Review Article

Laparoscopic hepatic resection for intrahepatic cholangiocarcinoma: a narrative review of the current literature

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Background and Objective: Intrahepatic cholangiocarcinoma (ICC) is the second most common liver malignancy and represents the 10% of cholangiocarcinoma (CCA). ICC has an aggressive behavior and radical surgical resection represent the only potentially curative treatment. Even though the laparoscopic approach played a key role in the surgical treatment of benign and malignant liver tumors, the role of laparoscopic liver resection (LLR) for ICC is still debated. The scarcity of data of literature, the controversy on adequate lymphadenectomy and the high technical difficulty of surgery for ICC are some of the factors related with the low rate of LLR for ICC. The aim of this study is to review the current literature regarding the role of the LLR in the treatment of ICC focusing on safety, feasibility, and oncological results.

Methods: A comprehensive review of the literature regarding the intraoperative and the short-term outcome as well as the oncological safety of the LLR for ICC was undertaken using the following combination of text words "intrahepatic cholangiocarcinoma", "laparoscopic surgery", "laparoscopic liver resection", "laparoscopic hepatectomy", "laparoscopy", "minimally invasive surgery". The inclusion criteria were full text peer review published papers describing a LLR for ICC and focusing on short- and long-term outcome. Among 1,645 manuscripts were selected for initial screening, 10 papers have been deemed eligible for the narrative review.

Key Content and Findings: LLR for ICC increased the recent period, since 2015 among studies a total of 573 patients were included in this analysis. The rate of major hepatectomies for ICC ranged between 33% and 75% for lesions with a median size ranging from 3.5 to 6 cm. Data regarding lymph-node dissection rate showed controversial results ranging between 9% and 85%, otherwise the rate of radical resection (R0) was consistently high with values ranging between 81% and 100%. Data coming from centers with a high experience in LLR are encouraging and showed that it is safe and feasible as it is related to similar morbidity and mortality to open liver resection (OLR), 9–30% and 0–7% for LLR and 19–50% and 0–4% for OLR, respectively. Likely, LLR offers adequate long-term outcome in terms of both 3-year disease-free survival (DFS) and 3-year overall survival (OS), 3-year DFS of 35–53% and 3-year OS of 20–78% for OLR compared to 3-year DFS of 38–60% and 3-year OS of 46–85% for LLR.

Conclusions: The results regarding the safety and feasibility of LLR for ICC are encouraging but the experience and the follow up of LLR are too preliminary to give conclusive indications especially on long-term outcome and further studies are required to confirm these results.

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Introduction

Cholangiocarcinoma (CCA) is the second most common primary malignant liver tumor, and it is classified according with the anatomical location in intrahepatic (ICC) and extrahepatic (ECC). The ICC which arises proximal to the second order bile ducts, represent approximately 10% of the CCA (1,2).

Even though liver resection remains the only potential curative treatment for patients with ICC, it has been estimated that less than 30% of ICC patients are resectable for advanced disease at the time of diagnosis. ICC patients without negative prognostic factors (vascular invasion, multifocal disease, nodal metastases) who underwent surgical resection with curative intent have a 3- and 5-year survival rates of 60–70% and 30–40% respectively (3-5).

In recent years, laparoscopic liver resection (LLR) gained a key role in the surgical treatment of malignant and benign liver tumors. The recent Southampton guidelines strongly supported the LLR for the management of HCC, benign, and metastatic disease with robust evidence, LLR is associated with less intraoperative blood loss, early oral feeding, fewer complications, shorter postoperative hospital stay, and similar oncological outcomes compared to open liver resections (OLR) (6-8).

Even though the laparoscopic approach has showed similar oncologic outcomes of patients with HCC and colorectal liver metastases, few data are available regarding the application of LLR for ICC patients (9,10).

Surgery with curative intent for ICC frequently require major hepatectomies and vascular/biliary reconstructions, as well as regional lymphadenectomy. The paucity of studies regarding the feasibility and safety of LLR for ICC, controversies about lymphadenectomy and the high technical skills required for perform this type of surgery are some of the limiting factors which could justify the limited diffusion of LLR for ICC (9,11-14).

The aim of this study is to review the current literature regarding the role of the laparoscopy in the treatment of ICC focusing on short-term and long term-outcome.

Specifically, due to the controversy of different aspects of LLR for ICC we aimed to analyze in our review the technical feasibility and safety of LLR, the oncological results in terms of radical resection rate and the adequacy of laparoscopic lymphadenectomy compared to OLR. Furthermore, we would like to investigate long-term outcomes in terms of disease-free survival (DFS) and overall survival (OS). We present the following article in accordance with the Narrative Review reporting checklist (available at https://ls.amegroups.com/article/view/10.21037/ls-22-17/rc).

Methods

We therefore designed and conducted this review with the aim to provide the actual evidence regarding the role of LLR of ICC.

Identification of eligible studies was performed by searching PubMed (Medline) Embase and Cochrane library. The following combination of text words were used “intrahepatic cholangiocarcinoma”, “laparoscopic surgery”, “laparoscopic liver resection” “laparoscopic hepatectomy” “laparoscopy” “minimally invasive surgery”.

Inclusion criteria were: (I) English language studies; (II) study reporting the use of a LLR of ICC; (III) studies reporting on at least one intraoperative, postoperative, and long-term oncological outcomes after laparoscopic resection for ICC.

After search, 1,645 manuscripts were selected for initial screening. Among them, 10 papers have been deemed eligible for the study.

The extracted data included authors, year of publication, number of patients, time of enrollment, time of follow-up, tumor characteristics (tumor size and number), type of surgical resection (e.g., major or minor hepatectomy, bile duct resection), oncological safety (rate of LND and number of harvested lymph nodes, rate of R0), perioperative and short-term outcome as well as long term outcome. If the data on long term outcome were not provided in the literature, Engauge Digitizer 11.1 software was used to extract the survival rate at the corresponding time point from the survival curves (http://plotdigitizer.sourceforge.net).

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	01/12/2021
Databases and other sources searched	PubMed (Medline) Embase and Cochrane library
Search terms used (including MeSH and free text search terms and filters)	"Intrahepatic cholangiocarcinoma", "laparoscopic surgery", "laparoscopic liver resection" "laparoscopic hepatectomy" "laparoscopy" "minimally invasive surgery"
Timeframe	No limit
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion criteria: (I) English language studies; (II) study reporting the use of a LLR of ICC; (III) studies reporting on at least one intraoperative, postoperative, and long-term oncological outcomes after laparoscopic resection for ICC
	Exclusion criteria: case reports, conference abstracts, and reviews were excluded; in the case of a mixed population (e.g., including gallbladder carcinoma, intrahepatic or distal cholangiocarcinoma), studies were excluded if there was no separate reporting of outcomes for ICC patients
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Abstracts were screened for eligibility by two independent researchers (M Tripepi, S Conci); any discrepancies were resolved by a third reviewer (A Ruzzenente); two independent researchers (M Tripepi and S Conci) screened full texts and selected studies for inclusion in the systematic review; discrepancies at this stage were resolved by discussion and consensus

LLR, laparoscopic liver resection; ICC, intrahepatic cholangiocarcinoma.

Characteristic of studies included in the analysis

All studies have been published since 2015. The studies included in our analysis were all retrospective studies and predominantly coming from Eastern centers (7/10; 70%). Moreover, 80% of studies on LLR have small patients' sample (<30 patients). 8 studies were monocentric, one study involved two referral centers and finally one study included data from a multicentric American database.

Here it the search strategy summary (*Table 1*).

Results

Role of staging laparoscopy in ICC

A subgroup of ICC patients (approximately 25%) are deemed unresectable at laparotomy because of metastases (liver, nodal, or peritoneal) or locally advanced disease with extensive vascular or biliary involvement (15).

The optimization of preoperative planning, and the improving in quality imaging such as the magnetic resonance imaging with cholangiopancreatography (MRI/MRCP) have improved the preoperative detection of liver metastases, reducing the number of unnecessary laparotomies (16).

Data on the role of a staging laparoscopy in ICC patients are scarce. Weber *et al*., in a study including 53 patients with ICC performed a staging laparoscopy in 22 patients with potentially resectable disease of whom 6 (27%) were deemed unresectable for peritoneal metastases (n=4) and intrahepatic metastases (n=2) (17). Likewise, Goere *et al*., in a small series on 11 ICC patients described a 36% yield and 67% accuracy of staging laparoscopy in detecting peritoneal carcinomatosis and liver metastases (18).

Given the recent improvement of quality of preoperative imaging, the utility of a diagnostic laparoscopy to assess the tumor resectability, remains unclear (15,18,19).

According with the Expert Consensus Statement from the American Hepato-Pancreato-Biliary Association the use of laparoscopic ultrasonography may further increase the utility of staging laparoscopy especially for detection of small intrahepatic metastases (20).

Russolillo *et al*. investigated the additional value of laparoscopic ultrasonography in patients with proximal biliary cancers, including 44 ICC patients. The authors reported a 11.4% yield of staging laparoscopy without the use of ultrasound that increased to 19% when intraoperative ultrasound was used (21).

In conclusion, the role of a staging laparoscopy in

Table 2 Characteristic of laparoscopic liver resection of ICC

First author	Year	Patients No.	Tumor size (cm)	Single tumor	Satellites/ multiple tumor	Major liver resection	Bile duct resection	LND	Number of harvested lymph nodes	Nodal status positive	R0 resection
Uy (12)	2015	11	4.2 [2–13]	NA	NA	6 (54%)	–	1 (9%)	NA	0	NA
Lee (23)	2016	14	3.5 [0–5]	NA	NA	7 (50%)	–	5 (35.7%)	4 [1–12]	4 (28%)	NA
Wei (10)	2017	30	3.5 [0–9]	26 (86%)	4 (14%)	13 (43%)	–	6 (20%)	NA	3 (10%)	30 (100%)
Zhu (24)	2019	18	6 [3–9]	14 (78%)	4 (22%)	10 (55%)	–	7 (39%)	NA	3 (17%)	17 (95%)
Martin (25)	2019	312	5 (3.14)	NA	NA	135 (44%)	21 (6.7%)	120 (39%)	LND 1–5: 93 (29.8%); LND >6: 27 (8.7%)	NA	247 (81%)
Kinoshita (26)	2019	15	2.6 (1.6)	NA	NA	NA	–	6 (40%)	NA	3 (20%)	14 (93%)
Kang (27)	2020	24	4.7 (3.3)	22 (92%)	2 (8%)	18 (75%)	–	6 (25%)	NA	NA	NA
Wu (28)	2020	18	NA	NA	NA	6 (33%)	–	NA	LN >6: 6 (33%)	NA	NA
Haber (29)	2020	27	6 [1.4–13]	NA	NA	19 (70%)	–	23 (85%)	8 [1–21]	6 (32%)	24 (89%)
Ratti (30)	2021	104	3.9 (1.7)	73 (70%)	31 (28%)	35 (33%)	–	87 (83.7%)	8 [5–11]	32 (37%)	101 (97%)

Variables are expressed as number (percentage), median [interquartile range] or mean (standard deviation). ICC, intrahepatic cholangiocarcinoma; LND, lymph node dissection; NA, not available.

ICC is still debated. Despite the risk of unexpected liver metastases has been reduced with improvements of the preoperative imaging assessment, staging laparoscopy with ultrasonography may be useful in high-risk patients (high levels of CA19-9, suspected vascular invasion and peritoneal disease).

LLR of ICC

The primary target of surgery for ICC should be to achieve a microscopically (R0) negative margins, incomplete resection (R1/R2) have been proved to be one of the most relevant factors associated with worse survival (22). To achieve a curative resection for ICC, extensive surgery is frequently necessary including major hepatectomies with vascular/biliary reconstructions and regional lymphadenectomy.

Although a growing number of studies have demonstrated safety of LLR for in major hepatectomies for large liver lesions, the available data regarding LLR for ICC are prevalently focused on small solitary tumors and minor hepatectomies.

Among the 10 studies included in this analysis, 573 patients underwent LLR for ICC with a rate of major hepatectomies for ICC ranging between 33% and 75% (10,12,23-30). for lesions with a median size ranging from 3.5 to 6 cm, a detailed description of the data is reported in *Table 2*.

Of note, laparoscopic biliary reconstruction has been described only in the study conducted by Martin *et al*., based on the National Cancer Database (NCDB), who reported 21 cases of laparoscopic bile duct resection among 312 LLR for ICC, on the contrary laparoscopic vascular reconstruction for ICC patients was not reported in literature (25).

According to the European Association for the Study of the Liver (EASL) guidelines for the treatment of ICC, a regional LND is recommended to achieve adequate staging information and reduce the incidence of locoregional recurrence (31). Although several single-institution series have demonstrated the feasibility of laparoscopic lymphadenectomy, the safety and adequacy of laparoscopic LND for ICC is still a matter of debate (9).

Haber *et al*., in a study regarding 27 LLR and 31 OLR for ICC, described an equal rate of LND between two groups (85% for LLR and 94% for OLR group, P=n.s) (29). Likewise, Kinoshita *et al*., in a study on 15 LLR and 21 OLR for ICC showed no difference in LND between the LLR and OLR group (40% *vs.* 30% respectively, P=n.s.) (26). Conversely, a lower rate of LND in the LLR was reported in the studies by Kang *et al.* (LLR 30% *vs.* 75.4% OLR;

P<0.001) and Ratti *et al.* (LLR 83% *vs.* OLR 88.5%; P=0.005) (27,30).

Data regarding the adequacy of LND, assessed with number of harvested lymph node, of single-high specialized centers showed similar results for LLR and OLR, with a median of 8 lymph node retrieved in the laparoscopic group (29,30). Conversely, a recent study of Martin *et al.* including data from the NCDB (National Cancer Database) of 2,309 resected ICC patients (1,997 OLR, 312 LLR) showed that patients who underwent a LLR were less likely undergo an LND compared to OLR group (LLR: 39%, n=120 *vs.* OLR: 61%, n=1,210, P<0.001), moreover an adequate lymph node evaluation (≥6 nodes) was less frequent in (LLR 9%, n=27 *vs.* OLR 15%, n=305, P<0.001) (25). These results should be evaluated in light of some limitations of this study, firstly, this is a national cancer database study, moreover in more than 40% of patients definitive diagnosis of ICC was accomplished only after surgical resection, accounting for the low rate of overall LND (the rate of dissection of one or more lymph node was only 58%, n=1,330).

Regarding the oncological safety of LLR, the reported R0 resection can be achieve in more than 80% (range, 81–100%) of patients who underwent LLR for ICC, with values comparable with OLR (10,24-26,29,30).

In a recent metanalysis on 6 retrospective studies, including 384 LLR and 2,147 OLR for ICC, Wei *et al.* reported that patients who underwent LLR had more commonly an R0 resection (81.6% for LLR *vs.* 73.8% for OLR, P=0.008), however, similarly to other reports, major hepatectomy rate and tumor size were significantly lower for LLR (32).

In conclusion, LLR for ICC is still prevalently reserved for smaller tumor which required a minor hepatectomy, Safety and feasibility of laparoscopic LND is still debated although, accordingly to recent single high volume centers data laparoscopic LND can be performed with similar results compared to OLR, allowing the retrieve of adequate number of lymph node without an increase of procedural complications (29,30,33).

Perioperative and short-term outcomes

Several studies have described the advantages of the LLR for other primary and secondary liver tumors in terms of reduction of intraoperative blood loss, transfusion rate and shorter hospital stay, however data on perioperative morbidity and mortality of LLR for ICC are more limited (34-36).

Ratti *et al.*, showed for LLR of ICC a reduction of overall postoperative morbidity (14.4% in LLR *vs.* 24% in OLR, P=0.002). In detail, patients who underwent LLR showed lower wound infection rate (1% in LLR *vs.* 3.8% in OLR group, P=0.05), lower biliary fistula rate (3.8% in LLR *vs.* 7.7% in OLR, P=0.03), lower rate of postoperative ascites (6.7% in LLR *vs.* 10.6% in OLR, P=0.04), and lower rate of lymphatic fistula (1.9% LLR *vs.* 6.7% in OLR, P=0.03) (30).

Regmi *et al.* in a recent meta-analysis on 8 papers showed no significant differences for the surgical time between LLR and OLR, a lower overall morbidity in LLR group while the rate of major complication rate was comparable between two group. However, OLR group shower higher rate of major hepatectomies and larger tumors (37).

Likewise, Wu *et al.*, in a study on 43 patients who underwent curative LLR (n=18) or OLR (n=25) for ICC, showed equal operative time, postoperative hospital stays, morbidity (including wound infection, bile leakage, liver failure and pneumonia) and mortality within 30 days, with similar rate of major resection between the two group (28).

In conclusion, the LLR for ICC has been demonstrated to be safe and feasible for ICC patients with similar operative time and a tendency to a lower rate of postoperative complications.

Long-term outcomes

Unfortunately, data on long-term outcomes for LLR in ICC are scarce and clinical studies are recent with a limited number of patients.

Single-center studies have showed comparable long-term outcome, in both 3- and 5-year DFS and 3- and 5-year OS between OLR and LLR resection for ICC (10,12,23,24,30).

A detailed description of DFS and OS data of available studies in literature is reported in *Table 3*.

Conversely from data reported by single-center studies, Regmi *et al.*, in a metanalysis on 8 papers containing 552 LLR and 2320 OLR demonstrated similar 3-, 5-year DFS and 3 years OS but lowed 5-year OS for the LLR group compared to OLR group (HR: 3.01; 95% CI: 2.16 to 4.19; P<0.001). However, in this study, the 5-year OS analysis was conducted evaluating data of only two studies (37).

Despite the results regarding the long-term outcome of LLR are encouraging, the experience and the follow up of LLR are too preliminary to give conclusive indications and further studies are required to confirm the role of LLR for long term outcomes of ICC.

Table 3 Long-term outcome of laparoscopic liver resection for ICC

First author	Year	SA	Patients	Recurrence rate, %	3-year OS, %	5-year OS, %	3-year DFS, %	5-year DFS, %
Uy (12)	2015	LLR	11	36.4	77.9	77.9	56.2	56.2
		OLR	26	46.2	66.2	66.2	39.4	39.4
Lee (23)	2016	LLR	14	21.4	84.6	NA	76.9‡	NA
		OLR	23	43.4	75.7	NA	56.7‡	NA
Wei (10)	2017	LLR	12	50	56.3	NA	43.8‡	NA
		OLR	20	60	32.7	NA	27.9‡	NA
Kinoshita (26)	2019	LLR	15	NA	58	58	NA	NA
		OLR	21	NA	78	67	NA	NA
Zhu (24)	2019	LLR	18	55.6	45.8	NA	37.8	NA
		OLR	36	61.1	38.2	NA	34.9	NA
Kang (27)	2020	LLR	24	NA	74.8	NA	59.9	NA
		OLR	24	NA	75.6	NA	41.8	NA
Wu (28)	2020	LLR	18	NA	47.1	NA	0‡	NA
		OLR	25	NA	20	NA	4‡	NA
Ratti (30)	2021	LLR	104	45.2	76†	NA	54†	NA
		OLR	104	56.7	69†	NA	53†	NA

†, data has been extracted from figures using the open-source software Plot Digitizer (https://plotdigitizer.sourceforge.net). ‡, data has been reported as RFS. ICC, intrahepatic cholangiocarcinoma; SA, surgical approach; LLR, laparoscopic liver resection; OLR, open liver resection; NA, not available; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival.

Discussion

In recent years impressive improvements have been made in LLR for malignant liver disease (6-8) and the benefit of minimally invasive surgery without compromising oncological outcome has been demonstrated for primary and secondary liver tumors. Conversely, laparoscopic treatment of ICC is still a matter of debate and data regarding the safety and feasibility of the LLR in these patients are recent and limited to small clinical series.

The limited use of the laparoscopic approach for ICC is related to different reasons. Firstly, ICC is a relative rare disease when compared to other liver tumors. Secondly, ICC has frequently an advanced stage at diagnosis, for these reasons radical surgery often requires major hepatectomies and associated complex surgical procedures (e.g., vascular resections, removal of adjacent organs and lymph node dissection). The complexity and the required technical skills performing these surgical procedures are the main reasons for the limited application of LLR in ICC (13,14).

However, the interest in LLR for ICC increased in recent years with most of the studies published in the last 5 years. Initially LLR was reserved at small and single tumors while recent reports described the safety of LLR in more complex procedures and the feasibility was demonstrated also in large and multiple ICC.

Similarly, to other liver malignances, the available data on LLR for ICC showed the safety of the procedure providing benefits in terms of intraoperative blood loss, functional recovery with similar overall morbidity and mortality (29,30).

The safety and feasibility of laparoscopic LND is still debated with discordant results for the overall rate of LND and the number of retrieved lymph nodes. More recent literature data seem to demonstrate the adequacy and safety of laparoscopic LND although confirming the complexity of this procedure.

The LLR has been related to good oncologic efficacy with R0 resections rate, OS and DFS similar to those reported for OLR (10,23,26,27). However, considering the relatively short follow up of the laparoscopic approach for

ICC, data regarding the long-term oncological outcome should be considered with caution and should be confirmed in larger studies.

There are several limitations of this study. First, all the studies included in this review are retrospective studies and most of them are single center study. Moreover, due of the relatively recent introduction of the laparoscopic technique for ICC, and the rarity of this tumor, the long-term results are still limited.

The available results should be considered preliminary. Further large multicentric well balance prospective studies with adequate oncological approach as well as a longer follow-up would be needed to confirm these data. Moreover, there has no randomized clinical trials involving LLR for ICC and this is needed to reduce the possible selection bias and clarify the risks *vs.* benefits and improve standardize the approach.

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Footnote

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