

Current status of laparoscopic radical hilar cholangiocarcinoma in Mainland China

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SUMMARY Our purpose was to explore the status of laparoscopic radical resection of hilar cholangiocarcinoma (LRRHcca) in Mainland China. Studies published before February 2020 were retrieved from CNKI database, Pubmed database and Wanfang database. Search terms included "hilar cholangiocarcinoma", "Klatskin tumor", "laparoscopy", "radical operation". Relevant articles regarding LRRHcca in Mainland China were also retrieved. 13 articles were included in this study, with a total of 189 cases. The operation time was 354 min (weighed average, WA), and the mean intraoperative blood loss was 324 mL (WA). The rate of negative margin (R0 rate) was 95.2%, and the number of lymph nodes received was 9.5 (WA). 2.6% of cases were converted to laparotomy. The incidence of postoperative complications was 21.2%, with 3.2% for those classified as Clavien-Dindo ≥ 3 , 12.2% for bile leakage, 1.6% for postoperative abdominal hemorrhage, 1.6% for liver insufficiency, and 1.1% for abdominal infection. In-hospital mortality was 0.5%, with mean postoperative hospital stay of 15 days (WA), and the rate of reoperation was 1.1%. The mean postoperative follow-up time was 16 months (WA), and 1-year overall survival rate was 84.5%. In conclusions, laparoscopic radical hilar cholangiocarcinoma is safe and feasible in experienced hands after careful selection of HCCA cases.

Keywords hilar cholangiocarcinoma, Klatskin tumor, laparoscopy, radical operation

1. Introduction

Hilar cholangiocarcinoma (HCCA), also known as Klatskin tumor, accounts for 60 -70% of the total incidence of cholangiocarcinoma. Radical surgical resection is the only chance for long-term survival of HCCA patients (1,2). Common bile duct resection, major liver resection, radical lymph node dissection, biliary reconstruction, and even vein or artery resection are required for R0 resection of HCCA. Laparoscopic radical resection of HCCA (LRRHcca) is rarely reported due to its technically demanding. Laparoscopy was originally used for HCCA exploration and tumor staging (3-5). Compared with laparoscopic surgery for liver or pancreatic cancer, LRRHcca is still in the exploratory stage. However, experience gained in other complex abdominal laparoscopic procedures and improvements of laparoscopic instruments have motivated surgeons to try LRRHcca. Since the first report of LRRHcca in Mainland China in 2003 (6), more and more hepatobiliary surgery centers in Mainland China have begun to perform this operation. Total laparoscopic resection was performed even for HCCA of Bismuth-IV

in the experienced center. Current limited clinical data suggest that LRRHcca was associated with minor injury, less pain, faster recovery, and fewer complications. These advantages have prompted more hepatobiliary surgeons to explore LRRHcca. This article reviewed the relevant articles of LRRHcca in Mainland China, and performed data extraction and analysis on China Mainland cases. This article reviewed the current status of LRRHcca and mainly focuses on the safety and feasibility of this operation.

2. Articles search strategies and analysis methods

2.1. Articles search strategies

Studies published before February 2020 were retrieved from CNKI database, PubMed database and Wanfang database. Search terms included "hilar cholangiocarcinoma", " Klatskin tumor", "laparoscopy", "radical operation". This study collected perioperative and prognostic data of LRRHcca from the retrieved articles. These data were subjected to statistical analysis. We screened out the following articles: (i) Chinese

articles without English abstracts. (ii) Articles with data loss. (iii) Articles using the same hospital cases, Articles with fewer cases (Figure 1).

2.2. Data extraction

(i) Basic information of the article: first author, year of publication, number of cases. (ii) Related conditions during the operation: surgical method, Bismuth classification, operation time, intraoperative blood loss, R0 resection rate, lymph node positive rate, and number of lymph node dissections during operation. (iii) Relevant postoperative conditions: morbidity, clavien-Dindo ≥ 3 , mortality, length of hospital stay, reoperation rate, follow-up after discharge, tumor metastasis or recurrence after discharge, and 1-year overall survival rate.

2.3. Statistical analysis

Weighted average (WA) is used to represent the statistical weighted average of different variables (operation time, intraoperative blood loss, etc.):

$$WA = (w_1x_1 + w_2x_2 + \dots + w_nx_n) / (w_1 + w_2 + \dots + w_n).$$

Where w is the number of cases in related articles, and x is the average value provided in the article or calculated after our statistics. For data presented as a median x value or missing data, x and its corresponding w is excluded.

3. Results

This article systematically reviewed 13 articles of LRRHcca in Mainland China (7-19). The total number of included cases was 189 (Table 1). Surgical method was described for 73.5% (139/189) of total cases. Among these cases, 43.2% (60/139) underwent liver resection. 54 patients underwent liver resection combined with caudate lobectomy, 2 patients did not receive caudate lobectomy, and 4 patients received caudate lobectomy alone. The distribution rates for Bismuth type I, II, III and IV were 41.8% (79/189), 22.8% (43/189), 24.3% (46/189), and 11.1% (21/189), respectively. The number of articles reported of laparoscopic radical

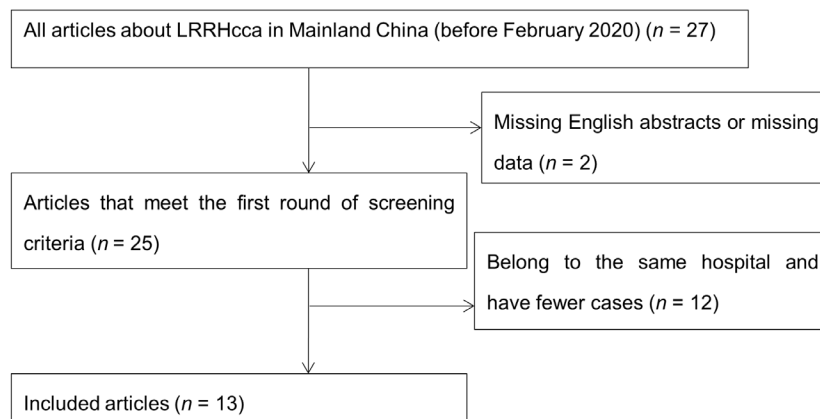


Figure 1. Screening process of LRRHcca related articles.

Table 1. Research Status of LRRHcca in Mainland China

First author (Ref.)	Publication year	Cases	Operation method (Hepatectomy, caudate lobectomy)	Bismuth-type classification (I:II:III:IV)
Jun Xu (7)	2010	4	1,0	1:1:1:1
Andong Zhu (8)	2012	38	NA,NA	13:18:7:0
Jianjun Li (9)	2012	3	1,0	2:0:1:0
Jun Li (10)	2017	9	2,4	1:3:2:3
Hongchao Zhu (11)	2018	7	0,0	7:0:0:0
Xueqing Liu (12)	2019	32	8,8	12:2:7:11
Yuhua Zhang (13)	2019	14	9,9	5:0:8:1
Xinyu Liu (14)	2019	6	6,6	0:0:3:3
Ruofan Wang (15)	2019	15	10,12	2:3:8:2
Yuxiao Zhu (16)	2019	14	2,2 [#]	7:5:2:0
Hua Luo (17)	2019	4	3,3	1:1:2:0
Chang Duan (18)	2019	13	0,0	13:0:0:0
Junjian Yuan (19)	2019	30	14,14	15:10:5:0
Total/mean	-	189	56,58	79:43:46:21

NA, not applicable. [#], This article only reported the surgical methods for 2 cases.

hilar cholangiocarcinoma in Mainland China increased significantly in 2019 (Figure 2), accounting for 61.5% (8/13), and only 38.5% during the nine years from 2010 to 2018 (5/13). The number of cases reported in laparoscopic radical hilar cholangiocarcinoma in Mainland China in 2019 accounted for 67.7% (128/189) and 32.3% (61/189) between 2010 and 2018.

3.1. Intraoperative situation

The intraoperative data of LRRHcca are demonstrated in Table 2, including operation time, intraoperative blood loss, negative rate of surgical margin (R0 rate) and so on. Mean operative time was reported in 92.6% (175/189) of cases, with WA value of 354 min. The mean intraoperative blood loss was reported in 75.7% (143/189) of cases, with WA value of 324 mL. The intraoperative margin negative rate (R0 rate) was reported in 100% (189/189) of cases, with a total rate of 95.2% (180/189). Lymph node-positive rates were reported in 58.7% (111/189) of cases, with a total

rate of 14.4% (16/111). The number of lymph nodes received was reported in 61.9% (117/189) of cases, with WA value of 9.5. Of the 189 patients, 5 patients were converted to laparotomy (2.6%), with 3 patients having tumor invasion of the portal vein, 1 patient having severe abdominal adhesions, and 1 patient having difficulty in separating tumor and bile duct under laparoscopy.

3.2. Postoperative situation

The postoperative conditions of LRRHcca are presented in Tables 3, 4 and 5. The postoperative complication rate was reported in 100% (189/189) of cases, and the overall complication rate was 21.2% (40/189); serious complications (Clavien-Dindo ≥ 3) occurred in 3.2% (6/189) of patients. The reoperation rate was 1.1% (2/189). In-hospital mortality was 0.5% (1/189). The average postoperative hospital stay was reported in 92.6% (175/189) of patients, ranging from 9.6 days to 27.6 days, and WA was 15 days.

Bile leakage is the most common complication

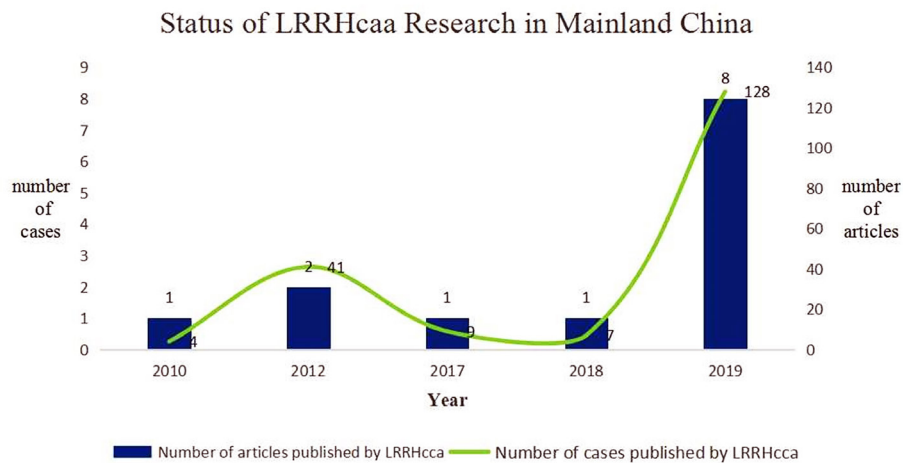


Figure 2. The number of cases and articles of LRRHcca in Mainland China. The line chart shows the number of articles published by LRRHcca over the years, and the bar chart shows the number of cases published by LRRHcca over the years.

Table 2. Intraoperative situation of LRRHcca in Mainland China

First author (Ref.)	Operation time (min)	Blood loss (mL)	R0, n (%)	lymph node positive rate, n (%)	Harvested lymph node, n	Conversion to laparotomy, n (%)
Jun Xu (7)	Mean 384	Mean 440	4 (100%)	NA	NA	0 (0%)
Andong Zhu (8)	Mean 267	Mean 83	38 (100%)	2 (5.3%)	Mean 9.4	0 (0%)
Jianjun Li (9)	Mean 520	Mean 333	3 (100%)	0 (0%)	NA	0 (0%)
Jun Li (10)	Mean 438	Mean 503	9 (100%)	NA	NA	0 (0%)
Hongchao Zhu (11)	Mean 248	Mean 156	7 (100%)	0 (0%)	Mean 9.3	0 (0%)
Xueqing Liu (12)	Mean 366	300 (75, 450)	24 (75%)	NA	NA	1 (3.1%)
Yuhua Zhang (13)	Mean 519	Mean 821	14 (100%)	NA	Mean 9.7	2 (14.3%)
Xinyu Liu (14)	Mean 590	Mean 400	5 (83.3%)	NA	NA	0 (0%)
Ruofan Wang (15)	Mean 404	Mean 502	15 (100%)	1 (6.7%)	Mean 9.5	2 (13.3%)
Yuxiao Zhu (16)	285 (190, 400)	175 (100, 500)	14 (100%)	3 (21.4%)	8 (6,15)	0 (0%)
Hua Luo (17)	Mean 616	Mean 468	4 (100%)	0 (0%)	NA	0 (0%)
Chang Duan (18)	Mean 260	Mean 177	13 (100%)	NA	Mean 9.6	0 (0%)
Junjian Yuan (19)	Mean 287	Mean 140	30 (100%)	10 (33.3%)	Mean 9.4	0 (0%)
Total/mean	35 4 (WA)	32 4 (WA)	180 (95.2%)	16 (14.4%)	9.5 (WA)	5 (2.6%)

NA, not applicable.

Table 3. Postoperative situation of LRRHcca in Mainland China

First author (<i>Ref.</i>)	Morbidity (%)	Mortality <i>n</i> (%)	LOS (days)	Clavien-Dindo ≥ 3 complications <i>n</i> (%)	Reoperation <i>n</i> (%)
Jun Xu (7)	0%	0 (0%)	Mean 15	0 (0%)	0 (0%)
Andong Zhu (8)	13.2%	0 (0%)	Mean 12	1 (2.6%)	1 (2.6%)
Jianjun Li (9)	66.7%	0 (0%)	Mean 16.7	0 (0%)	0 (0%)
Jun Li (10)	44.4%	0 (0%)	Mean 15.7	0 (0%)	0 (0%)
Hongchao Zhu (11)	0%	0 (0%)	Mean 10.7	0 (0%)	0 (0%)
Xueqing Liu (12)	15.6%	0 (0%)	Mean 27.6	0 (0%)	0 (0%)
Yuhua Zhang (13)	50%	1 (7.1%)	Mean 17.8	5 (35.7%)	1 (7.1%)
Xinyu Liu (14)	16.7%	0 (0%)	Mean 16.5	0 (0%)	0 (0%)
Ruofan Wang (15)	20%	0 (0%)	Mean 9.6	0 (0%)	0 (0%)
Yuxiao Zhu (16)	14.3%	0 (0%)	NA	0 (0%)	0 (0%)
Hua Luo (17)	25%	0 (0%)	Mean 14.3	0 (0%)	0 (0%)
Chang Duan (18)	23.1%	0 (0%)	Mean 10.6	0 (0%)	0 (0%)
Junjian Yuan (19)	23.3%	0 (0%)	Mean 8.9	0 (0%)	0 (0%)
Total/mean	40 (21.2%)	1 (0.5%)	15 (WA)	6 (3.2%)	2 (1.1%)

LOS, length of hospital stay. NA, not applicable.

Table 4. Details of postoperative complications of LRRHcca in Mainland China

First author (<i>Ref.</i>)	Abdominal Hemorrhage, <i>n</i> (%)	Abdominal infection, <i>n</i> (%)	Bile leak, <i>n</i> (%)	Hepatic insufficiency, <i>n</i> (%)	Others, <i>n</i> (%)
Jun Xu (7)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Andong Zhu (8)	1 (2.6%)	0 (0%)	3 (7.9%)	0 (0%)	1 (2.6%)
Jianjun Li (9)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	1 (33.3%)
Jun Li (10)	0 (0%)	0 (0%)	2 (22.2%)	0 (0%)	2 (22.2%)
Hongchao Zhu (11)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Xueqing Liu (12)	0 (0%)	0 (0%)	1 (3.1%)	2 (6.3%)	2 (6.3%)
Yuhua Zhang (13)	1 (7.1%)	0 (0%)	5 (35.7%)	0 (0%)	1 (7.1%)
Xinyu Liu (14)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)
Ruofan Wang (15)	0 (0%)	0 (0%)	1 (6.7%)	0 (0%)	2 (13.3%)
Yuxiao Zhu (16)	0 (0%)	0 (0%)	2 (14%)	0 (0%)	0 (0%)
Hua Luo (17)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)
Chang Duan (18)	0 (0%)	2 (15.4%)	1 (7.8%)	0 (0%)	0 (0%)
Junjian Yuan (19)	1 (3.3%)	0 (0%)	5 (16.7%)	0 (0%)	1 (3.3%)
Total/mean	3 (1.6%)	2 (1.1%)	23 (12.2%)	3 (1.6%)	9 (4.8%)

Table 5. Short-term effect of LRRHcca in Mainland China

First author (<i>Ref.</i>)	follow-up time (months)	Metastasis or Recurrence, <i>n</i> (%)	mortality during the follow-up, <i>n</i> (%)	1-year overall Survival, (%)
Jun Xu (7)	NA	NA	NA	NA
Andong Zhu (8)	Mean 12.5	1 (2.6%)	2 (5.3%)	97.4%
Jianjun Li (9)	Mean 57	0 (0%)	0 (0%)	100%
Jun Li (10)	Mean 17	NA	2 (22.2%)	77.8%
Hongchao Zhu (11)	12-18	0 (0%)	0 (0%)	100%
Xueqing Liu (12)	NA	NA	NA	80%
Yuhua Zhang (13)	NA	NA	NA	62.5%
Xinyu Liu (14)	7 (1,42)	0	0 (0%)	NA
Ruofan Wang (15)	6-60	3 (20%)	4 (26.7%)	NA
Yuxiao Zhu (16)	16 (3,24)	1 (7.1%)	1 (7.1%)	NA
Hua Luo (17)	1-4	0 (0%)	0 (0%)	NA
Chang Duan (18)	36-60	NA	NA	74.4%
Junjian Yuan (19)	6-12	3 (10%)	3 (10%)	NA
Total/mean	16 (WA)	8 (6.8%)	12 (8.6%)	84.5%

NA, not applicable.

after laparoscopic hilar cholangiocarcinoma radical resection, with a result of 12.2% (23/189). The rates of ascites fluid, pulmonary infections, stress ulcers, anastomotic edema, wound infection, liquefaction of the incision fat were 1.1% (2/189), 1.1% (2/189), 1.1%

(2/189), 0.5% (1/189), 0.5% (1/189), and 0.5% (1/189), respectively. The incidence of postoperative abdominal bleeding was 1.6% (3/189). Liver dysfunction happened at the rate of 1.6% (3/189) and the incidence of abdominal infection was 1.1% (2/189).

The average postoperative follow-up time was reported in 26.5% (50/189) of cases, the median postoperative follow-up time was reported in 47% (89/189) cases, and data was lost in 26.5% (50/189) cases, the mean follow-up time was 16 months (WA). Detailed follow-up results were obtained in 61.9% (117/189) of the cases, disease free survival rate was 93.2% (109/117). Since the follow-up time corresponding to disease free survival is median or missing, the time for disease free survival is not summarized. 74.1% (140/189) of cases reported the survival situation in detail, 8.6% (12/140) of cases died during follow-up. Death due to tumor recurrence and metastasis, cardiovascular and cerebrovascular disease, liver failure were 5.7% (8/140), 2.1% (3/140) and 0.7% (1/140), respectively. The 1-year overall survival rate was 84.5%.

4. Discussion

4.1. Development history

The first case of LRRHcca in Mainland China was reported by Professor Liu (6) in 2003. Since this article lacks English abstract, it is not included in this study. This article reported a case of hilar cholangiocarcinoma, who underwent hemi-hepatectomy without caudate lobe resection and extrahepatic bile duct resection. A negative margin of bile duct incision was achieved. In 2008, Chen *et al.* (20) conducted LRRHcca for 4 patients. All 4 patients underwent extrahepatic bile duct resection combined with partial hepatic hilar resection, but did not undergo extensive hepatectomy with caudate lobe resection. These indicate that laparoscopic techniques were feasible for the resection of hilar bile duct tumors, hilar lymph node dissection, and biliary reconstruction. After 2012, the series of LRRHcca articles gradually increased (9,11,21). In recent years, LRRHcca has developed very rapidly in Mainland China. The number of articles in 2019 was 1.6 times the total from 2010 to 2018, and the number of cases reported in 2019 was 2.1 times the number from 2010 to 2018. Although this failed to represent the annual LRRHcca operation volume, it suggested that LRRHcca has gradually become a hot spot for hepatobiliary surgeons. More and more minimally invasive hepatobiliary centers have begun to try this operation.

4.2. Technical aspects

Radical surgery for hilar cholangiocarcinoma requires extensive hepatectomy including combined caudate lobe resection, thorough lymph node dissection, and difficult bile-enteric anastomosis techniques to ensure adequate margins. This is technically difficult even in traditional open surgery. The development of LRRHcca represents the development of laparoscopic techniques. In recent years, the accumulated experience of laparoscopic liver

resection, laparoscopic radical gastrectomy, laparoscopic pancreaticoduodenectomy, and other complex operations laid a solid foundation in technical aspects for exploring LRRHcca. Currently, laparoscopic caudate lobe resection, high bile-gut anastomosis, and thorough lymph node dissection have become routine and mature techniques in many China Mainland laparoscopic centers. This will inevitably lead to the exploration and development of LRRHcca. However, for cases requiring vascular resection and reconstruction, laparoscopy is not recommended. Even if successful cases of portal vein resection and reconstruction under laparoscopy were reported, open surgery is still recommended to ensure the safety of the operation. Only 3 (1.6%) of the 189 patients underwent portal vein resection and reconstruction (12,14), and none underwent hepatic artery resection and reconstruction. Preoperative CT, MRCP and 3D imaging results were used to determine the location, size and invasion range of the tumors. Preliminary judgment of resectability can be achieved by preoperative examination while final judgment can only be confirmed through intraoperative exploration. Although vascular resection and reconstruction is feasible during laparoscopic pancreatoduodenectomy (LPD), which has good operating space and stump angle, it is extremely difficult and risky for LRRHcca, which has limited vascular angle and operating space. Among 189 cases, Bismuth-I type accounted for 41.8%, Bismuth-II type accounted for 22.8%, Bismuth-III type accounted for 24.3%, and Bismuth-IV type accounted for 11.1%. Since difficulty of operation is dramatically increased for cases of Bismuth III and IV, surgeons are recommended to explore LRRHcca starting from cases of Bismuth-I and II.

4.3. Perioperative safety

Although the data regarding the average operation time, average blood loss and postoperative complication rate in this article suggest that LRRHcca in Mainland China is safe and reliable, these retrospective studies probably have selection bias of data reporting. Based on the recently published data from our center (13), the average postoperative hospital stay was 23 days, and the Clavien-Dindo ≥ 3 rate was 35%. More clinical research is needed to further confirm safety and prognosis of LRRHcca.

4.4. Oncology efficacy

The statistical data in this study showed that the R0 rate of LRRHcca in Mainland China was 95.2%, suggesting that laparoscopy is associated with a better R0 rate. The positive rate of resection margin directly affects the prognosis of patients (22). Hepatectomy was performed in 43.2% (60/139) of the patients that described the specific surgical method, and less than half of the patients

underwent liver resection to achieve a rate of nearly 100% R0. Since Bismuth-I type and Bismuth-II type accounted for a total of 64.6% of the patients, most of these two types of patients can achieve curative resection after bile duct resection. In the initial stage of LRRHcca, the surgeon will tend to choose cases of Bismuth-I and Bismuth-II. Compared with the 1-year overall survival data of open radical hilar cholangiocarcinoma in Mainland China (23), the postoperative efficacy of LRRHcca is not significantly different from that of open surgery (71.1%).

5. Conclusions

The data in this paper indicates that laparoscopic radical hilar cholangiocarcinoma is safe and feasible in experienced hands after careful selection of HCCA cases. Surgeons with enough experience in laparoscopic operations and sophisticated skills are encouraged to explore this challenging operation. The clinical value of this operation will be verified by high-quality clinical trials in the future.

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