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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

# Laparoscopic Approach to Intrahepatic Cholangiocarcinoma is Associated with an Exacerbation of Inadequate Nodal Staging

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## ABSTRACT

**Introduction.** Laparoscopic approach to liver resection is feasible and safe, though its utilization with intrahepatic cholangiocarcinoma (ICC) remains poorly documented. We sought to evaluate the use laparoscopy for ICC, and to examine adherence to oncologic standards.

**Methods.** The National Cancer Database was queried for patients who underwent resection for ICC. Patients were stratified by laparoscopic (LLR) versus open liver resection (OLR). Clinicopathologic parameters and hospital volumes were recorded.

**Results.** In total, 2309 patients with ICC underwent hepatic resection (1997 OLR, 312 LLR) between 2010 and 2015. LLR increased from 12 to 16% during the study period and was utilized more commonly than OLR for wedge and segmental resections (56% vs. 33%, $p < 0.001$). Nodal evaluation was performed in 58% of all patients with ICC and was significantly more common in patients undergoing OLR (61%, $n = 1210$) versus LLR (39%, $n = 120$), $p < 0.001$. Of the 120 patients undergoing LLR with any nodal evaluation, 31% ($n = 37$) had a single node evaluated. Patients who underwent LLR were less likely to have $\geq 6$ lymph nodes evaluated compared with those who underwent OLR (9% vs. 15%, respectively, $p < 0.001$).

**Conclusions.** The use of laparoscopy for ICC is associated with an exacerbation of inadequate nodal evaluation compared with open resections.

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Intrahepatic cholangiocarcinoma (ICC) represents a subtype of bile duct adenocarcinoma involving the small ducts within the liver and accounts for approximately 10% of cholangiocarcinoma cases in the United States.[1,2] Like many other gastrointestinal tract cancers, complete surgical resection offers the potential for cure. However, the prognosis remains poor with most patients succumbing to recurrence following tumor resection.[2–5] One of the strongest predictors of poor outcomes is the presence of lymph node metastasis (LNM), which occurs in 33% of patients with early stage (T2) cancers.[6,7] According to a retrospective review of the SEER database, the median overall survival for patients with positive LNM was 19 months compared with 77 months for patients without LNM (when $\geq 6$ lymph nodes were evaluated).[5] The negative correlation between LNM and overall survival has led to the American Joint Committee on Cancer (AJCC) to recommend a portal lymph node dissection with at least six lymph nodes retrieved at the time of resection.[8]

In 2008, experts in both laparoscopic and open liver resections developed the first international consensus guideline, The Louisville Statement, in an effort to define appropriate recommendations for laparoscopic liver surgery.[9] The consensus from this conference was that laparoscopic liver surgery is safe in the hands of an experienced surgeon, and subsequent consensus statements have echoed this finding.[9–11] While laparoscopic liver resection (LLR) has been established to be safe and effective for minimally invasive liver resection for hepatocellular carcinoma and liver metastasis, the adaptation of LLR for ICC has been less well defined. In a recent review of 2804 patients undergoing laparoscopic liver resection, cholangiocarcinoma made up less than 7% of total cases.[12]

Despite defined AJCC guidelines for lymphadenectomy in ICC, past examinations of lymph node dissection in ICC have indicated that only 25% of patients receive adequate sampling with open surgery.[8] Due to the additional technical challenges associated with lymphadenectomy using minimally invasive techniques, potential exists for further underutilization. We sought to examine the current trends of LLR for ICC using a large, national database, and to examine the adequacy of lymphadenectomy when stratified by operative approach.

## METHODS

### *Cohort Selection*

The National Cancer Database (NCDB) was queried for ICC between 2010 and 2015. Patients with ICC were identified using the International Classification of Disease for Oncology, 3rd edition (ICD-O-3) with the primary site code specific to intrahepatic bile duct (22.1) as well as the histology code for cholangiocarcinoma (8160). Surgical cases were classified as segmentectomy, hepatectomy, extended hepatectomy, bile duct excision, and bile duct excision with partial hepatectomy. Concomitant local ablative therapy, when performed at the time of resection, was grouped into the most invasive procedure and all cases involving transplantation were excluded. Finally, cases were classified as open or laparoscopic based on surgical approach (Supplemental Fig. 1). To capture final outcomes of LLR, those cases that were started laparoscopically and converted to open were included in the open cohort, which is in line with definitions established in The Louisville Statement.[9]

Basic demographic data were collected on all patients. Geographic information was categorized as Eastern United States (New England, Middle Atlantic, South Atlantic), Western United States (Pacific and Mountain), and Central United States (East North Central, East South Central, West North Central, West South Central). Finally, treatment center volume data were collected and stratified as high (HVC) for the top 10% (16 + cases over the study period) or low (LVC) for the remainder of the centers.

### *Oncologic Outcomes*

The degree of lymph node dissection was evaluated for patients through the variable "Regional Lymph Nodes Examined." This variable was defined for downstream analysis as 0, 1–5, or $\geq$ 6 nodes examined. This classification system was used to stratify patients as those receiving LND in accordance with AJCC guidelines in comparison to those with no lymph node evaluation or suboptimal evaluation. The adequacy of surgical margins was defined as R0, R1, R2, or "positive not otherwise specified." In addition, the number of patients who received adjuvant chemotherapy and radiation, and the days to adjuvant therapy initiation were examined.

### *Statistical Analysis*

Descriptive statistics were calculated for all variables of interest. Continuous variables were summarized using means, whereas categorical variables were summarized using frequency and percentages. Comparisons of categorical variables were performed using the Chi square or Fisher's exact test, whereas continuous variables were compared with the two-sided Student's $t$ test. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY).

## RESULTS

### *Patients*

Utilizing the NCDB from 2010 to 2015, 2309 patients were identified as having received an operation for a diagnosis of ICC (Supplemental Fig. 1). Within this cohort, 53% ($n$ = 1224) of patients were diagnosed based on preoperative biopsy; the remaining 47% ($n$ = 1085) of patients were diagnosed based on final surgical pathology. Of the 2309 operations included, 1997 were performed open (OLR), whereas 312 were LLR. There was no difference in technique used based on any of the collected demographic data (Table 1).

### *Utilization of Minimally Invasive Surgery*

The use of laparoscopic surgery gradually increased over the study period accounting for 12% of cases in 2010 and increasing to 16% of cases in 2015 (Fig. 1). LLR was utilized more frequently for hepatic wedge resections or segmentectomy compared to more formal hemi-hepatectomy, extended hemi-hepatectomy, or procedures requiring a bile duct resection ($p < 0.001$). LLR was utilized more

**TABLE 1** Univariable analysis of demographic factors associated with manage of node-positive ICC

| Variables | Open liver resection N = I997 (%)[a,b] | Laparoscopic liver resection N = 312 (%)[a,b] | p value |
|---|---|---|---|
| Age (mean) | 63.9 | 64.7 | 0.25 |
| Sex | | | 0.119 |
| Male | 933 (46.7) | 131 (42) | |
| Female | 1064 (53.3) | 181 (58) | |
| Race | | | 0.738 |
| Caucasian | 1705 (85.4) | 270 (86.5) | |
| African American | 131 (6.6) | 20 (6.4) | |
| Asian | 105 (5.3) | 12 (3.8) | |
| Other | 56 (2.8) | 10 (3.2) | |
| Year of diagnosis | | | 0.239 |
| 2010 | 307 (15.4) | 41 (13.1) | |
| 2011 | 295 (14.8) | 37 (11.9) | |
| 2012 | 338 (16.9) | 47 (15.1) | |
| 2013 | 323 (16.2) | 50 (16) | |
| 2014 | 345 (17.3) | 63 (20.2) | |
| 2015 | 389 (19.5) | 74 (23.7) | |
| Type of hospital | | | 0.758 |
| Low volume | 999 (50.0) | 159 (51.0) | |
| High volume | 998 (50.0) | 153 (49.0) | |
| Location | | | 0.602 |
| East | 931 (48) | 151 (50) | |
| Central | 770 (39.7) | 111 (36.8) | |
| West | 237 (12.2) | 40 (13.2) | |
| Population density | | | 0.113 |
| Metro (> 20,000 people) | 1620 (83.1) | 261 (86.7) | |
| Urban (2500–20,000 people) | 297 (15.2) | 39 (13) | |
| Rural (< 2500 people) | 32 (1.6) | 1 (0.3) | |
| Mean distance traveled (miles) | 78.6 | 80.5 | 0.876 |

[a]Missing variables not displayed

[b]Rounded to nearest decimal

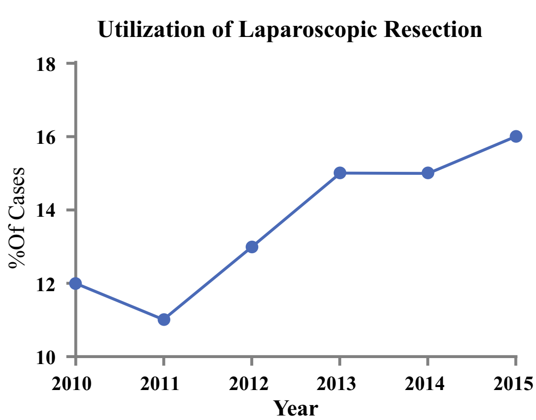


**FIG. 1** Percentage of resections for intrahepatic cholangiocarcinoma performed laparoscopically by year

frequently for smaller tumors (mean 5.0 cm vs. 6.4 cm, $p < 0.001$; Table 2).

*Lymph Node Evaluation*

Of all patients undergoing resections for cholangiocarcinoma, 58% ($n = 1330$) underwent some form of lymph node evaluation (one or more nodes). When stratified by center volume, six nodes were evaluated more commonly in HVC (HVC 56.3%, LVC 43.7%, $p < 0.001$). Operations performed at LVC were more likely to have zero lymph nodes examined (56.9%) compared with HVC (43.1%; $p < 0.001$). Nodal evaluations were more common for patients with clinically node-positive disease; 31.3% ($n = 83$) had $\geq 6$ nodes evaluated and 40% ($n = 106$)

**TABLE 2** Univariable analysis of preoperative factors and surgical outcomes associated with laparoscopic liver resection

| Variables | Open $n$ = 1997(%) | Laparoscopic $n$ = 312(%) | $p$ value |
|---|---|---|---|
| Preoperative biopsy | | | 0.323 |
| No | 778 (41.3) | 120 (41.5) | |
| Yes | 1058 (56.2) | 166 (57.4) | |
| Neoadjuvant chemotherapy | | | 0.566 |
| No | 602 (30.1) | 91 (29.2) | |
| Yes | 206 (10.3) | 27 (8.7) | |
| Neoadjuvant radiation | | | 0.533 |
| No | 229 (82.4) | 32 (86.5) | |
| Yes | 49 (17.6) | 5 (13.5) | |
| Surgery | | | < 0.001 |
| Wedge/segmentectomy | 659 (33) | 175 (56) | |
| Hemi-hepatectomy | 769 (38.5) | 88 (28.2) | |
| Extended hepatectomy | 319 (16) | 28 (9) | |
| Bile duct resection | 47 (2.4) | 2 (0.6) | |
| Bile duct and partial hepatectomy | 203 (10.2) | 19 (6.1) | |
| Clinical stage | | | 0.776 |
| 1 | 677 (33.9) | 115 (36.9) | |
| 2 | 380 (19) | 58 (18.6) | |
| 3 | 114 (5.7) | 15 (4.8) | |
| 4 | 289 (14.5) | 39 (12.5) | |
| Lymphadenectomy | | | < 0.001 |
| 0 nodes | 768 (38.8) | 192 (61.5) | |
| 1–5 nodes | 905 (45.8) | 93 (29.8) | |
| > 6 nodes | 305 (15.4) | 27 (8.7) | |
| Margin status | | | 0.021 |
| RO | 1451 (76.9) | 247 (81.3) | |
| Rl | 283 (15) | 26 (8.6) | |
| R2 | 22 (1.2) | 4 (1.3) | |
| Positive (not otherwise specified) | 132 (7) | 27 (8.9) | |
| Tumor size (mean) | 6.40 (SD 5.52) | 5.01 (SD 3.14) | < 0.001 |
| Adjuvant radiation | | | 0.306 |
| No | 1701 (85.8) | 275 (88.1) | |
| Yes | 260 (13.1) | 36 (11.5) | |
| Adjuvant chemotherapy | | | 0.284 |
| No | 1102 (57.5) | 183 (60.8) | |
| Yes | 814 (42.5) | 118 (39.2) | |
| Days to radiation (mean) | 87.0 (SD 52.1) | 87.3 (SD 54.0) | 0.972 |
| Days to chemotherapy (mean) | 63.3 (SD 34.7) | 60.1 (SD 31.0) | 0.410 |

had $\geq$ 1 node evaluated, $p < 0.001$. Conversely, patients with clinically stage I disease had zero nodal evaluation in 61.0% ($n$ = 399) of cases compared with 28.7% ($n$ = 76) of clinically Stage IVa cases, $p < 0.001$.

Patients undergoing OLR were significantly more likely to undergo lymph node examination than patients undergoing LLR (61% vs. 37%), respectively, $p < 0.001$. Of 120 patients undergoing LLR with nodal evaluation, 31% ($n$ = 37) had a single node evaluated. Patients who underwent a LLR were less likely to undergo an adequate lymph node evaluation ($\geq$ 6 nodes) compared with those who underwent OLR (9%, $n$ = 27 vs. 15%, $n$ = 305, respectively, $p < 0.001$, Fig. 2). When examining lymph node evaluation and center volume for patient undergoing LLR, there was no difference when the evaluation was stratified by six nodes (HVC $n$ = 17 vs. LVC $n$ = 10) or zero nodal evaluation (HVC $n$ = 105 vs. LVC $n$ = 119), $p$ = 0.27.

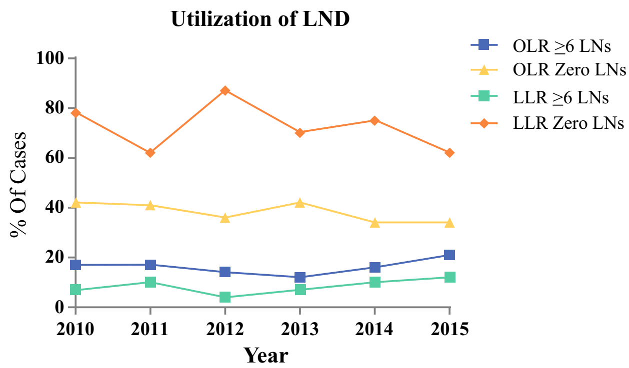


**FIG. 2** Percentage of cases per year by open and laparoscopic approach where zero lymph nodes were evaluated, as well as cases were six or more lymph nodes were evaluated

*Adjuvant Therapy*

The utilization of adjuvant therapy was examined in relation to lymph node retrieval. In total, 41% of patients received adjuvant chemotherapy and 13% received adjuvant radiotherapy. Adjuvant chemotherapy was administered to 51.3%, 47.6%, and 32.7% of patients with $\geq$ 6, 1–5, and zero LN evaluated on final pathology, respectively ($p < 0.001$). Adjuvant radiation therapy was administered to 19.8%, 15.1%, and 8.4% of patients with $\geq$ 6, 1–5, and zero LN evaluated on final pathology, respectively ($p < 0.001$). The use of adjuvant therapy did not differ significantly when patients were stratified by operative approach (OLR vs. LLR; Table 2).

## DISCUSSION

Formal lymphadenectomy is an important adjunct to liver resection for ICC. Thorough lymph node examination provides important prognostic information, which often influences further treatment decisions. This has become particularly true with the recent reporting of the Adjuvant Capecitabine May Extend Survival in Biliary Tract Cancer (BILCAP) study, which demonstrated improved OS with adjuvant capecitabine (BILCAP trial, 2018 ASCO Abstract #4006). Although several single-institution series have demonstrated the feasibility of portal lymphadenectomy with laparoscopy, we hypothesized that adherence to oncologic standards would be suboptimal when evaluated across a broad spectrum of care centers in the United States.[13–15] Upon examination of the NCDB dataset for intrahepatic bile duct cancers, we found that nearly two-thirds of patients undergoing laparoscopic resections for ICC had zero lymph nodes evaluated on final pathology, with less than 10% undergoing removal of six or more lymph nodes.

The most recent AJCC guidelines recommends a minimum of six lymph nodes sampled at the time of resection to appropriately stage ICC.[8] Historically, the use of LND during OLR for ICC in the United States has been low, with only 25% of patients receiving adequate sampling.[8] In our analysis, the proportion of patients receiving an evaluation of an adequate number of lymph nodes is substantially lower than what has previously been reported. Of note, our findings demonstrate that even in cases of clinically node positive disease over 25% of patients had zero nodal evaluation and only 31% had the recommended number of nodes evaluated. We observed a significantly lower compliance rate to the AJCC guidelines in LLR compared with OLR. Strikingly, nearly two-thirds of LLR cases reported a complete absence of lymph node evaluation. This finding implies that patients undergoing LLR are less likely to receive adequate LND and that in a majority of these cases the nodal basin appears to be entirely overlooked. Multiple studies from single centers have attempted to establish noninferiority of laparoscopic resection of ICC (Table 3). Notably, Ratti et al. concluded that LLR was equivalent to OLR with regards to the number of nodes retrieved during resection. However, only 50% of patients who underwent LLR also had a LND compared with 97% of patients in the OLR cohort.[13] In a more recent single-center study, the same authors demonstrated that LLR resulted in a higher percentage of complete LND as well as fewer LND associated complications.[15] Although specific single-center experiences may provide exemplary models, they do not appear to be representative of national trends for hepatic resections in ICC. Our data indicate that even in the highest volume centers, lymph node evaluation does not appear to reflect what is being reported from highly specialized single centers.

In our series, nearly half of patients did not receive adjuvant chemotherapy. While the BILCAP trial has reported a survival advantage with adjuvant capecitabine, routine application is currently controversial. Previous work from the NCBD has shown that in patients with aggressive tumor phenotypes, such as lymph node metastasis and increased tumor size, adjuvant chemotherapy does convey a survival advantage.[16] In addition a meta-analysis of all biliary tract cancers supported the use of adjuvant chemotherapy in patients with lymph node positive disease given a statistically significant survival advantage.[17] While no level 1 data currently exists, based on the aforementioned studies, the most recent NCCN guidelines do recommend adjuvant therapy in the setting of lymph node metastasis. It should nevertheless be noted that despite its benefit for prognostication, adequate LND itself has not been shown to convey any survival benefit.[18–20] Consequently, there does appear to be a trend towards adjuvant therapy utilization in patients receiving lymphadenectomy.

**TABLE 3** Literature review of the utilization of laparoscopic liver resection for intrahepatic cholangiocarcinoma

| Article | Number of laparoscopic ICC cases | Number of cases in which iymphadenectomy was performed *n* (%) | Number of nodes evaluated |
|---|---|---|---|
| Wei et al. 2017 Surg Endosc[24] | 30 | 6 (20%) | NR |
| Ratti et al. 2016 Surg Endosc[14] | 20 | 10 (50%) | Median 7 (5–11) |
| Lee et al. 2016 Surg Endosc[15] | 14 | 5 (36%) | Median 4 (1–12) |
| Uy et al. 2015 J Laparocndosc Adv Surg Tech[25] | 11 | 1 (9%) | NR |

Adjuvant chemotherapy and radiation was utilized more frequently with $\geq 1$ node evaluated, and was highest with $\geq 6$ nodes evaluated. It therefore follows that the inability to establish nodal staging is associated with inaccurate prognosis and can influence the utilization of adjuvant therapy.

In this study, we evaluated only the laparoscopic approach to minimally invasive liver resections and excluded other minimally invasive techniques. The da Vinci Surgical System platform (Intuitive Surgical, Sunnyvale, CA) is a relatively new technology as it applies to minimally invasive liver resection and until recently has had limited adoptance for complex liver surgery.[21,22] It is reasonable to consider that using this platform would possibly lead to greater lymph node retrieval during liver resection for ICC. Quijano et al. published a report of their experience in 13 robotic-assisted liver surgeries, including one case of cholangiocarcinoma. In this report, the authors note the robot's magnified three-dimensional view and increased degrees of freedom in the articulating arms leading to an easier lymphadenectomy compared to laparoscopy.[21]

While the decision to perform a LLR is typically predicated on patient characteristics and surgeon experience, the complexity of the case is also a determinant. Interestingly in patients who underwent a preoperative biopsy with a confirmed diagnosis of ICC, there was no difference in the utilization of operative technique. In addition, there is no difference in technique in patients with clinical stage IVa disease before resection, which represents those patients with clinically node-positive disease. While laparoscopic major hepatectomies and difficult segmentectomies have been shown to be safe, the learning curve for these procedures remains steep with a minimum of 45–75 cases needed for proficiency.[23,24] We noted that for ICC, segmental and wedge resections were performed more commonly in a minimally invasive fashion, whereas major hepatectomies were most commonly achieved through a standard open technique. Despite its increasing utilization and applications for other disease processes, our analysis indicated that LLR is not broadly used for major hepatic resections in patients with ICC, which may be related to the aforementioned learning curve.

As a retrospective review or a large database, there are inherent limitations to our study. As a national database that accrues from multiple hospitals, there is the possibility for errors in the reporting and collection of data. In addition, due to the structure of the reported variables, it is not possible to ascertain the exact location of the tumor, which may have affected treatment recommendations, such as the decision for OLR or LLR and represents, therefore, potential selection bias. In addition, more than 40% of patients in this cohort were diagnosed with ICC after surgical resection, and it is unknown what premise guided their original resection and thus the decision to undergo a LND. Finally, because this study period took place before the adaptation of AJCC 8 and the addition of the six lymph node evaluation formal recommendation and as such could explain the overall low rates of LND.

## CONCLUSIONS

When evaluating minimally invasive surgery as an alternative to a well-established oncologic surgical technique, safety and feasibility should be ensured and noninferiority must be established. Our data indicate that laparoscopy may pose a challenge to adoption of standard oncologic recommendations for LND in ICC in many centers across the United States. We feel that efforts to refine and perfect the technique of laparoscopic LND must be stressed for LLR to be considered an equivalent oncologic resection to OLR. We are hopeful that the challenges of minimally invasive liver resection can be mitigated with improved specialized training, advances in technology, and with the use of the robot in properly selected patients.

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