributed continuous data, respectively. The chi-square and Fisher's exact test were used for categorical data. Two-tailed $p < 0.05$ is considered statistically significant.

Propensity score matching (PSM) was used to match the groups for potential confounders [18]. The PSM algorithm was an optimal 1:1 pair matching procedure using the MatchIt package in R that utilizes the optmatch package

Table 1. Perioperative results and characteristics of patients undergoing liver resection for intrahepatic cholangiocarcinoma.

		Unmatched cohort			Matched cohort		
Parameters	All ($n=136$)	**Laparoscopic (n = 50)**	Open ($n=86$)	p Value	Laparoscopic ($n=50$)	Open ($n=50$)	p Value
Age, years, mean (SD)	64.2 (9.8)	65.5 (9.2)	63.4 (10.2)	0.22	65.5 (9.2)	65.4 (10.6)	0.94
Male gender, n (%)	60 (44.1%)	23 (46%)	37 (43%)	0.74	23 (46%)	22 (44%)	0.84
Body mass index, kg/m^2, mean (SD)	27.5 (5.1)	28.3 (4.2)	27 (5.4)	0.17	28.3 (4.2)	27.2 (4.8)	0.26
Underlying liver disease, n (%)	50 (36.8%)	22 (44%)	28 (32.6%)	0.18	22 (44%)	20 (40%)	0.69
CEA, ng/mL, median (range)	2.9 (0.4–183)	3 (0.4–21)	2 (0.4–183)	0.59	3 (0.5–21)	2.6 (0.9–183)	0.85
CA 19–9, U/mL, median (range)	32 (0.1–12000)	24 (0.1–325)	33.5 (2–12000)	0.15	24 (0.1–325)	43 (2–12000)	0.037
AFP, ng/mL, median (range)	4 (4–890)	4 (0.6–890)	4 (0.4–172)	0.67	4 (0.6–890)	4 (0.4–172)	0.67
ASA grade $\geq$ III, n (%)	75 (55.1%)	28 (56%)	47 (54.7%)	0.88	28 (56%)	28 (56%)	1.0
Number of tumors $\geq$ 3, n (%)	19 (14%)	6 (12%)	13 (15.1%)	0.61	6 (12%)	6 (12%)	1.0
Bi–lobar tumor location, n (%)	34 (25%)	3 (6%)	31 (36%)	<0.01	3 (6%)	3 (6%)	1.0
Previous liver surgery, n (%)	12 (8.8%)	3 (6%)	9 (10.5%)	0.54	3 (6%)	4 (8%)	1.0
Preoperative chemotherapy, n[a]	12	3	9	0.37	3	5	0.47
Southampton difficulty score, median (SD)	34.9 (16.6)	27.7 (15.7)	39.4 (15.6)	<0.01	27.7 (15.7)	35.2 (16.2)	0.022
Major resection, n (%)	88 (64.7%)	19 (38%)	69 (80.2%)	<0.01	19 (38%)	37 (74%)	<0.01
Lymph node dissection, n (%)	67 (49.3%)	10 (20%)	57 (66.3%)	<0.01	10 (20%)	30 (60%)	<0.01
Operative time, min, mean (SD)	268 (53–795)	209 (122)	302 (160)	0.02	209 (122)	294 (156)	<0.01
Red blood cell transfusion, n (%)	26 (19.1%)	4 (8%)	22 (25.6%)	0.01	4 (8.2%)	10 (20%)	0.09
Conversion, n (%)	5 (10%)	5 (10%)	–	–	5 (10%)	–	–
Postoperative complications, n (%)	65 (47.8%)	15 (30%)	50 (58.1%)	<0.01	15 (30%)	26 (52%)	0.025
Severe complications, n (%)	47 (34.6%)	12 (24%)	35 (40.7%)	0.048	12 (24%)	19 (38%)	0.13
CCI[b], median (range)	33.7 (8.7–100)	37.1 (20.9–100)	33.6 (8.7–100)	0.27	37.1 (20.9–100)	33.7 (8.7–100)	0.44
Reoperation, n (%)	16 (11.8%)	2 (4%)	14 (16.3%)	0.03	2 (4%)	8 (16%)	0.046
Readmission, n (%)	18 (13.2%)	5 (10%)	13 (15.1%)	0.39	5 (10%)	7 (14%)	0.54
90–day mortality, n (%)	10 (7.4%)	2 (4%)	8 (9.3%)	0.32	2 (4%)	5 (10%)	0.44
Intensive care unit stay, days, median (range)	1 (1–16)	0 (0–13)	1 (0–16)	<0.01	0 (0–13)	1 (0–16)	<0.01
Length of hospital stay, days, median (range)	7 (1–60)	5 (1–29)	9 (2–60)	<0.01	5 (1–29)	8 (2–60)	<0.01

[a]Incomplete data.
[b]Comprehensive complication index.

[19,20]. The PSM model was a generalized linear model with "probit" link, having type of surgical procedure as the outcome and all the potential confounders as predictors. The analysis was conducted by a biostatistician.

The Kaplan-Meier method was used to estimate survival and corresponding survival curves were plotted. Survival was described as median (95% confidence interval), and the log-rank test was applied to compare the survival between the groups. Two-tailed $p < 0.05$ is considered statistically significant.

Results

Perioperative outcomes and pathology findings

One hundred thirty-six patients underwent liver resection for ICC within the study period including 50 laparoscopic and 86 open resections. Patient characteristics were comparable in the two groups (Table 1). In an unmatched analysis, open approach was associated with a higher rate of bi-lobar disease (36 vs 6%, $p < 0.01$), more frequent major liver resections (80.2 vs 38%, $p < 0.01$) and higher rate of performed regional lymphadenectomy (66.3 vs 20%, $p < 0.01$). Longer mean operative time (302 vs 209, $p < 0.01$) and higher incidence of red blood cell transfusion (25.6 vs 8%, $p = 0.01$) were observed in open liver resections. The latter was associated with higher rate of postoperative complications, severe complications, reoperations, as well as with longer hospital stay. Specific details regarding postoperative complications and those requiring reoperation are presented in Table 2.

After PSM, bi-lobar disease spread was similar between the groups. Open liver resections were still associated with major resections, regional lymphadenectomy and longer operative time. The incidence of postoperative complications and reoperations were also higher after open surgery, although the rates of severe complications were not significantly different. Laparoscopic approach was associated with shorter intensive care unit (ICU) and hospital stay (5 vs 8 days, $p < 0.01$).

Before PSM, pathology findings had demonstrated larger tumor size (73.6 vs 55.1 mm, $p = 0.01$) and higher incidence of R1 resection in patients undergoing open surgery (Table 3). After PSM, specimen weight and number of detected lymph nodes remained higher for open surgery.

Long-term outcomes

After excluding the patients who had died within 90-days of surgery ($n = 10$), the remaining 126 were analyzed for long-term outcomes. Median follow-up was 51 (47–55, 95% CI) months. Adjuvant chemotherapy was administered in 29 patients without significant differences between the groups (Table 4). The incidence of recurrence was similar in the two groups. Median recurrence-free and overall survival in the total cohort were 14.7 and 40.7 months, respectively, while 3-year recurrence-free and overall survival rates were 36.9 and

Table 2. Type of postoperative complications and incidence of reoperations after open and laparoscopic surgery for intrahepatic cholangiocarcinoma.

	Surgical approach			
	Laparoscopic		Open	
Complications	Number	Reoperation ($n=2$)	Number	Reoperation ($n=14$)
Ileus			2	2
Bile leakage	5	1	14	2
Pneumonia	1			
Pulmonary embolism	1		5	
Pneumothorax			1	
Pleural effusion	3		3	
Respiratory failure	2		3	
Renal failure	1			
Liver failure	1		3	
Transient liver insufficiency	1		7	
Fever			3	
Ascites	2		3	
Peritonitis			1	1
Intraabdominal bleeding	1	1	2	2
Intraabdominal abscess			3	3
Ulcer perforation			1	1
Wound infection			1	
Wound rupture			3	3
Delayed gastric emptying			1	
Acute pancreatitis	1		1	
Hemodynamic instability (dehydration)			1	
Urinary tract infection			1	
Multiorgan failure			2	
Sepsis			4	
Acute coronary syndrome	1			
Cardiac tamponade			1	

53.1%, respectively. No differences were observed between the patients undergoing laparoscopic and open surgery in terms of recurrence-free and overall survival before or after matching (Figure 1).

Subgroup analysis

Separate analyses were performed in the unmatched cohort of patients undergoing minor and major hepatectomy for ICC (Supplementary Table 1). No differences were found in patient characteristics. Minor resections provided similar intraoperative results regardless of surgical approach. There was a trend toward increased rate of postoperative morbidity (35.3 vs 12.9%, $p=0.13$), reoperations (11.8 vs 0%, $p=0.12$) and longer ICU stay following open surgery although none were statistically significant. Laparoscopic minor hepatectomy was associated with shorter postoperative hospital stay (3 (1–29) vs 6 (2–41), $p=0.01$), respectively. Both open major and minor hepatectomies were associated with increased frequency of regional lymphadenectomy. Other intra- and postoperative outcomes were similar.

Tumor size, the incidence of R1 and other pathology parameters were similar. No differences were found in long-term outcomes following laparoscopic and open resections for both minor and major hepatectomy.

Discussion

Findings from this study representing pooled data from four European expert centers in liver surgery indicate that laparoscopic liver resection for ICC is associated with favorable short-term surgical outcomes compared with its open counterpart. The advantages are particularly related to lower incidence of postoperative complications, reoperations and shorter hospital stay. These results are in line with those observed in the largest comparative studies from the Western world [10,21,22]. At the same time, one should consider that the extent of surgery was not similar in laparoscopic and open cohort, even after applying PSM. Although the latter allowed for minimizing selection bias, the proportions of major hepatectomies and regional lymphadenectomy remained significantly higher for open surgery. Since both above-mentioned parameters are well-known risk factors for complications after liver resection [23,24], sub-group analyses were conducted stratifying for the type of hepatectomy. As a result, the above-mentioned advantages of laparoscopy were found to be mostly associated with minor hepatectomy, while no significant differences were detected for major hepatectomy. To the best of our knowledge, this is the first report on ICC to include sub-group analyses of minor/major hepatectomy for laparoscopic and open resections.

Regional lymphadenectomy was performed in roughly half of the patients included in this study and nearly 3 times more often performed during open approach compared to laparoscopy. These findings are comparable to those seen in the analysis of nationwide databases in the US and France [10,25]. Furthermore, most of the literature data indicate that lymphadenectomy is performed in less than 40% of laparoscopic resections [10,11,21,22,25,26–34] (Supplementary Table 2). These observations seem to reflect surgeons' reluctancy towards performing routine lymphadenectomy during liver resection for ICC, especially in the setting of laparoscopic surgery. A possible reason for inadequate

Table 3. Pathology findings in patients undergoing laparoscopic and open resection for intrahepatic cholangiocarcinoma.

Parameters	All ($n=136$)	Unmatched cohort Laparoscopic ($n=50$)	Unmatched cohort Open ($n=86$)	p Value	Matched cohort Laparoscopic ($n=50$)	Matched cohort Open ($n=50$)	p Value
Tumor size, mm, mean (SD)	66.8 (40.1)	55.1 (31.5)	73.6 (43.1)	0.01	55.1 (31.5)	58.1 (29.2)	0.63
Specimen weight, gram, median (range)	400 (20–2222)	256 (69–1180)	614 (20–2222)	0.001	256 (69–1180)	480 (20–1512)	0.014
R1, n^b	34	8	26	0.047	8	8	0.93
Tumor stage, n (%)				0.09			0.34
T1	67 (49.3%)	29 (58%)	38 (44.2%)		29 (58%)	25 (50%)	
T2	44 (32.4%)	17 (34%)	27 (31.4%)		17 (34%)	14 (28%)	
T3	12 (8.8%)	1 (2%)	11 (12.8%)		1 (2%)	6 (12%)	
T4	13 (9.5%)	3 (6%)	10 (11.6%)		3 (6%)	5 (10%)	
Nodal stage, n^a				0.47			0.69
N0	44	8	36		8	20	
N1	23	2	21		2	10	
Detected lymph nodes, median (range)	2 (0–20)	1 (0–20)	2 (0–15)	0.001	1 (0–20)	2 (0–15)	0.002
Positive lymph nodes, median (range)	0 (0–4)	0 (0–2)	0 (0–4)	0.06	0 (0–2)	0 (0–4)	0.13
Tumor differentiation (poor), n^c	35	14	21	0.31	14	9	0.24
Vascular invasion, n^d	43	13	30	0.17	13	16	0.31
Perforation of the visceral peritoneum, n^e	17	3	14	0.052	3	8	0.07

[a]Lymphadenectomy performed in 67 cases.
[b]Data missing in 6 cases.
[c]Data missing in 13 cases.
[d]Data missing in 9 cases.
[e]Data missing in 10 cases.

Table 4. Long-term oncologic outcomes in patients undergoing laparoscopic and open resection for intrahepatic cholangiocarcinoma (patients that had died after surgery were excluded).

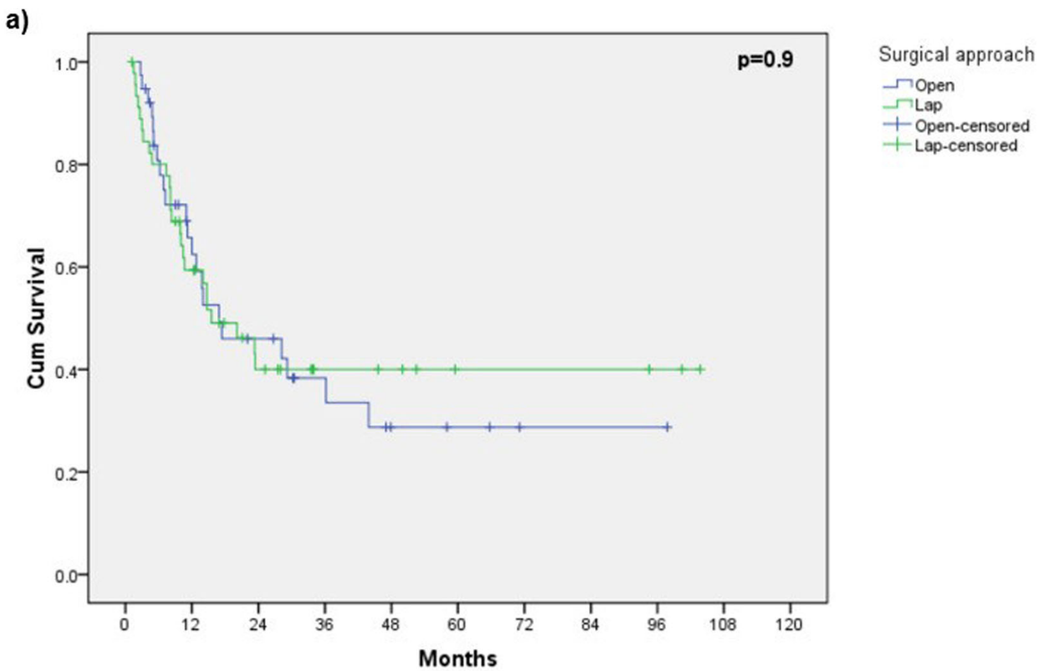
Parameters	All ($n=126$)	Unmatched Laparoscopic ($n=48$)	Unmatched Open ($n=78$)	p Value	Matched Laparoscopic ($n=48$)	Matched Open ($n=45$)	p Value
Adjuvant chemotherapy, n^a	29	13	16	0.41	13	6	0.11
Recurrence, n^b	68	25	43	0.34	25	22	0.64
Recurrence type, n^b				0.37			0.41
Intrahepatic	34	14	22		14	9	
Extrahepatic	15	7	8		7	6	
Both	17	4	13		4	7	
Survival, months, median (95% CI)							
Recurrence-free	14.7 (9.4–20)	15.5 (5.2–25.8)	14 (9.2–18.8)	0.64	15.5 (5.2–25.8)	16.9 (1.2–35)	0.9
1 year	59.9%	59.4%	60.1%		59.4%	62.4%	
3 years	36.9%	40%	35.3%		40%	38.3%	
Overall	40.7 (29.6–51.7)	47.6 (18.4–76.8)	36.4 (26.2–46.6)	0.29	47.6 (18.4–76.8)	40.7 (26.2–46.6)	0.43
3 years	53.1%	55.8%	51.2%		55.8%	56%	
5 years	40.5%	47.2%	37%		47.2%	43.2%	

[a]Data not available in six patients.
[b]Data not available in 12 patients.

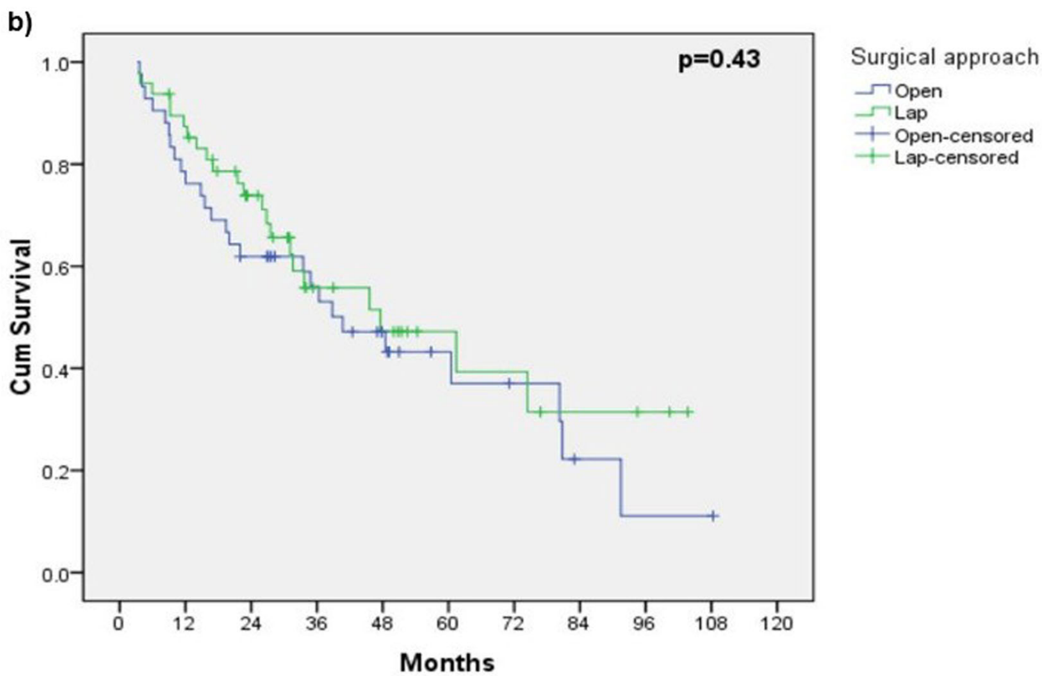
lymphadenectomy can be unclear oncologic benefits, as conflicting results have been reported. Although clinical practice has changed at most centers over the years, in this retrospective study, lymphadenectomy was not performed routinely for ICC, which may partly explain the difference between laparoscopic and open groups. Current guidelines recommend routine lymphadenectomy in ICC aimed at resection of at least six lymph nodes to achieve adequate disease staging and better local control [35–37]. In contrast, some studies and meta-analyses have failed to confirm the oncologic benefits of routine lymphadenectomy [23,38,39]. That has led to re-evaluation of preoperative data and suggestion of parameter-based nomograms that would aid in selecting the patients benefiting most of this procedure [40,41].

This study demonstrates that oncologic outcomes, especially long-term results, are similar for laparoscopic and open resections, whenever the minimally-invasive approach is found feasible. This is mostly in agreement with the meta-analyses published to date [6,42–44,45] (Supplementary Table 3). At the same time, these reported significant differences in negative resection margin and recurrence rates [6,42–44], which was not the case in our study. Inferior rate of negative resection margins and higher recurrence rates after open surgery reported in these meta-analyses come from the US registry-based analysis [25] and the European bi-institutional study [21]. The former was affected by selection bias as more advanced disease was present in the open surgery arm, while Ratti and co-workers have found only statistically marginal the difference in recurrence ($p=0.05$). In our opinion, surgical approach itself can hardly be associated with margin positivity and recurrence in liver resection for ICC, provided that the surgeons have adequate expertise in either technique. This seems to be supported by the fact that recurrence-free and overall survival are similar in our study. In the same way, similar long-term outcomes were observed in the recent meta-analyses [42–44].

This study has several limitations that must be acknowledged. First and foremost, this was a retrospective study with all inherent biases. Second, patient selection was based



Patients at risk											
Open resection	38	20	13	8	4	3	1	1	1	-	-
Lap resection	46	25	13	7	6	3	3	3	2	-	-



Patients at risk											
Open resection	45	33	25	19	12	7	5	2	1	1	-
Lap resection	48	41	28	14	11	6	5	3	2	-	-

Figure 1. Recurrence-free (a) and overall survival (b) following laparoscopic and open liver resection for intrahepatic cholangiocarcinoma (matched cohort).

on the view of the surgeon, which might result in that peripherally situated ICC were more likely to be considered for laparoscopic approach, while bi-lobar or centrally located lesions were resected by open approach. Although PSM was used to minimize treatment selection bias, it can hardly be excluded given the persistence of significantly larger proportion of major resections and lymphadenectomy in the open arm. At the same time, sub-group analyses were applied to address the issue with major resections. Third, given the relatively small sample size, potential risk for type II error remains to be present. Finally, some data on pathology-related parameters and recurrence were missing from the final dataset.

Laparoscopic resection for ICC is associated with several short-term benefits compared to open surgery in our cohort, while long-term oncologic outcomes are comparable. Thus, patients with resectable ICC may be considered for laparoscopic resection in expert centers with sufficient expertise, especially when lymphadenectomy is not paramount. Possible selection criteria for laparoscopic surgery are to be defined in the future studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by South-Eastern Norway Regional Health Authority [grant number 2020067] to SY.

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