




# Long-term outcomes of laparoscopic versus open liver resection for intrahepatic combined hepatocellular-cholangiocarcinoma with propensity score matching

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## Abstract

**Background:** Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary hepatic neoplasm. Currently, there are no well-structured studies that analyze the feasibility of laparoscopic liver resection in cHCC-CCA alone. This retrospective cohort study aimed to compare the long-term survival of laparoscopic liver resection with open liver resection in cHCC-CCA.

**Methods:** Patients with a postoperative pathologic report of cHCC-CCA who underwent liver resection from August 2004 to December 2017 were included in this study. Kaplan-Meier survival analysis was performed to analyze the 3-y disease-free survival and 3-y overall survival. Propensity score matching was done to reduce the influence of confounding variables.

**Results:** A total of 145 patients were pathologically confirmed to have cHCC-CCA, of which 10 patients were excluded due to having received palliative surgery. Of the remaining 135 patients, 43 underwent laparoscopic and 92 underwent open liver resection; propensity score matching yielded 30 patients for each group. The 3-y overall survival was 38 (88.4%) in the laparoscopic group and 84 (91.3%) in the open group before propensity score matching ( $P = .678$ ), and 25 (83.3%) and 28 (93.3%), respectively, after matching ( $P = .257$ ). The 3-y disease-free survival was 24 (55.8%) in the laparoscopic group and 32 (34.8%) in the open group before matching ( $P = .040$ ), and 17 (56.7%) and 16 (53.3%), respectively, after matching ( $P = .958$ ). The hospital stay was shorter in the laparoscopic group before and after matching, while other operative outcomes were similar in both groups.

**Conclusion:** Laparoscopic liver resection for cHCC-CCA is technically feasible and safe, having a shorter hospital stay without compromising oncological outcomes.

Seung Jae Lee and So Hyun Kang equally contributed to this study.

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## KEYWORDS

cholangiocarcinoma, hepatectomy, laparoscopy, minimally invasive surgical procedures

## 1 | INTRODUCTION

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary solid tumor in the liver that is reported to have an incidence ranging from 1.0% up to 14.3% of all primary liver malignancies.<sup>1-5</sup> It contains both the histopathological components of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). In 1949, a classification system for cHCC-CCA was first reported by Allen et al,<sup>3</sup> categorizing it into double tumor, combined type, and mixed type. The system was revised in 1985<sup>2</sup> into collision, transitional, and fibrolamellar tumor types. Currently, these tumors are believed to have originated from hepatic precursor cells, and the fourth World Health Organization (WHO) classification<sup>6</sup> described the cHCC-CCA tumors using two histological categories: a classic type and subtypes with stem cell features. Recent studies show that cHCC-CCA patients have worse survival outcomes compared to HCC patients, while having similar or worse survival compared to ICC patients.<sup>4,7-10</sup>

Laparoscopic liver resection is now being performed worldwide for the treatment of several liver diseases, including malignant tumors.<sup>11-13</sup> However, there is little evidence regarding laparoscopic liver resection for cHCC-CCA and currently no report on long-term survival of cHCC-CCA after laparoscopic liver resection. This study aims to analyze the long-term safety of laparoscopic liver resection on cHCC-CCA compared to open liver resection.

## 2 | METHODS

### 2.1 | Study design and endpoints

This study included patients who underwent liver resection at Seoul National University Hospital and Seoul National University Bundang Hospital from August 2004 to December 2017, who turned out to have cHCC-CCA at the pathologic report. Those who received palliative surgery were excluded. Electronic medical records were reviewed for operative and postoperative outcome, recurrence, and survival. Patients were divided into open and laparoscopic liver resection groups according to the type of surgery performed. Primary endpoints were 3-y disease-free survival and 3-y overall survival, while pathologic and operative outcome, postoperative complication, and recurrence pattern were set as secondary endpoints. Postoperative complications were classified according to the Clavien–Dindo system,<sup>14</sup> and early complication was defined as complications within 30 postoperative days (PODs). This study was approved by the Institutional Review Board (H-2009-184-1162, H-1809-493-406) at Seoul National University Hospital and Seoul National University Bundang Hospital, and is in accordance with the ethical standards of the Helsinki Declaration.

### 2.2 | Preoperative evaluation

All patients were evaluated preoperatively for risk of liver resection with laboratory examinations including complete blood count, liver function tests, renal function tests, tumor markers; radiologic examination including liver computed tomography (CT), liver magnetic resonance imaging (MRI), chest CT, and/or positron emission tomography (PET); and other examinations such as electrocardiography and pulmonary function tests. Surgery was performed in patients who had tolerable liver function, without signs of severe portal hypertension, or evidence of extrahepatic metastasis, and with American Society of Anesthesiologists (ASA) grade less than 3. The indications and the type of liver resection were not different for open and laparoscopic surgery.

### 2.3 | Surgical procedure

Patients were given comprehensive information regarding the advantages and disadvantages of laparoscopic and open liver resection, and the type of operation was chosen after a thorough discussion with the patient. Detailed procedures of open liver resection and laparoscopic liver resection are described in a previous report.<sup>12</sup>

Anatomical resections were generally more preferred if the future liver remnant was adequate, otherwise nonanatomical resections were used. When three or more segments of the liver were resected, the operation was classified as a major operation as described in the Second International Consensus Conference for Laparoscopic Liver Resection.<sup>15</sup>

For open liver resection, the inverted L-shaped incision was made. A Cavitron ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, CO, USA), LigaSure (ValleyLab, Avante, San Clemente, CA, USA) and

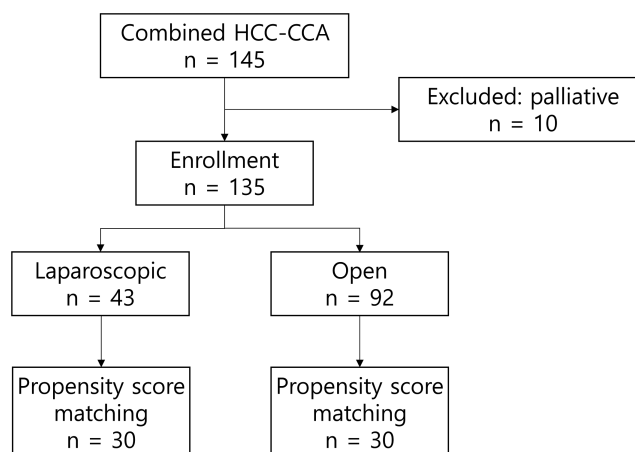


FIGURE 1 Patient flowchart

bipolar forceps were used for parenchymal dissection. Layer-by-layer closure of vertical and horizontal wound was performed.

For laparoscopic liver resection, 5–6 small incisions (5 mm, 11 mm, or 12 mm) were made in the umbilical, left, and right side of the patient's abdomen for port placement as intended by the surgeon. CUSA with laparoscopic long tip or laparoscopic ultrasonic devices were used for parenchymal resection. The specimen was pulled out through an elongated port site or through making an additional Pfannenstiel incision.

## 2.4 | Statistical analysis

Categorical data were presented as numbers and percentages; descriptive data were presented as mean  $\pm$  standard deviation or median (range). The Kaplan–Meier method was used to analyze the survival data. Significance was defined as a *P*-value of  $<.05$ .

Propensity scores were calculated per patient with confounding factors: age, gender, prior treatment, resection type, liver status, maximum size (diameter), number of tumors, pathologic T staging, pathologic and N staging; and matching was done one-to-one with the nearest-neighbor matching method.

All statistical analyses were performed using SPSS 25 (SPSS, Chicago, IL, USA) or the R software (v. 3.3.3, R Foundation for Statistical Computing, Vienna, Austria).

## 3 | RESULTS

A total of 145 patients who underwent liver resection for cHCC-CCA from August 2004 to December 2017 were included in the analysis.

Ten patients who had palliative surgery were excluded. Among the remaining 135 patients, 43 patients had laparoscopic liver resection and 92 patients had open liver resection. After propensity score matching, 30 patients from each group were selected for analysis (Figure 1).

Patient demographics are shown in Table 1. The mean age was  $58.93 \pm 9.55$  y in the laparoscopic group and  $56.17 \pm 11.66$  y in the open group ( $P = .179$ ). In both groups, most of the patients did not receive prior treatment (laparoscopic = 79.1%, open = 76.1%,  $P = .809$ ). Nineteen patients (44.2%) in the laparoscopic group had liver cirrhosis at the time of operation, and 36 patients (39.1%) had cirrhosis in the open group ( $P = .829$ ). After propensity score matching, the mean age was  $57.43 \pm 10.03$  y in the laparoscopic group and  $56.27 \pm 9.86$  y in the open group ( $P = .651$ ); both groups showed same ratio of patients without prior treatment (83.3%,  $P = .912$ ); and patients who had liver cirrhosis at the time of operation was 11 (36.7%) in the laparoscopic and 10 (33.3%) in the open group.

Table 2 shows the pathologic outcome of both groups. There was a significant difference in tumor number between the two groups, with 37 (86%) of patients with a single tumor in the laparoscopic group versus only 62 (67.4%) of patients with a single tumor in the open group ( $P = .022$ ), while after propensity score matching there was no statistical difference (laparoscopic = 26, open = 25,  $P = .718$ ). The maximum diameter of tumors was  $3.79 \pm 2.55$  cm in the laparoscopic group and  $4.74 \pm 2.73$  cm in the open group ( $P = .059$ ); after propensity matching, the tumor size was  $3.93 \pm 2.67$  cm and  $3.33 \pm 1.46$  cm, respectively ( $P = .286$ ). There was no statistical difference in pathologic T stage and N stage between the two groups before and after propensity score matching.

TABLE 1 Patient demographics

	Before matching		P-value	After matching		P-value
	Laparoscopic (N = 43)	Open (N = 92)		Laparoscopic (N = 30)	Open (N = 30)	
Gender			.720			.197
Male	31 (72.1%)	69 (75.0%)		22 (73.3%)	26 (86.7%)	
Female	12 (27.9%)	23 (25.0%)		8 (26.7%)	4 (13.3%)	
Age	$58.93 \pm 9.55$	$56.17 \pm 11.66$	.179	$57.43 \pm 10.03$	$56.27 \pm 9.86$	.651
Prior treatment			.809			.912
None	34 (79.1%)	70 (76.1%)		25 (83.3%)	25 (83.3%)	
TACE	4 (9.3%)	13 (14.1%)		1 (3.3%)	1 (3.3%)	
RFA	1 (2.3%)	3 (3.3%)		1 (3.3%)	2 (6.7%)	
Both	4 (9.3%)	6 (6.5%)		3 (10.0%)	2 (6.7%)	
Liver state			.829			.962
Normal	4 (9.3%)	11 (12.0%)		3 (10.0%)	3 (10.0%)	
Chronic infection	20 (46.5%)	44 (47.8%)		16 (53.3%)	17 (56.7%)	
Cirrhosis	19 (44.2%)	36 (39.1%)		11 (36.7%)	10 (33.3%)	
Preop AFP	$256.7 \pm 568.2$	$2422.5 \pm 9912.4$	.049	$270.5 \pm 641.2$	$1337.5 \pm 4371.9$	.229
Preop CA19-9	$13.2 \pm 9.6$	$58.7 \pm 128.5$	.023	$13.9 \pm 9.4$	$46.2 \pm 109.4$	.364

TABLE 2 Pathologic outcome

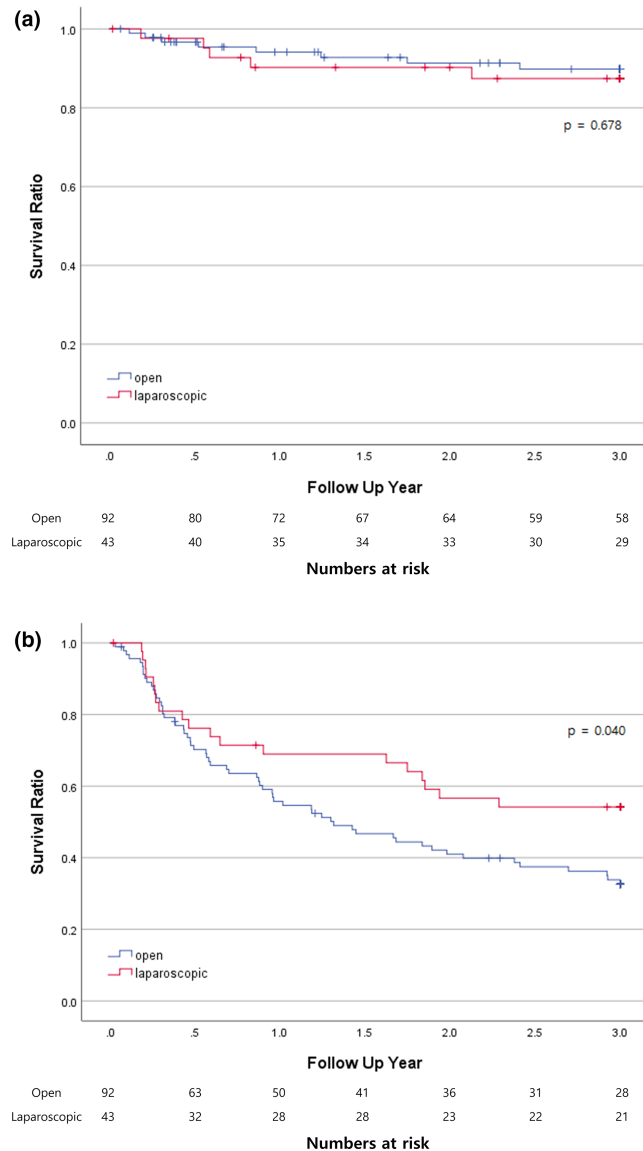
	Before matching			After matching		
	Laparoscopic (N = 43)	Open (N = 92)	P-value	Laparoscopic (N = 30)	Open (N = 30)	P-value
Tumor number			.022			.718
1	37 (86.0%)	62 (67.4%)		26 (86.7%)	25 (83.3%)	
2 or more	6 (14.0%)	30 (32.6%)		4 (13.3%)	5 (16.7%)	
Tumor max size (cm)	3.79 ± 2.55	4.74 ± 2.73	.059	3.93 ± 2.67	3.33 ± 1.46	.286
T stage			.403			.064
Tis	0 (0.0%)	1 (1.1%)		0 (0.0%)	0 (0.0%)	
T1	16 (37.2%)	32 (34.8%)		10 (33.3%)	18 (60.0%)	
T2	25 (58.1%)	45 (48.9%)		18 (60.0%)	9 (30.0%)	
T3	2 (4.7%)	11 (12.0%)		2 (6.7%)	3 (10.0%)	
T4	0 (0.0%)	3 (3.3%)		0 (0.0%)	0 (0.0%)	
N stage			.211			.301
N0	5 (11.6%)	8 (8.7%)		3 (10.0%)	1 (3.3%)	
N1	0 (0.0%)	6 (6.5%)		0 (0.0%)	0 (0.0%)	
Nx	38 (88.4%)	78 (84.8%)		27 (90.0%)	29 (96.7%)	

TABLE 3 Operative outcome

	Before matching			After matching		
	Laparoscopic (N = 43)	Open (N = 92)	P-value	Laparoscopic (N = 30)	Open (N = 30)	P-value
Major resection			.417			.284
Yes	20 (46.5%)	36 (39.1%)		13 (43.3%)	9 (30.0%)	
No	23 (53.5%)	56 (60.9%)		17 (56.7%)	21 (70.0%)	
Lymph node dissection			.576			.301
Not performed	38 (88.4%)	78 (84.8%)		27 (90.0%)	29 (96.7%)	
Performed	5 (11.6%)	14 (15.2%)		3 (10.0%)	1 (3.3%)	
Tumor margin (cm)	0.93 ± 0.84	0.90 ± 0.83	.861	1.04 ± 0.96	1.15 ± 1.02	.666
Operation time (min)	264.1 ± 136.8	246.6 ± 102.6	.457	258.9 ± 130.7	240.6 ± 91.6	.531
Estimated blood loss (mL)	403.5 ± 448.9	672.1 ± 899.2	.023	395.0 ± 324.4	490.7 ± 394.5	.312
Hospital stay (d)	9.0 ± 2.7	15.8 ± 9.8	<.001	8.5 ± 2.4	15.0 ± 10.9	.004
Op related early Cx (Clavien–Dindo ≥III)			.237			.554
None	41 (95.3%)	82 (89.1%)		29 (96.7%)	28 (93.3%)	
Yes	2 (4.7%)	10 (10.9%)		1 (3.3%)	2 (6.7%)	
Follow-up, d	1350 (3485)	1665 (5757)		1319 (3104)	2143 (5757)	
3-y overall survival	38 (88.4%)	84 (91.3%)	.678	25 (83.3%)	28 (93.3%)	.257
3-y disease-free survival	24 (55.8%)	32 (34.8%)	.040	17 (56.7%)	16 (53.3%)	.958

The operative outcome is shown in Table 3. The proportion of patients who underwent major hepatectomy was similar in both groups (laparoscopic = 46.5%; open = 39.1%;  $P = .417$ ), and there was no difference in the proportion of patients who underwent lymph node dissection (LND). The tumor margin was  $0.93 \pm 0.84$  cm in laparoscopic and  $0.90 \pm 0.83$  cm in open group ( $P = .861$ ). The mean operation time was  $264.1 \pm 136.8$  min in

the laparoscopic group and  $246.6 \pm 102.6$  min in the open group ( $P = .457$ ). Estimated blood loss (EBL) was significantly lower in the laparoscopic group with  $403.5 \pm 448.9$  mL compared to  $672.1 \pm 899.2$  mL of the open group ( $P = .023$ ). Hospital stay was also shorter in the laparoscopic group, with statistical significance ( $9.0 \pm 2.7$  d vs  $15.8 \pm 9.8$  d,  $P < .001$ ). The early complication rate was similar in both groups (laparoscopic = 4.7%, open = 10.9%,

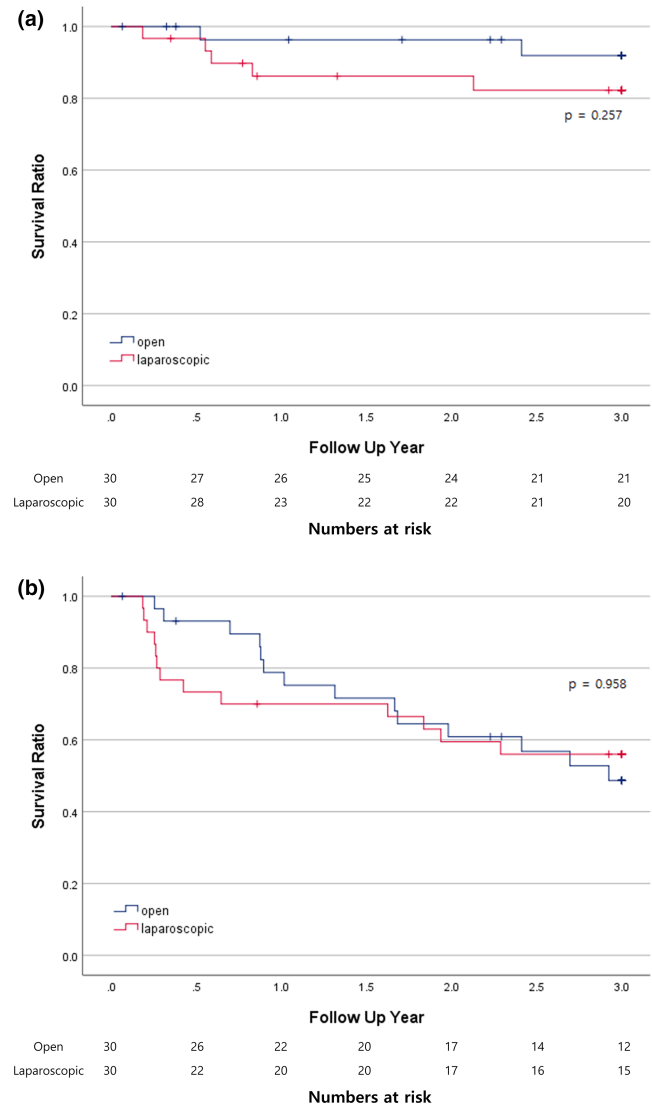


**FIGURE 2** Survival analysis between open liver resection and laparoscopic liver resection for combined hepatocellular and cholangiocarcinoma. (a) Kaplan-Meier plot of overall survival, (b) Kaplan-Meier plot of disease-free survival

$P = .237$ ). After propensity score matching, the hospital stay was the only category that showed statistical significance, with laparoscopic  $8.5 \pm 2.4$  d and open  $15.0 \pm 10.9$  d ( $P = .004$ ).

Figure 2 shows the 3-y overall survival and 3-y disease-free survival for both groups. In Figure 2a, the 3-y overall survival for the laparoscopic group and open group was 38 out of 43 (88.4%) and 78 out of 92 (91.3%), respectively ( $P = .678$ ). In Figure 2b, the 3-y disease-free survival was higher in the laparoscopic group, with 24 out of 43 (55.8%) compared to the open group with 32 out of 92 (34.8%) with statistical significance ( $P = .04$ ).

Figure 3 shows the 3-y overall survival and 3-y disease-free survival for both groups after propensity score matching. The 3-y overall survival and 3-y disease-free survival both showed no statistical significance in the difference between two groups with 3-y overall survival for the laparoscopic group and open group 25 (83.3%) and



**FIGURE 3** Survival analysis between open liver resection and laparoscopic liver resection for combined hepatocellular and cholangiocarcinoma after propensity score matching. (a) Kaplan-Meier plot of overall survival, (b) Kaplan-Meier plot of disease-free survival

28 (93.3%), respectively ( $P = .257$ ) and the 3-y disease-free survival for the laparoscopic group and open group 17 (56.7%) and 16 (53.3%), respectively ( $P = .958$ ).

There was a total of 78 recurrences, with 46 (59.0%) recurrences in the remaining liver, 14 (17.9%) recurrences in lung, 9 (11.5%) metastases in lymph nodes, 3 (3.8%) peritoneal seedings, and 6 (7.7%) recurrence in other organs. The recurrence pattern was further divided into laparoscopic and open groups, and is shown in Table 4.

## 4 | DISCUSSION

This study is the first report of a survival analysis of laparoscopic liver resection compared to open liver resection in cHCC-CCA alone with propensity score matching. Goodman et al<sup>2</sup> reported an incidence of

TABLE 4 Recurrence of combined hepatocellular and cholangiocarcinoma after surgery

	Before matching			After matching		
	Laparoscopic (n = 19, 44.2%)	Open (n = 59, 64.1%)	Total (n = 78)	Laparoscopic (n = 12, 40%)	Open (n = 13, 43%)	Total (n = 25)
Remnant liver	11 (57.9%)	35 (59.3%)	46 (59.0%)	6 (50.0%)	7 (53.8%)	13 (52.0%)
Lung	5 (21.1%)	9 (15.2%)	14 (17.9%)	3 (25.0%)	4 (30.8%)	7 (28.0%)
Lymph nodes	2 (10.5%)	7 (11.9%)	9 (11.5%)	2 (16.7%)	1 (7.7%)	3 (12.0%)
Peritoneal seeding	1 (5.3%)	2 (3.4%)	3 (3.8%)	1 (8.3%)	1 (7.7%)	2 (8.0%)
Others	0 (0%)	6 (12%)	6 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

2.4%, while Allen and Lisa reported an incidence of 14.3%<sup>3</sup> of all hepatic malignancies. This discrepancy is possibly due to the difference in the classification and definition of cHCC-CCA, and, according to the American Hepato-Pancreato-Biliary Association (AHPBA)-sponsored consensus meeting,<sup>16</sup> the strict definition of cHCC-CCA are thought to be tumors of Allen and Lisa type C<sup>3</sup> and type II of Goodman et al.<sup>2</sup> Nevertheless, cHCC-CCA is a rare disease, and reports of laparoscopic liver resection for cHCC-CCA are scarce. Most of the current published literature include some cHCC-CCA cases in the application of laparoscopic liver resection for liver malignancies. Lai et al<sup>17</sup> reported the long-term outcome of 30 consecutive cases of laparoscopic liver resection, and among them, two cases were cHCC-CCA. The same group also reported a series of robotic liver resection, and among the 42 patients one patient had cHCC-CCA.<sup>18</sup> Toyama et al<sup>19</sup> also reported a case of one patient with cHCC-CCA who underwent single-incision laparoscopic hepatectomy. With little scientific evidence of laparoscopic liver resection on cHCC-CCA, this study is the first to show a long-term survival outcome of laparoscopic liver resection on cHCC-CCA alone.

In addition, studies on the long-term prognosis of cHCC-CCA after curative resection are also rare. Lee et al<sup>4</sup> analyzed 60 patients with cHCC-CCA who underwent curative resection. The overall survival after 30 mo was 35.8%. In the population analysis by Garancini et al,<sup>20</sup> the Surveillance, Epidemiology, and End Results (SEER) database had 465 patients with cHCC-CCA. Among them, 65.2% did not undergo any invasive treatment. Patients who underwent liver transplant, major hepatectomy, and minor hepatectomy had a 5-y overall survival of 41.1%, 28.1%, and 27.1% respectively. Jung et al<sup>21</sup> followed 100 patients with cHCC-CCA who underwent curative hepatectomy, and the analyzed 3-y overall survival was 77.3%. In this study, the 3-y overall survival for the open procedure was 91.3%, and the laparoscopic group was 88.4%, which are both comparable to the reported 3-y survival.

Hospital stay and estimated blood loss were favorable in the laparoscopic group. Other studies also show that laparoscopic liver resection reduces the hospital stay in patients compared to open liver resection.<sup>12,13,22,23</sup> Some studies also report less blood loss in the laparoscopic liver resection group.<sup>24-27</sup> Topal et al<sup>27</sup> reviewed 359 patients who underwent partial hepatectomy and used propensity score matching (n = 76 per group) to compare laparoscopic and open liver resection. These findings suggest that for patients' operative outcome laparoscopic surgery is favorable over open surgery. However,

laparoscopic liver resection is still an innovative procedure with a high learning curve, and proper selection of appropriate cases is needed.<sup>13</sup> In the years that we investigated, laparoscopic surgery cases were more concentrated in the years 2010 and onward compared to the early 2000s, while open surgery cases were similar in number throughout the years. The reason for this is mainly because in the early 2000s laparoscopic surgery was just beginning to be performed in our institutions and the indications for laparoscopic surgery were not yet established. As experience accumulated, more laparoscopic surgery cases were performed in the later years of our study.

Recurrence pattern was also analyzed, and current studies report about 50.0%–57.7% of recurrences to be intrahepatic.<sup>4,28</sup> In this study, 59% (46 out of 78) recurred patients had their recurrence in the remnant liver that shows a similar pattern to HCC.

Despite the originality of this study, there are some limitations that need to be addressed. First, the study was done in a retrospective matter, and the decision to perform open versus laparoscopic surgery could have been biased. While propensity score matching was done with the intention to correct some of these biases, it still has limitations when compared with a prospective study design. Second, since most of the cases were thought to be HCC prior to surgery, only 19 cases (14%) underwent lymph node dissection. More cases are needed to provide insight regarding the role of lymph node dissection in cHCC-CCA. Third, throughout the 14 y that we investigated, only 135 patients underwent liver resection for cHCC-CCA, and after propensity score matching the total number of patients was 60, with 30 for each group. Nevertheless, this study is the first to compare long-term outcomes of laparoscopic liver resection and open liver resection for patients with cHCC-CCA alone.

## 5 | CONCLUSION

In our study, laparoscopic liver resection for cHCC-CCA had comparable 3-y overall survival and disease-free survival compared to open hepatectomy. The results provide evidence that laparoscopic liver resection may be safe and feasible, having a shorter hospital stay without compromising oncological outcomes.

## CONFLICT OF INTEREST

This study was approved by the Institutional Review Board (H-2009-184-1162, H-1809-493-406) at Seoul National University Hospital



and Seoul National University Bundang Hospital. Due to the retrospective nature of the study, individual consent was waived. The authors declare no conflicts of interest for this article.

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