Qin *et al. Hepatoma Res* 2024;10:40
DOI: 10.20517/2394-5079.2024.65

Hepatoma Research

Original Article

Open Access

Check for updates

Evaluation of the outcomes of staging laparoscopy in intrahepatic cholangiocarcinoma patients undergoing surgical resection: a multicenter retrospective study in China

Delong Qin[1,2,3], Jialu Chen[1,2,3], Yue Tang[1,2,3], Zonglong Li[1,2,3], Zhimin Geng[4], Hong Wu[5], Yinghe Qiu[6], Tianqiang Song[7], Xianhan Mao[8], Yu He[9], Zhangjun Cheng[10], Wenlong Zhai[11], Jingdong Li[12], Xiao Liang[13], Ruixin Lin[14], Di Tang[15], Chuandong Sun[16], Zhaohui Tang[1,2,3]

[1]Department of General Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China.
[2]Department of Blood Transfusion, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China.
[3]Shanghai Key Laboratory of Biliary Tract Disease Research, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China.
[4]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi, China.
[5]Department of Liver Surgery, Liver Transplantation Center, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China.
[6]Department of Biliary Surgery, Eastern Hepatobiliary Hospital Affiliated to Naval Medical University, Shanghai 200433, China.
[7]Department of Hepatobiliary Oncology, Tianjin Medical University Cancer Hospital, Tianjin 300060, China.
[8]Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital, Changsha 410005, Hunan, China.
[9]Department of Hepatobiliary Surgery, The First Hospital Affiliated to Army Medical University, Chongqing 400038, China.
[10]Department of Hepatobiliary Surgery, Zhongda Hospital of Southeast University, Nanjing 210009, Jiangsu, China.
[11]Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China.
[12]Department of Hepatobiliary Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, Sichuan, China.
[13]Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310000, Zhejiang, China.
[14]Department of Hepatobiliary and Pancreatic Surgery, Norman Bethune Second Hospital, Jilin University, Changchun 130041, Jilin, China.
[15]General Surgery Department, Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen 528403, China.
[16]Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Qingdao University, Qingdao 266003, Shandong, China.

Correspondence to: Dr. Zhaohui Tang, Department of General Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, No.1665, Kongjiang Road, Shanghai 200092, China. E-mail: jowittang@gmail.com

How to cite this article: Qin D, Chen J, Tang Y, Li Z, Geng Z, Wu H, Qiu Y, Song T, Mao X, He Y, Cheng Z, Zhai W, Li J, Liang X, Lin R, Tang D, Sun C, Tang Z. Evaluation of the outcomes of staging laparoscopy in intrahepatic cholangiocarcinoma patients undergoing surgical resection: a multicenter retrospective study in China. *Hepatoma Res* 2024;10:40. https://dx.doi.org/10.20517/2394-5079.2024.65

Received: 30 Apr 2024 **First Decision:** 12 Aug 2024 **Revised:** 3 Sep 2024 **Accepted:** 14 Sep 2024 **Published:** 27 Sep 2024

Academic Editor: Matteo Donadon **Copy Editor:** Yu-Fei Wang **Production Editor:** Yu-Fei Wang

Abstract

Aim: To evaluate the perioperative outcomes and postoperative survival of applying staging laparoscopy (SL) in intrahepatic cholangiocarcinoma (ICC) patients undergoing surgical resection.

Methods: A retrospective analysis was performed on all selected ICC patients who underwent curative-intent resection with/without applying staging laparoscopy from January 2010 to August December 2021. Perioperative outcomes and postoperative survival were analyzed. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were performed to reduce the bias due to confounding variables in the SL group and the non-SL group. Multivariate Cox analysis was used to ascertain the independent predictor of survival for ICC patients.

Results: A total of 279 patients (24.1%) were included in the SL group, while 881 patients (75.9%) were included in the non-SL group. Compared with the non-SL group, the SL group had lower blood loss, smaller tumor size, higher R0 resection rate, and shorter hospital stay, but a higher incidence of postoperative complications. The OS of the SL group was better than that of the non-SL group (Median OS: 31 months *vs.* 20 months). The 1-, 3-, and 5-year overall survival rates of the SL group were 77.9%, 45.1%, and 32.9%, respectively, while the non-SL group had rates of 63.9%, 31.3%, and 18.4%. SL was confirmed as an independent predictor of survival by multivariate Cox analysis.

Conclusion: ICC patients receiving SL had better perioperative outcomes and significantly prolonged overall survival after resection surgery. The subgroup analysis results support the use of routine SL.

Keywords: Staging laparoscopy, intrahepatic cholangiocarcinoma, resection surgery, postoperative outcomes.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a primary liver cancer that originates from the epithelial cells of the bile ducts within the liver. Over the past two decades, the incidence and mortality rates of ICC have shown a significant upward trend globally[1]. Generally, ICC is more common in Asian countries than in Western countries, with the incidence rate in China increasing by an average of 11% annually[2,3]. ICC accounts for approximately 10% to 15% of primary liver cancers[1]. Among malignant liver tumors, ICC ranks second in prevalence, second only to hepatocellular carcinoma[1,4]. ICC is insidious in onset, with early clinical symptoms that are often indistinct and a lack of effective screening methods. Consequently, the disease progresses rapidly, leading to a majority of patients being diagnosed at an advanced stage, by which time local invasion or distant metastasis has already occurred[5]. According to data from the National Center for Health Statistics Database, the overall 5-year survival rate of all ICC patients is only about 9%[6]. Surgical resection is the only treatment method that may potentially cure ICC. However, due to patients frequently missing the optimal surgical treatment window and the limitation of surgical quality, only 15% of patients diagnosed with ICC between 1983 and 2010 underwent resection with a 5-year survival rate of approximately 30%-40% after surgery, and the postoperative recurrence rate reached as high as 60%[7].

Updating surgical concepts to improve the quality of surgical treatment can significantly prolong the long-term survival of ICC patients who have the opportunity to undergo surgical resection. For example, in the past period, the application of laparoscopic liver resection, the selection of anatomical and non-anatomical liver resection, the number and scope of lymph node dissection, the scope of liver resection, the application of portal vein embolization (PVE) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and other surgical concepts have been updated, significantly reducing surgical injuries and improving long-term survival for ICC patients undergoing surgical resection[8-13]. Laparoscopy has been widely used in ICC resection surgery and laparoscopic hepatectomy has gradually replaced traditional open hepatectomy as an important surgical option. Laparoscopic hepatectomy has been proven to have better surgical outcomes and comparable oncological outcomes and survival outcomes than open hepatectomy, especially for those with a high risk of very early recurrence[14,15].

In addition to its application in resection surgery, laparoscopy also plays an important role in the preoperative staging of tumors, which is also known as staging laparoscopy (SL). SL is a minimally invasive surgical procedure used to determine the extent of cancer within the abdominal cavity, particularly useful for staging gastrointestinal and gynecological cancers[16]. SL is usually performed several days before open surgery to assist in making surgical decisions, although the necessity of SL may vary across countries and different health systems. Computed tomography (CT), abdominal ultrasound (US), magnetic resonance imaging (MRI), positron emission tomography (PET), and other imaging techniques have achieved great success in the diagnosis and staging of biliary tract tumors, and have become the most commonly used preoperative tumor staging methods with advantages such as non-invasive, convenient, and low-cost. However, according to data from two studies, approximately 46% of ICC cases were unable to accurately identify small cancerous and metastatic lesions during the preoperative imaging period, resulting in incorrect tumor staging evaluations[17,18]. Due to the lack of detection of tumor metastasis during tumor staging, these patients underwent failed and unnecessary open resection surgeries. Therefore, applying SL for accurate tumor staging before surgery can help reduce unnecessary open resection and improve the rate of curative resection.

Studies addressing the role of staging laparoscopy for ICC are limited and the number of cases is too small; furthermore, most of these studies are focusing on all hepatobiliary malignancies rather than specifically targeting ICC types[17,19]. These two studies indicate that SL has a significant advantage in detecting occult metastatic lesions in ICC, reducing meaningless resection surgeries by 25%-36%[17,19]. Accurate preoperative staging is crucial for the resection surgery of ICC patients, especially for open resection surgery which is costly and risky. In China, there are still a large number of hospitals using open resection surgery to treat ICC. Therefore, this study retrospectively analyzed case data from 14 large Hepatobiliary surgery centers in China from 2010 to 2021 regarding the use of SL in ICC patients, using propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) statistical processing methods to mitigate bias, with the aim of evaluating the benefits of SL in ICC patients undergoing surgical resection and further better guiding the surgical treatment.

METHODS

Patients

Patients with ICC undergoing curative-intent resection between January 2010 and December 2021 at 14 hospitals in China (the First Affiliated Hospital of Xi’an Jiaotong University, Eastern Hepatobiliary Hospital Affiliated to Naval Medical University, West China Hospital of Sichuan University, Tianjin Medical University Cancer Hospital, the First Hospital Affiliated to Army Medical University, Hunan Provincial People’s Hospital, the First Affiliated Hospital of Zhengzhou University, Zhongda Hospital of Southeast University, Affiliated Hospital of North Sichuan Medical College, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, the Seventh Affiliated Hospital of Sun Yat-sen University, the Second Norman Bethune Hospital of Jilin University, Shaw Hospital Affiliated to Zhejiang University School of Medicine, Department of Hepatobiliary and Pancreatic Surgery, and the Affiliated Hospital of Qingdao University) who satisfied the following inclusion criteria, and who had been successfully followed were included as retrospective study subjects. The institution review board of each institution approved this study. Unified Case Report Form (CRF) was distributed to these 14 centers, where standard demographic, laboratory, and clinicopathologic data were collected and uniformly assigned. The follow-up deadline was December 2021.

The inclusion criteria were as follows: (1) Postoperatively pathological diagnosed as ICC; (2) Preoperative evaluation indicated that the patient could tolerate surgery without serious heart, lung, brain, and kidney vital organ lesions; (3) Underwent curative intent resection; (4) Without definite distant metastases. The exclusion criteria included: (1) Patients with a prior or concurrent other malignancy; (2) Preoperatively imaging evidence of definite distant metastases; (3) Incomplete clinical data and follow-up information; (4) Underwent neoadjuvant therapy. Based on whether they received staging laparoscopy, ICC patients meeting the inclusion and exclusion criteria mentioned above were divided into SL and non-SL groups. It is important to note that, due to the current lack of universal guidelines for the application of SL in ICC patients, the decision to perform SL was primarily made by physicians based on a comprehensive assessment, such as the patient's individual situation and the physician's proficiency.

Staging laparoscopy was conducted under general anesthesia with the patient in the supine position. A disposable trocar was inserted below the umbilicus, followed by the insertion of two additional trocars into the right and left upper quadrants, respectively. Upon entry into the abdominal cavity, 250 mL of warm saline was injected into the peritoneal cavity. Careful irrigation was essential to prevent the dissemination of the primary tumor. A minimum of 100 mL of fluid was aspirated from the peritoneal cavity and promptly sent for centrifugation and cytological examination. A systematic examination of the peritoneal cavity was then performed in a clockwise direction, starting from the right quadrant. Any suspicious lesions were biopsied and sent for frozen section pathology to assess the presence of metastases[15].

Data collection

The diagnosis and pathological evaluation were in accordance with the World Health Organization (WHO) defining criteria (2010). The tumor stage was determined according to the American Joint Council on Cancer (AJCC) 8th edition tumor-node-metastasis classification system. Standard demographic, perioperative clinicopathological, preoperative symptoms and tumor-related characteristics were collected. Intraoperative data and postoperative characteristics, including lymph node dissection status, blood loss, tumor size, surgical margin, pathological differentiation, postoperative complications and hospital stay days, were collected based on final pathology reports.

Statistical analysis

All statistical analyses were performed with the SPSS 27.0 (SPSS, Chicago, IL, United States) software package. Nominal data were compared using χ^2 tests or Continuity Correction, continuous parametric data using *t*-tests, and non-parametric data using Mann-Whitney tests. The log-rank test was used in univariate analysis. A *P*-value of < 0.05 was considered statistically significant. Propensity score matching (PSM) and inverse probability treatment weighting (IPTW) were used to mitigate bias. The propensity score analysis was performed with 1:1 exact matching. The weights of IPTW were calculated by generating a logistic regression model to predict the probability of each patient who underwent curative-intent resection either receiving or not receiving SL on the basis of 13 defined preoperative variables to standardize the two groups.

RESULTS

A total of 1,472 ICC patients were collected between 2010 and 2021. According to inclusion and exclusion criteria, a total of 1,160 eligible ICC patients were included in this study, including 243 (including 87 in SL group) patients from the First Affiliated Hospital of Xi'an Jiaotong University, 127 patients (none in SL group) from Eastern Hepatobiliary Hospital Affiliated to Naval Medical University, 114 (including 7 SL group) patients from West China Hospital of Sichuan University, 147 (including 6 SL group) patients from Tianjin Medical University Cancer Hospital, 58 (including 4 SL group) patients from the First Hospital Affiliated to Army Medical University, 108 (including 43 SL group) patients from Hunan Provincial People's Hospital, 35 patients from the First Affiliated Hospital of Zhengzhou University, 33 (including 2 SL group) patients from Zhongda Hospital of Southeast University, 37 (including 11 SL group) patients from Affiliated Hospital of North Sichuan Medical College, 24 (including 3 SL group) patients from Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, 37 (none in SL group) patients from the Seventh Affiliated Hospital of Sun Yat-sen University, 25 (including 5 SL group) patients from the Second Norman Bethune Hospital of Jilin University, 134 (including 101 SL group) patients from Shaw Hospital Affiliated to Zhejiang University School of Medicine, 38 (including 8 SL group) patients from the Affiliated Hospital of Qingdao University. A total of 279 patients (24.1%) were included in the SL group, while 881 patients (75.9%) were included in the non-SL group [Figure 1].

An overview of baseline characteristics is provided in Table 1. There was no significant difference between the non-SL group and the SL group in the vast majority of characteristics, except for albumin [41.0 (36.9, 44.2) g/L *vs.* 39.9 (36.4, 42.7) g/L, $P = 0.006$]. Preoperative symptoms are defined as one or more of the tumor-related discomfort symptoms, such as abdominal pain, bloating, jaundice, weight loss, fever, recurrent cholangitis, and others. Prior to surgery, one or more imaging techniques including CT, MRI, and US were used to examine the patient. If imaging evidence indicates the presence of malignant tumors in the intrahepatic bile ducts, which are consistent with postoperative pathological examination, it is defined as a clear preoperative imaging diagnosis. If not, it is defined as an unclear preoperative imaging diagnosis. Postoperative complications include ascites, abdominal infection, bile leakage, liver failure, bleeding, pleural effusion, lung infection, incision infection, and other related complications.

Perioperative outcomes and postoperative survival

The perioperative outcomes of the SL group and non-SL group were evaluated [Table 2]. There was no significant difference in lymph node dissection status between the non-SL group and the SL group (P = 0.951), while there were statistical differences in all other main characteristics, including blood loss [300 (200, 600) mL *vs.* 300 (150, 600) mL, $P = 0.046$], tumor size [5.00 (3.00, 7.50) cm *vs.* 4.50 (3.00, 7.00) cm, P = 0.025], surgical margin (92%R0 *vs.* 98%R0, $P < 0.001$), pathological differentiation ($P < 0.001$), postoperative complications (with complications, 46% *vs.* 57%, $P = 0.002$) and hospital stay days [12 (8, 16) days *vs.* 10 (7, 14) days, $P = 0.002$]. It is worth noting that the SL group is only inferior to the non-SL group in terms of the frequency of postoperative complications. Other major Perioperative characteristics indicate that the SL group has better perioperative outcomes than the non-SL group.

The postoperative survival outcomes of the SL group and non-SL group were evaluated as well [Figure 2]. The median overall survival (OS) of non-SL group ICC patients was 24.0 months (95%CI, 22.9-26.0 months). The 1-, 3-, and 5-year overall survival rates were 70.9%, 37.3%, and 21.8%, respectively. In comparison, the median OS of SL group ICC patients was 30.0 months (95%CI, 21.4-38.6 months). The 1-, 3-, and 5-year overall survival rates were 77.9%, 47.7%, and 32.8%, respectively.

In order to better evaluate the survival outcomes between the two groups, we further conducted subgroup analyses on risk factors such as cholelithiasis, preoperative symptoms, and CA199 levels [Figure 3]. The subgroup analysis results showed that ICC patients without cholelithiasis and preoperative symptoms had better OS after receiving SL compared to those who did not receive SL. Furthermore, regardless of whether the level of CA19-9 is high ($P = 0.053$) or low ($P = 0.090$), there is no statistically significant difference in OS between the corresponding SL group and non-SL group patients.

Table 1. Baseline characteristics; *n* (%) or median (interquartile range)

Characteristics	Non-SL, *n* = 881	SL, *n* = 279	*P*-value
Gender			0.659
Male	483 (55%)	149 (53%)	
Female	398 (45%)	130 (47%)	
Age (years)	60 (51, 66)	61 (53, 67)	0.120
Cholelithiasis			0.492
No	744 (84%)	231 (83%)	
Yes	137 (16%)	48 (17%)	
CA199 (U/mL)	82 (23, 638)	47 (16, 565)	0.133
ALB (g/L)	41.0 (36.9, 44.2)	39.9 (36.4, 42.7)	0.006*
Tbil (umol/L)	14 (10, 20)	14 (11, 20)	0.694
ALT (U/L)	26 (17, 45)	24 (17, 43)	0.555
HBV/HCV infection			0.473
With	211 (24%)	61 (21.9%)	
Without	670 (76%)	218 (78.1%)	
N stage			0.524
N0	536 (61%)	176 (63%)	
N1	245 (28%)	74 (27%)	
N2	9 (1.0%)	0 (0%)	
Nx	91 (10%)	29 (10%)	
Child-Pugh score			0.247
1	774 (88%)	252 (90%)	
2	105 (12%)	27 (9.7%)	
3	2 (0.2%)	0 (0%)	
Imaging diagnosis			0.100
No	77 (8.7%)	16 (5.7%)	
Yes	804 (91%)	263 (94%)	
Preoperative symptoms			0.218
No	316 (36%)	111 (40%)	
Yes	565 (64%)	168 (60%)	
ECOG score			0.068
0	426 (48%)	111 (40%)	
1	393 (45%)	156 (56%)	
2	59 (6.7%)	12 (4.3%)	
3	2 (0.2%)	0 (0%)	
4	1 (0.1%)	0 (0%)	

*P < 0.05. SL: Staging laparoscopy.

Perioperative outcomes and postoperative survival after PSM and IPTW

Considering that the non-SL group and SL group contain a large number of variables, there may be confounding factors, which may lead to biases in the evaluation results that affect the correctness of the conclusion. Therefore, we used the methods of propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) to mitigate bias here, making the evaluation more accurate.

The baseline characteristics and perioperative outcomes after PSM are provided in Table 3. After 1:1 matching, there was no significant difference in all baseline characteristics between the non-SL group and the SL group. In the perioperative outcomes, there was no significant difference in lymph node dissection status and pathological differentiation, but other major characteristics showed significant differences

Table 2. Perioperative characteristics; *n* (%) or median (interquartile range)

Perioperative characteristics	Non-SL, *n* = 881	SL, *n* = 279	*P*-value
Tumor size	5.00 (3.00, 7.50)	4.50 (3.00, 7.00)	0.025*
Surgical margin			< 0.001*
R0	807 (92%)	274 (98%)	
R1	74 (8.4%)	5 (1.8%)	
Pathological differentiation			< 0.001*
Low	235 (27%)	123 (44%)	
Medium	565 (64%)	130 (47%)	
High	81 (9.2%)	26 (9.3%)	
Lymph node dissection			0.951
No	389 (44%)	123 (44%)	
Yes	492 (56%)	156 (56%)	
Blood loss	300 (200, 600)	300 (150, 600)	0.046*
Postoperative complications			0.002*
No	476 (54%)	121 (43%)	
Yes	405 (46%)	158 (57%)	
Hospital stay (day)	12 (8, 16)	10 (7, 14)	0.002*

**P* < 0.05. SL: Staging laparoscopy.

between the non-SL group and the SL group, including blood loss [400 (200, 675) mL *vs.* 300 (150, 600) mL, *P* = 0.007], tumor size [5.00 (3.40, 7.50) cm *vs.* 4.50 (3.00, 7.00) cm, *P* = 0.013], surgical margin (92%R0 *vs.* 99%R0, *P* < 0.001), postoperative complications (with complications, 46% *vs.* 57%, *P* = 0.010), and hospital stay days [11 (8, 16) days *vs.* 10 (7, 14) days, *P* = 0.037].

The postoperative survival outcomes [Figure 4] and subgroup analysis [Figure 5] of the SL group and non-SL group after PSM were evaluated as well. Consistent with the results before PSM, the OS of the SL group was better than that of the non-SL group (Median OS: 31 months *vs.* 20 months). The 1-, 3-, and 5-year overall survival rates of the SL group were 77.9%, 45.1%, and 32.9%, while the rates of the non-SL group were 63.9%, 31.3% and 18.4%, respectively. Similarly, consistent with the results before PSM, ICC patients without cholelithiasis had better OS after receiving SL compared to those who did not receive SL. However, remarkably, following PSM, the survival outcomes for ICC patients improved after receiving SL, irrespective of their CA19-9 levels or the presence of preoperative symptoms.

We then used the IPTW method to process the initial data and evaluated the baseline characteristics and perioperative outcomes of the SL group and the non-SL group [Table 4]. The difference between groups of baseline characteristics after IPTW was consistent with the PSM, and the evaluation results of perioperative outcomes were also consistent.

Staging laparoscopy was confirmed as an independent predictor of survival by multivariate Cox analysis

To further validate the reliability of the aforementioned results, we conducted a multivariate Cox regression analysis to ascertain whether staging laparoscopy serves as an independent predictor of survival. Consistent with our expectations, the multivariate Cox analysis confirmed that SL is indeed an independent predictor of survival. The detailed results of this analysis are presented in Table 5 and Figure 6.

Table 3. The baseline characteristics and perioperative outcomes after PSM; *n* (%) or median (interquartile range)

Characteristic	Non-SL, *n* = 274	SL, *n* = 274	*P*-value
Gender			0.607
Male	151 (55%)	145 (53%)	
Female	123 (45%)	129 (47%)	
Age (years)	61 (53, 67)	60 (53, 67)	0.894
Cholelithiasis			0.909
No	228 (83%)	227 (83%)	
Yes	46 (17%)	47 (17%)	
CA199 (U/mL)	52 (19, 475)	46 (16, 544)	> 0.999
ALB (g/L)	40.1 (36.3, 43.9)	39.9 (36.5, 42.7)	0.665
Tbil (umol/L)	13 (10, 18)	14 (11, 20)	0.137
ALT (U/L)	27 (18, 41)	25 (17, 44)	0.398
HBV/HCV infection			0.316
With	211 (24%)	61 (21.9%)	
Without	670 (76%)	218 (78.1%)	
N stage			0.433
2	3 (1.1%)	0 (0%)	
N0	163 (59%)	174 (64%)	
N1	83 (30%)	71 (26%)	
Nx	25 (9.1%)	29 (11%)	
Child-Pugh score			0.876
1	246 (90%)	247 (90%)	
2	27 (9.9%)	27 (9.9%)	
3	1 (0.4%)	0 (0%)	
Imaging diagnosis			0.707
No	14 (5.1%)	16 (5.8%)	
Yes	260 (95%)	258 (94%)	
Preoperative symptoms			0.217
No	96 (35%)	110 (40%)	
Yes	178 (65%)	164 (60%)	
ECOG score			0.933
0	120 (44%)	109 (40%)	
1	123 (45%)	153 (56%)	
2	29 (11%)	12 (4.4%)	
3	1 (0.4%)	0 (0%)	
4	1 (0.4%)	0 (0%)	
Tumor size	5.00 (3.40, 7.50)	4.50 (3.00, 7.00)	0.013*
Surgical margin			< 0.001*
R0	253 (92%)	270 (99%)	
R1	21 (7.7%)	4 (1.5%)	
Pathological differentiation			0.893
Low	111 (41%)	120 (44%)	
Medium	146 (53%)	128 (47%)	
High	17 (6.2%)	26 (9.5%)	
Lymph node dissection			0.194
No	107 (39%)	122 (45%)	
Yes	167 (61%)	152 (55%)	
Blood loss (mL)	400 (200, 675)	300 (150, 600)	0.007*
Postoperative complications			0.010*
No	147 (54%)	117 (43%)	

Yes	127 (46%)	157 (57%)	
Hospital stay (day)	11 (8, 16)	10 (7, 14)	0.037*

*$P < 0.05$. SL: Staging laparoscopy; PSM: propensity score matching.

DISCUSSION

Staging laparoscopy was first proposed for preoperative staging of gastric cancer in 1987 and has since been widely used in the surgical treatment of various types of tumors[20]. SL displayed a higher accuracy in detecting peritoneal involvement than computed tomography and positron emission tomography scans and is now a recommended step for preoperative work in most published guidelines[16]. In the past period, a large number of studies aimed at evaluating the benefits of SL for patients have been published, providing sufficient evidence for the widespread clinical application of SL[21-25]. Most previous studies have confirmed the role of SL in detecting imaging occult metastases. However, some researchers argue that SL requires patients to undergo an additional minimally invasive surgery, which can lead to an increase in operative time and overall medical costs, and in the long run, SL does not bring significant improvement in survival[26,27]. In particular, there is currently significant controversy over the role of routine SL[28,29].

ICC is a highly malignant tumor that is prone to metastasis in the early stages; thus, the application of SL is reasonable for ICC patients. However, evidence of its efficacy is currently scarce and inconclusive. There are currently few studies evaluating the role of SL in ICC patients, mainly a few prospective studies with insufficient case numbers or studies that include all biliary tumors[17,19]. A recent literature snapshot paper on the role of staging laparoscopy for intrahepatic cholangiocarcinoma reviewed all current research articles about SL in ICC patients[30]. After analyzing a total of 5 studies involving 119 patients who accepted SL, the authors drew a conclusion that the role of SL for patients with a preoperative diagnosis of ICC remains unclear[30]. Therefore, larger studies involving more patients that comprehensively evaluate the benefits of SL are urgently needed. In the past two decades, many Chinese hospitals have extensively explored the application of SL in ICC patients. Collecting comprehensive information on these explorations and evaluating them appropriately can help us better understand the role of SL in the surgical treatment of ICC, ultimately guiding us to better use SL to improve the benefits of ICC patients. In this study, we retrospectively collected 279 ICC patients who received SL from 10 large ICC surgical treatment centers in China from 2010 to 2021. In addition, we also collected 881 ICC patients who did not receive SL as the control group.

We compared the baseline characteristics between the SL group and the non-SL group to ensure that the preoperative status of patients between the two groups was similar, in order to facilitate subsequent evaluation of perioperative outcomes and overall survival outcomes. Due to the retrospective property of this study, as well as the potential impact between different variables and between variables and final outcomes, subsequent analysis of the original case data will inevitably lead to bias. Therefore, we further adopted PSM and IPTW methods to mitigate bias, which had been proven effective in previous studies[31,32]. After PSM and TPTW, there was no significant difference in all baseline characteristics between the two groups. Continuously, further evaluation of perioperative outcomes and overall survival outcomes was carried out. The evaluation results of the SL group and non-SL group indicated that the SL group has better perioperative outcomes and postoperative survival outcomes than the non-SL group. Compared with the non-SL group, the SL group had a higher success rate of R0 resection, smaller tumor size, less blood loss, and shorter hospital stay. Although we were unable to obtain yield and sensitivity values in this study due to limitations in retrospective studies, higher R0 resection and smaller tumor size suggest that the use of SL can still significantly benefit ICC patients. Surprisingly, the incidence of postoperative complications in the SL group was significantly higher than that in the non-SL group, which contradicted the results of a previous

Table 4. The baseline characteristics and perioperative outcomes after IPTW; *n* (%) or median (interquartile range)

Characteristic	Non-SL, *n* = 881	SL, *n* = 279	*P*-value
Gender			0.627
Male	483 (55%)	149 (53%)	
Female	398 (45%)	130 (47%)	
Age (years)	60 (51, 66)	61 (53, 67)	0.235
Cholelithiasis			0.319
No	744 (84%)	231 (83%)	
Yes	137 (16%)	48 (17%)	
CA199 (U/mL)	82 (23, 638)	47 (16, 565)	0.435
ALB (g/L)	41.0 (36.9, 44.2)	39.9 (36.4, 42.7)	0.539
ALT (U/L)	26 (17, 45)	24 (17, 43)	0.489
HBV/HCV infection			0.533
With	211 (24%)	61 (21.9%)	
Without	670 (76%)	218 (78.1%)	
N stage			0.590
N0	536 (61%)	176 (63%)	
N1	245 (28%)	74 (27%)	
N2	9 (1.0%)	0 (0%)	
Nx	91 (10%)	29 (10%)	
Child-Pugh score			0.280
1	774 (88%)	252 (90%)	
2	105 (12%)	27 (9.7%)	
3	2 (0.2%)	0 (0%)	
Imaging diagnosis			0.217
No	77 (8.7%)	16 (5.7%)	
Yes	804 (91%)	263 (94%)	
Preoperative symptoms			0.180
No	316 (36%)	111 (40%)	
Yes	565 (64%)	168 (60%)	
ECOG score			0.526
0	426 (48%)	111 (40%)	
1	393 (45%)	156 (56%)	
2	59 (6.7%)	12 (4.3%)	
3	2 (0.2%)	0 (0%)	
4	1 (0.1%)	0 (0%)	
Tumor size (cm)	5.00 (3.00, 7.10)	4.50 (3.00, 7.00)	< 0.001*
Surgical margin			< 0.001*
R0	817 (93%)	264 (95%)	
R1	64 (7.3%)	15 (5.4%)	
Pathological differentiation			< 0.001*
Low	356 (40%)	2 (0.7%)	
Medium	438 (50%)	257 (92%)	
High	87 (9.9%)	20 (7.2%)	
Lymph node dissection			0.382
No	356 (40%)	156 (56%)	
Yes	525 (60%)	123 (44%)	
Blood loss (mL)	300 (200, 600)	400 (200, 800)	< 0.001*
Postoperative complications			< 0.001*
No	571 (65%)	26 (9.3%)	
Yes	310 (35%)	253 (91%)	

Hospital stay (day)	11 (8, 15)	13 (9, 17)	< 0.001*

*P < 0.05. SL: Staging laparoscopy; IPTW: inverse probability of treatment weighting.

study[33]. We considered that this situation may arise because patients who had undergone SL often subsequently received laparoscopic liver resection. Due to limited visibility and restricted operating space, as well as the surgeon's potential lack of proficiency, the surgical duration is inevitably longer than open abdominal surgery. Prolonged surgical time can lead to an increased risk of complications such as infections and bile leakage. In terms of survival outcomes, the SL group had a longer median OS time and higher 1-, 3-, and 5-survival rates. This survival benefit is obvious. In addition, we further conducted subgroup analysis in order to achieve better stratification of ICC patients. The results of subgroup analysis show that the survival outcomes for ICC patients improved after receiving SL, irrespective of their CA19-9 levels or the presence of preoperative symptoms, and ICC patients without cholelithiasis had better OS after receiving SL as well. Our subgroup analysis conclusions supported the application of routine SL in ICC patients.

Due to the unique biological characteristics of ICC, the concept of using laparoscopic liver resection to treat ICC is still in dispute[34,35]. The debate about the use of laparoscopic liver resection in ICC mainly focuses on the difficulty of performing high-quality lymph node dissection under laparoscopy, insufficient tumor margins due to lack of tactile sensation, and tumor dissemination caused by vibration of energy surgical instruments such as ultrasound knives or pneumoperitoneum[36]. Due to limitations in concepts and technical conditions, many hospitals in China are still using traditional open resection surgery to treat ICC. Furthermore, the application of laparoscopic liver resection in ICC has not yet formed a widely accepted consensus and is still being explored. Consequently, in this scenario, a reasonable SL plays an irreplaceable role in reducing unnecessary and failed open resection.

Drawing upon empirical evidence from Western nations, prevailing guidelines for ICC recommend the routine staging laparoscopy in suspicious unresectable ICC patients or those with predisposing factors for metastatic dissemination[29,37,38]. However, there have been no studies evaluating SL outcomes in Chinese ICC patients reported so far. Our study was expected to provide necessary evidence support for developing SL recommendations that are more in line with Chinese ICC patients.

Some limitations of this study must be acknowledged. First, the retrospective nature of the studies may result in the results of our evaluation not fully reflecting the accurate outcomes. Second, due to the use of ICC medical record data from 14 medical centers in this study, we are unable to verify whether each hospital has adopted a unified operating procedure and standard when implementing SL, which may affect the accuracy of some data, such as postoperative complications. Thirdly, in this study, we find that the proportion of SL implementation varies among different medical centers, indicating that different physicians may have different preferences for SL. This may lead to selection bias in this study. Finally, we could not get specific information on yield and sensitivity values, which is due to the retrospective property of this study as well. More prospective studies with detailed follow-ups are needed in the future.

In conclusion, this article is the first to specifically focus on the safety and feasibility of receiving staging laparoscopy for Chinese ICC patients. It also represents the largest and most representative study to date on ICC patients undergoing SL. This multicenter, retrospective study demonstrates that ICC patients who underwent SL experienced better perioperative outcomes and significantly prolonged overall survival following resection surgery. Considering the ongoing debate about the necessity of SL for ICC patients, we hope this study will provide robust evidence-based data to inform future research in this area.

Table 5. The multivariate Cox analysis of ICC patients in this study

Characteristic	Totals	HR (95%CI)	*P*-value
Gender			0.713
Male	632	Reference	
Female	528	0.971 (0.829-1.137)	
Age (years)			0.005*
Age < 58	484	Reference	
Age ≥ 58	676	1.011 (1.003-1.019)	
Cholelithiasis			0.583
No	975	Reference	
Yes	185	1.060 (0.861-1.305)	
CA19-9 level			< 0.001*
Low	453	Reference	
High	707	1.517 (1.266-1.818)	
CEA level			< 0.001*
Low	815	Reference	0.539
High	345	1.543 (1.290-1.864)	
HBV/HCV infection			0.808
With	272	Reference	
Without	888	1.024 (0.847-1.238)	
N stage			< 0.001*
N0	712	Reference	
N1	319	1.557 (1.300-1.846)	
N2	9	0.802 (0.352-1.824)	
Nx	120	0.796 (0.565-1.120)	
Child-Pugh score			0.408
1	1,026	Reference	
2	132	0.578 (0.078-4.259)	
3	2	1.021 (0.744-1.402)	
Imaging diagnosis			0.897
No	93	Reference	
Yes	1,067	1.021 (0.744-1.402)	
Preoperative symptoms			< 0.001*
No	427	Reference	
Yes	733	1.552 (1.292-1.864)	
ECOG score			0.006*
0	537	Reference	
1	549	0.876 (0.736-1.042)	
2	71	1.138 (0.826-1.566)	
3	2	4.478 (1.049-19.123)	
4	1	14.949 (1.936-115.404)	
Staging laparoscopy			0.020*
No	881	Reference	
Yes	279	0.780 (0.633-0.961)	
Surgical margin			< 0.001*
R0	1,081	Reference	
R1	79	1.817 (1.320-2.499)	
Pathological differentiation			< 0.001*
Low	358	Reference	
Medium	695	0.395 (0.138-1.133)	
High	107	0.531 (0.184-1.535)	

Lymph node dissection			0.003*
No	512	Reference	
Yes	648	0.772 (0.650-0.917)	
Postoperative complications			0.337
No	543	Reference	
Yes	563	1.084 (0.919-1.278)	

*P < 0.05. SL: Staging laparoscopy; IPTW: inverse probability of treatment weighting; ICC: intrahepatic cholangiocarcinoma; CI: confidence interval; HR: hazard ratio.

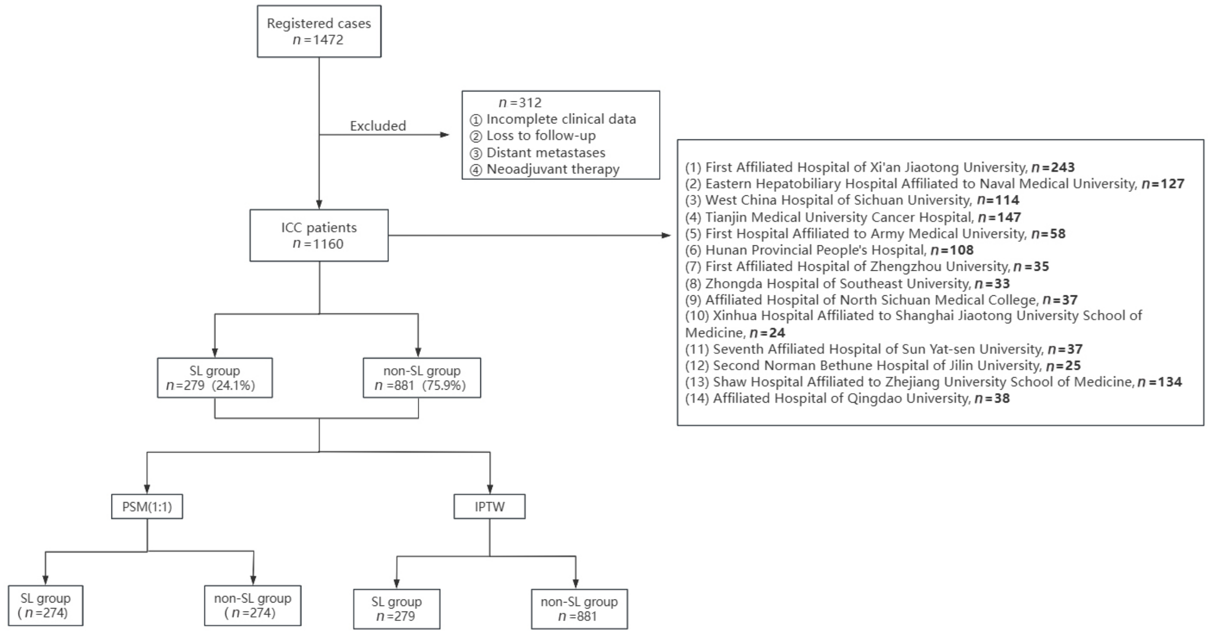

Figure 1. Flowchart of the patient selection, group assignment processes and statistical processing. ICC: Intrahepatic cholangiocarcinoma; SL: staging laparoscopy; PSM: propensity score matching; IPTW: inverse probability of treatment weighting.

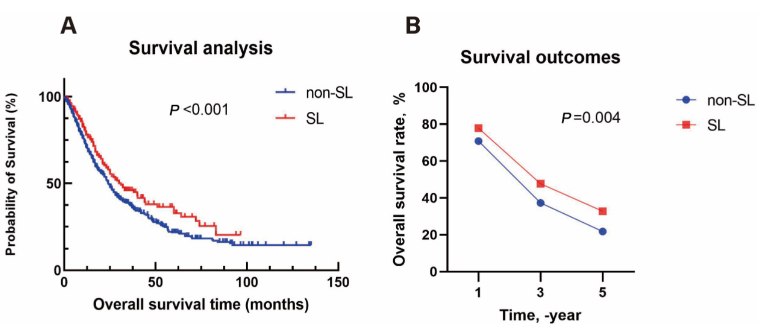

Figure 2. The postoperative outcomes of the SL group and non-SL group. (A) Kaplan-Meier survival analysis; (B) The 1-, 3-, and 5-year overall survival rates of the SL group and non-SL group. SL: Staging laparoscopy.

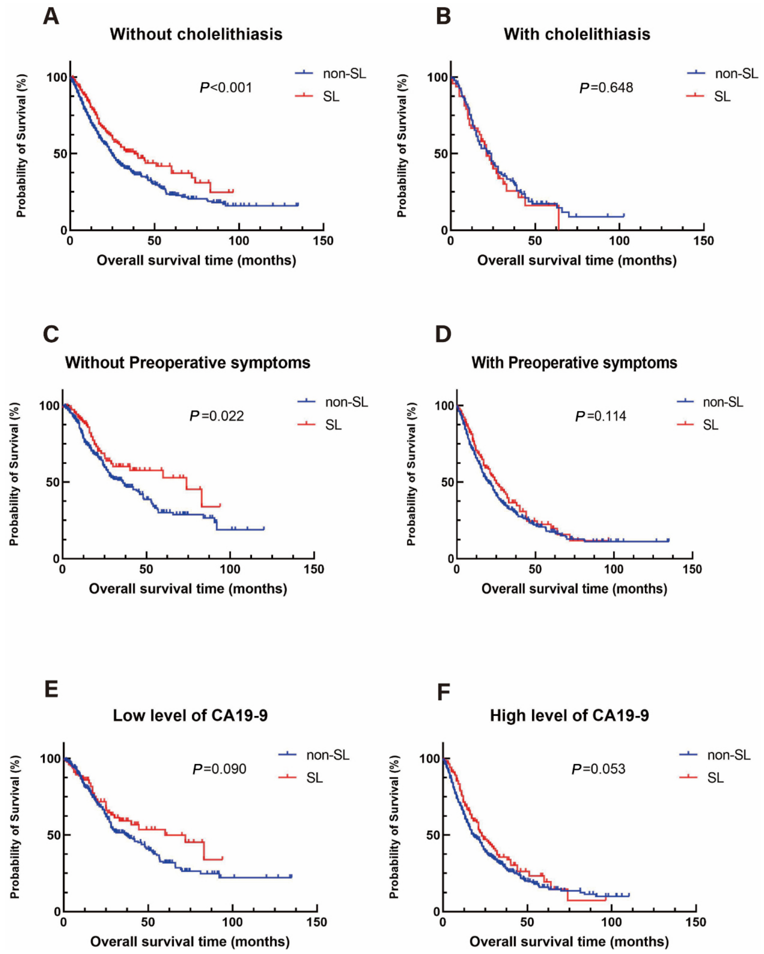

Figure 3. Subgroup analysis of Kaplan-Meier survival analysis according to risk factors of the SL group and non-SL group. (A, B) With/without cholelithiasis; (C, D) With/without preoperative symptoms; (E, F) High/low CA199 levels. SL: Staging laparoscopy.

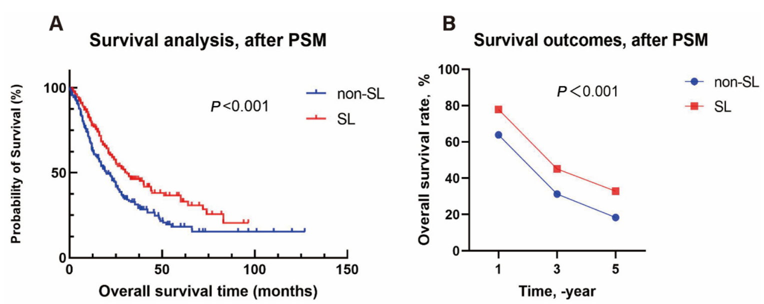

Figure 4. The postoperative outcomes of the SL group and the non-SL group after PSM. (A) Kaplan-Meier survival analysis; (B) The 1-, 3-, and 5-year overall survival rates of the SL group and non-SL group. SL: Staging laparoscopy; PSM: propensity score matching.

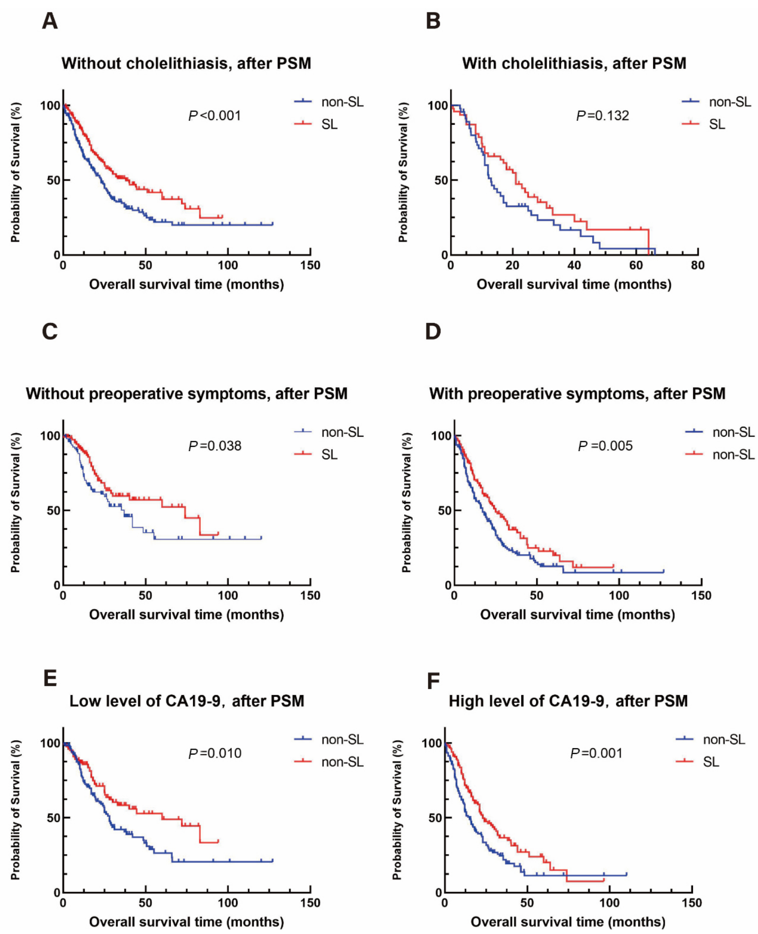

Figure 5. Subgroup analysis of Kaplan-Meier survival analysis according to risk factors of the SL group and the non-SL group after PSM. (A, B) With/without cholelithiasis; (C, D) With/without preoperative symptoms; (E, F) High/low CA199 levels. SL: Staging laparoscopy; PSM: propensity score matching.

Variable	HR	lower 95%CI	upper 95%CI	*P*-value
Gender	0.971	0.829	1.137	0.713
Age	1.011	1.003	1.019	0.005
Cholelithiasis	1.060	0.861	1.305	0.583
CA19-9	1.517	1.266	1.818	0.001
CEA	1.543	1.290	1.864	0.001
HBV/HCV	1.024	0.847	1.238	0.808
Imaging diagnosis	1.021	0.744	1.402	0.897
Preoperative symptoms	1.552	1.292	1.864	0.001
Staging laparoscopy	0.780	0.633	0.961	0.020
Surgical margin	1.817	1.320	2.499	0.001
Lymph node dissection	0.772	0.650	0.917	0.003
Postoperative complications	1.084	0.919	1.278	0.337

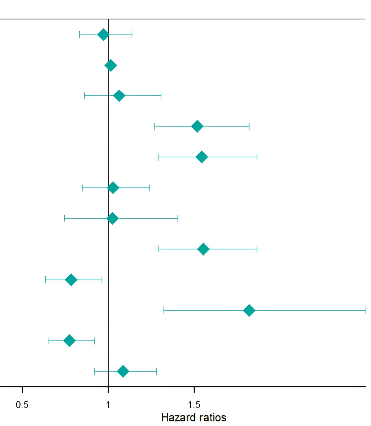

Figure 6. Multivariate Cox analysis of independent prognostic factors in ICC patients. ICC: Intrahepatic cholangiocarcinoma.

DECLARATIONS

Authors' contributions

Study concepts: Tang Z
Study design: Qin D
Data acquisition: Geng Z, Wu H, Qiu Y, Song T, Mao X, He Y, Cheng Z, Zhai W, Li J, Liang X, Lin R, Tang D, Sun C
Quality control of data and algorithms: Qin D
Data formal analysis and interpretation: Qin D
Statistical analysis: Qin D
Manuscript preparation: Qin D
Manuscript review: Chen J, Tang Y, Li Z
Manuscript revision: Qin D
Financial support: Tang Z

Availability of data and materials

The data utilized in this study originate from a clinical research project on intrahepatic cholangiocarcinoma, which has received approval from the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-JDYXY-2018-002). This database is collaboratively shared among the 14 research centers participating in this study. Due to patient data security and privacy policies, the raw data cannot be shared.

Financial support and sponsorship

This work was supported by the National Science Foundation of China (No.81772521), Multicenter Clinical Research Project of Shanghai Jiaotong University School of Medicine (No.DLY201807), and Clinical Training Program of Shanghai Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine (No.17CSK06).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-JDYXY-2018-002). All patients have signed informed consent forms for relevant treatments.

Consent for publication

Not applicable.

REFERENCES

1. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: epidemiology and risk factors. *Liver Int* 2019;39 Suppl 1:19-31. DOI PubMed
2. Florio AA, Ferlay J, Znaor A, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. *Cancer* 2020;126:2666-78. DOI PubMed PMC
3. Chinese society of liver cancer cholangiocarcinoma cooperative G. Available from: http://www.zhxhwk.com/#/Journal/Journaldetail?id=282487 [Last accessed on 27 Sep 2024].
4. Sirica AE, Gores GJ, Groopman JD, et al. Intrahepatic cholangiocarcinoma: continuing challenges and translational advances.

Hepatology 2019;69:1803-15. DOI PubMed PMC

5. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020;17:557-88. DOI PubMed PMC
6. Yao KJ, Jabbour S, Parekh N, Lin Y, Moss RA. Increasing mortality in the United States from cholangiocarcinoma: an analysis of the National Center for Health Statistics Database. *BMC Gastroenterol* 2016;16:117. DOI PubMed PMC
7. Amini N, Ejaz A, Spolverato G, Kim Y, Herman JM, Pawlik TM. Temporal trends in liver-directed therapy of patients with intrahepatic cholangiocarcinoma in the United States: a population-based analysis. *J Surg Oncol* 2014;110:163-70. DOI PubMed
8. Si A, Li J, Yang Z, et al. Impact of anatomical versus non-anatomical liver resection on short- and long-term outcomes for patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2019;26:1841-50. DOI
9. Zhao X, Gao FW, Jiang KY, et al. Laparoscopic or open liver resection for intrahepatic cholangiocarcinoma: a meta-analysis and systematic review. *Front Oncol* 2023;13:1096714. DOI PubMed PMC
10. Zhang XF, Xue F, Dong DH, et al. Number and station of lymph node metastasis after curative-intent resection of intrahepatic cholangiocarcinoma impact prognosis. *Ann Surg* 2021;274:e1187-95. DOI PubMed
11. Dai YS, Hu HJ, Lv TR, Hu YF, Zou RQ, Li FY. The influence of resection margin width in patients with intrahepatic cholangiocarcinoma: a meta-analysis. *World J Surg Oncol* 2023;21:16. DOI PubMed PMC
12. Glantzounis GK, Tokidis E, Basourakos SP, Ntzani EE, Lianos GD, Pentheroudakis G. The role of portal vein embolization in the surgical management of primary hepatobiliary cancers: a systematic review. *Eur J Surg Oncol* 2017;43:32-41. DOI PubMed
13. Li J, Moustafa M, Linecker M, et al. ALPPS for locally advanced intrahepatic cholangiocarcinoma: did aggressive surgery lead to the oncological benefit? *Ann Surg Oncol* 2020;27:1372-84. DOI PubMed PMC
14. Li HJ, Wang Q, Yang ZL, et al. Laparoscopic versus open hepatectomy for intrahepatic cholangiocarcinoma: systematic review and meta-analysis of propensity score-matched studies. *Eur J Surg Oncol* 2023;49:700-8. DOI
15. Li Z, Li Z, Zhang L, et al. Staging laparoscopy for locally advanced gastric cancer in Chinese patients: a multicenter prospective registry study. *BMC Cancer* 2018;18:63. DOI PubMed PMC
16. de Manzoni G, Roviello F. Correction to: gastric cancer: the 25-year R-evolution. In: de Manzoni G, Roviello F, editors. Gastric cancer: the 25-year R-evolution. Cham: Springer International Publishing; 2022. pp. C1-C1. DOI
17. Goere D, Wagholikar GD, Pessaux P, et al. Utility of staging laparoscopy in subsets of biliary cancers : laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. *Surg Endosc* 2006;20:721-5. DOI
18. Vollmer CM, Drebin JA, Middleton WD, et al. Utility of staging laparoscopy in subsets of peripancreatic and biliary malignancies. *Ann Surg* 2002;235:1-7. DOI PubMed PMC
19. D'Angelica M, Fong Y, Weber S, et al. The role of staging laparoscopy in hepatobiliary malignancy: prospective analysis of 401 cases. *Ann Surg Oncol* 2003;10:183-9. DOI
20. Popova TN, Korzhenskiĭ FP, Aleksandrova MI. The use of laparoscopy in the staging of stomach cancer. Available from: https://pubmed.ncbi.nlm.nih.gov/2961127/ [Last accessed on 2024 Sep 24].
21. Tse KY, Ngan HY. The role of laparoscopy in staging of different gynaecological cancers. *Best Pract Res Clin Obstet Gynaecol* 2015;29:884-95. DOI PubMed
22. Jambor MA, Ashrafizadeh A, Nahm CB, et al. The role of staging laparoscopy in pancreatic adenocarcinoma and its effect on patients' survival. *World J Surg Oncol* 2022;20:337. DOI PubMed PMC
23. van Dongen JC, Versteijne E, Bonsing BA, et al. The yield of staging laparoscopy for resectable and borderline resectable pancreatic cancer in the PREOPANC randomized controlled trial. *Eur J Surg Oncol* 2023;49:811-7. DOI PubMed
24. Bird N, Elmasry M, Jones R, et al. Role of staging laparoscopy in the stratification of patients with perihilar cholangiocarcinoma. *Br J Surg* 2017;104:418-25. DOI
25. Lv TR, Yang C, Regmi P, et al. The role of laparoscopic surgery in the surgical management of gallbladder carcinoma: a systematic review and meta-analysis. *Asian J Surg* 2021;44:1493-502. DOI
26. Tapper E, Kalb B, Martin DR, Kooby D, Adsay NV, Sarmiento JM. Staging laparoscopy for proximal pancreatic cancer in a magnetic resonance imaging-driven practice: what's it worth? *HPB (Oxford)* 2011;13:732-7. DOI PubMed PMC
27. Benedetti Panici P, Perniola G, Tomao F, et al. An update of laparoscopy in cervical cancer staging: is it a useful procedure? *Oncology* 2013;85:160-5. DOI
28. Dunne DF, Gaughran J, Jones RP, et al. Routine staging laparoscopy has no place in the management of colorectal liver metastases. *Eur J Surg Oncol* 2013;39:721-5. DOI
29. Cholangiocarcinoma Working Group. Italian clinical practice guidelines on cholangiocarcinoma - part ii: treatment. *Dig Liver Dis* 2020;52:1430-42. DOI
30. Coletta D, Scarinci A, Grazi GL, Patriti A. The role of staging laparoscopy for intrahepatic cholangiocarcinoma: a snapshot of the current literature. *J Laparoendosc Adv Surg Tech A* 2023;33:1019-24. DOI PubMed
31. Grose E, Wilson S, Barkun J, et al. Use of propensity score methodology in contemporary high-impact surgical literature. *J Am Coll Surg* 2020;230:101-112.e2. DOI
32. Davidson JT 4th, Jin LX, Krasnick B, et al. U.S. Extrahepatic Biliary Malignancy Consortium. Staging laparoscopy among three subtypes of extra-hepatic biliary malignancy: a 15-year experience from 10 institutions. *J Surg Oncol* 2019;119:288-94. DOI PubMed PMC
33. Chang L, Stefanidis D, Richardson WS, Earle DB, Fanelli RD. The role of staging laparoscopy for intraabdominal cancers: an

evidence-based review. *Surg Endosc* 2009;23:231-41. DOI PubMed

34. Regmi P, Hu HJ, Paudyal P, et al. Is laparoscopic liver resection safe for intrahepatic cholangiocarcinoma? *Eur J Surg Oncol* 2021;47:979-89. DOI
35. Wei F, Wang G, Ding J, Dou C, Yu T, Zhang C. Is it time to consider laparoscopic hepatectomy for intrahepatic cholangiocarcinoma? *J Gastrointest Surg* 2020;24:2244-50. DOI PubMed
36. Martin SP, Drake J, Wach MM, et al. Laparoscopic approach to intrahepatic cholangiocarcinoma is associated with an exacerbation of inadequate nodal staging. *Ann Surg Oncol* 2019;26:1851-7. DOI PubMed PMC
37. Association for the Study of the Liver. EASL-ILCA clinical practice guidelines on the management of intrahepatic cholangiocarcinoma. *J Hepatol* 2023;79:181-208. DOI PubMed
38. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015;17:669-80. DOI PubMed PMC