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# Oncologic safety of laparoscopic radical cholecystectomy in pT2 gallbladder cancer

## A propensity score matching analysis compared to open approach

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**Abstract**

The role of laparoscopic radical cholecystectomy (LRC) in the surgical management of T2 gallbladder carcinoma (GBC) is still controversial.

The medical records of patients with T2 GBC treated with radical cholecystectomy were retrospectively reviewed. In this study, we compare the short- and long-term oncologic outcomes, using propensity score matching analysis, of patients with T2 GBC who underwent LRC and open radical cholecystectomy (ORC).

Among 183 patients, 86 were selected by propensity score matching (LRC = 43 and ORC = 43). The ORC group underwent more extensive surgery (liver resections and extended lymph node dissections [ELND]) than the LRC group. The LRC group had less operative blood loss, shorter length of hospital stay, fewer complications, and had the earlier start of adjuvant chemotherapy. There was no significant difference between the laparoscopic and open surgery groups in terms of 5-year overall survival rate (64.6% vs 80.4%, $P = .214$) and disease-free survival rate (77.1% vs 82.2%, $P = .641$). A subgroup analyses showed that liver resection and ELND had no survival advantage compared to no liver resection and regional lymph node dissection, respectively.

Our LRC approach is safe and effective, with long-term survival comparable to that of ORC.

**Abbreviations:** AJCC = American joint committee on cancer, ASA = American Society of Anesthesiologists, BMI = body mass index, CA = cancer antigen, CEA = carcinoembryonic antigen, CT = computed tomography, DFS = disease-free survival, ELND = extended lymph node dissection, EUS = endoscopic ultrasound, GBC = gallbladder cancer, LRC = laparoscopic radical cholecystectomy, MRI = magnetic resonance imaging, ORC = open radical cholecystectomy, OS = overall survival, RLND = regional lymph node dissection.

**Keywords:** gallbladder cancer, laparoscopy, propensity score matching, radical cholecystectomy, survival



## 1. Introduction

Complete surgical resection remains the optimal treatment for gallbladder cancer (GBC). Simple cholecystectomy, either through an open or laparoscopic approach, for early T1a tumors is an adequate treatment as long as proper tissue handling is observed in order to avoid tumor spillage.[1,2] For a patient with a T1b or more advanced tumor, open radical cholecystectomy (ORC) remains the recommended curative treatment.[3,4]

The role of laparoscopic radical cholecystectomy (LRC) in the surgical management of gallbladder cancer remains controversial. In the era of minimally invasive surgery, the laparoscopic surgical approach is now widely adopted in different gastrointestinal malignancies.[5–7] However, most surgeons remain skeptical about adopting the laparoscopic approach in the surgical management of GBC. Some of the possible reasons include the risk of tumor spillage and dissemination,[8,9] port-site recurrences,[10] and complexity of lymphadenectomy and liver resection.

Several studies have suggested the oncologic feasibility of the laparoscopic approach in the treatment of T2 GBC.[11] As long as the oncologic principles of open surgery are followed, LRC can be potentially applied to achieve a comparable oncologic outcome to that of the open approach for T2 GBC.

In this study, patients with T2 GBC who underwent LRC and patients with T2 GBC who underwent ORC were compared after a propensity score matching (PSM) analyses. The primary aim was to compare the long-term outcomes (overall survival [OS] and disease-free survival [DFS]) of patients with GBC and ORC. The secondary aim was to compare the short-term outcomes (intraoperative and post-operative).

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## 2. Materials and methods

### 2.1. Study design

The medical records of patients with GBC who underwent surgical procedures at the Yonsei University Health System in Seoul, Korea, between 2005 and 2017 were retrospectively reviewed using the electronic medical records database. We identified 183 patients with pathologically confirmed T2 GBC who underwent radical cholecystectomy. Exclusion criteria were incomplete clinical and histologic data, patients who underwent combined common bile resection, and grossly involved aortocaval lymph nodes on preoperative Computed Tomography scan. The study protocol was approved by the Yonsei Institutional Review Board and the need for written informed consent was waived.

### 2.2. Data collection

Demographic data such as age, sex, and clinical presentation including the presence of symptoms were recorded. The preoperative serum cancer antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) levels and pathologic data, such as tumor location, size, grade, lymph node status, and lymphovascular and perineural invasions, were reviewed. The 8th edition of the American Joint Committee on Cancer Staging Manual (AJCC) was used for cancer staging.[12] In this cohort, regional lymph node dissection (RLND) includes dissection along the cystic duct, pericholedochal, posterosuperior pancreaticoduodenal, retroportal, and hepatic artery node groups, whereas extended lymph node dissection (ELND) includes RLND plus aortocaval (16A and B) lymph node dissection.

### 2.3. Indication and for LRC

The indication for surgery and the type of approach were discussed for every patient during weekly hepatobiliary and pancreas conference. Patients with suspected GBC in preoperative imaging, either with transabdominal ultrasonography or computed tomography scan, underwent further imaging evaluations such as endoscopic ultrasonography, magnetic resonance imaging, and positron emission tomography scan for proper clinical staging prior to surgery. Likewise, patients with an incidental finding of GBC after a laparoscopic cholecystectomy subsequently underwent further imaging evaluations such as magnetic resonance imaging and positron emission tomography scan before the re-operation.

### 2.4. Surgical technique

LRC was performed through 5 abdominal ports, with the patient in a reverse Trendelenburg position and tilted to the lateral left. A 12-mm trocar was placed at the umbilicus, and pneumoperitoneum was established. Staging laparoscopy was performed; if there was no sign of distant metastasis, the additional 4 trocars were inserted (Fig. 1). Full kocherization was performed, and aortocaval fatty tissue was sampled and sent for frozen section analysis. If the frozen section was negative for tumor, radical resection was continued. Simple cholecystectomy was performed if no evidence tumor invasion on the liver bed, otherwise wedge liver resection with at least a 1-cm margin from the gallbladder bed. However, whether to perform wedge liver resection and aortocaval lymph node dissection or not was at the discretion of the surgeon and was not routinely performed in our institution. Cystic duct margin was sent for frozen section, and if positive for tumor, common bile duct resection was indicated. Lymphadenectomy was performed to include all lymph nodes from the common hepatic artery up to the right and left hepatic arteries, skeletonizing the structures in the hepatoduodenal ligament and all nodes in the retropancreatic area. Specimens were collected using an endo-pouch.

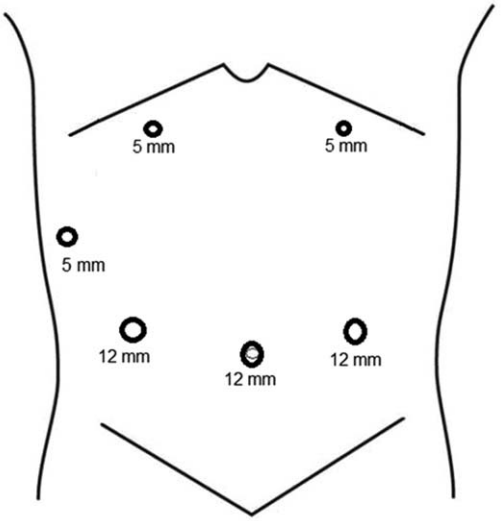


**Figure 1.** Placement of trocars in laparoscopic radical cholecystectomy.

For ORC, a J-shaped right subcostal incision was performed. Also, liver resection (wedge resection or segment 4b/5) was not routinely performed for gallbladder cancer with no liver bed invasion by frozen section. Likewise, the extent of lymphadenectomy depended on the preference and intraoperative decision of the surgeons. Some surgeons performed the ELND in patients without intraoperative evidence (by frozen section) of metastasis, and liver resection in patients without evidence of liver invasion (T2 GBC in frozen section).

### 2.5. Primary endpoints

The primary endpoints of this study were the long-term survival and short-term outcomes of patients with T2 GBC treated with LRC or ORC. OS was calculated from the date of surgery to the date of death or last follow-up. Patients were also followed up regularly for serum CA 19-9 and CEA level determination and computed tomography scan, to detect tumor recurrence. DFS was calculated from the date of surgery to the date of recurrence or last follow-up. Short-term outcomes were determined on the basis of postoperative complications and classified according to the Clavien-Dindo classification, lengths of hospital stay, and early start of adjuvant chemotherapy.

### 2.6. Literature review

A detailed searched in PubMed, Web of Science and Cochrane Library for studies of LRC for T2 gallbladder cancer to compare to our result in terms of 5-years survival rate. Search terms were titled to Title or Abstract: “gallbladder cancer” or “T2 gallbladder cancer” and “laparoscopic” OR “laparoscopy”.

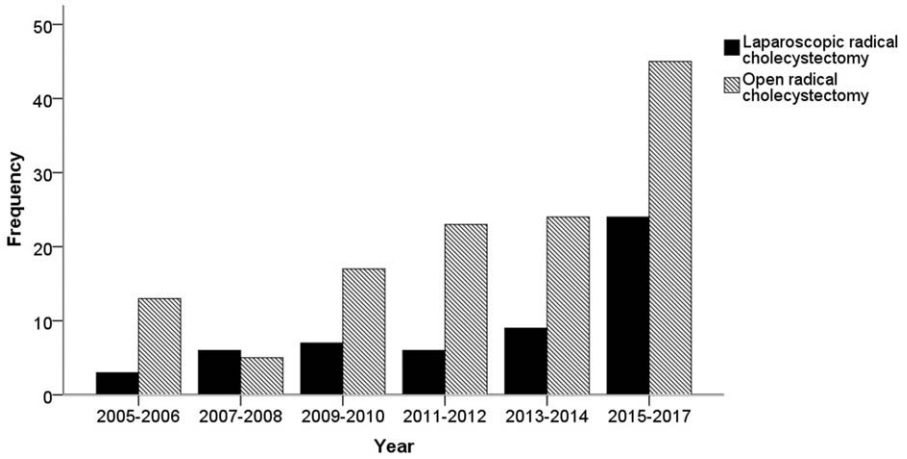


**Figure 2.** Proportion of patients with T2 gallbladder cancer who underwent laparoscopic radical cholecystectomy and open cholecystectomy from 2005 to 2007.

### 2.7. Statistical analysis

To decrease the risk of confounding bias in this cohort, patients in the LRC and ORC group were matched using PMS using the NCSS 12 Statistical Software (NCSS, LLC. Kaysville, UT).

Propensity scores were estimated by logistic regression analysis, with treatment strategy group (LRC vs ORC) as dependent variable and age, sex, ASA score, BMI score, preoperative CEA and CA 19-9 level, and tumor location as independent variables. Matching was performed according to the "nearest neighbour" method using a 0.2-width caliper, and at a1:1 ratio.

Further statistical analysis was performed using IBM SPSS Statistics, version 22 (SPSS Inc., Chicago, IL). Categorical variables were expressed as frequencies (%), whereas continuous variables were presented as means with their range or ±standard deviation. The means of continuous variables were compared using an independent sample *t* test. Categorical variables were compared using the Pearson $\chi^2$ test. OS was calculated on the basis of the time from surgery to death or last follow-up. OS and DFS were estimated using the Kaplan–Meier method and compared using a log-rank test.

## 3. Results

### 3.1. Patients' characteristics

A total of 183 patients with T2 GBC underwent radical cholecystectomy from 2005 to 2017, comprising 128 (69.9%) ORC and 55 (30.1%) LRC. Figure 2 shows the number of cases of LRC performed from 2005 to 2017. The choice of LRC over ORC has been steadily increasing according to time period.

Figure 3 summarizes the process of PMS. Among 183 patients, 142 were included in the analysis. Baseline characteristics of the pre-matched and post-matched groups are detailed in Table 1. Although not statistically significant, patient on the ORC group had more elevated CEA and CA 19-9 level compared to LRC group. After PMS, 86 matched patients were observed (n=43 for both LRC and ORC group). There were no significant group differences in the baseline clinicopathologic characteristics such as age, ASA score, BMI, tumor location, tumor size, grade, and lymphovascular and perineural invasion were similar between the groups. In particular, the CEA and CA 19-9 showed a very similar level between the two groups after matching ($P=.345$ to $P=.707$, respectively). Likewise, both groups had received similar adjuvant chemotherapy. Notably, the surgical approach (liver resection and extent of lymph node dissection) was significantly different between the two groups. Although majority of the patients (n=61, 70.9%) underwent simple cholecystectomy, patients in the LRC group mostly received simple cholecystectomy only compared to the ORC group (84% vs 53%, respectively). Moreover, patients in the ORC group mostly underwent ELND compared to LRC group (65.1% vs 19.4%, respectively).

### 3.2. Primary endpoint: long-term oncologic outcomes

***3.2.1. LRC vs ORC.*** At a median follow-up of 32 months (2–125 months), there was no difference between the LRC and ORC groups in terms of 5-year OS and 5-year DFS. The 1-, 3-, and 5-year OS was 97.6%, 72.6%, and 64.0% for the LRC group and 97.3%, 87.0%, and 80.4% for the ORC group, respectively ($P=.214$) (Fig. 4A). Similarly, the 1-, 3-, and 5-year DFS rate after a curative-intent resection was 92.3%, 82.6%, and 77.1% for LRC and 89.7%, 87.0%, and 82.2% for the ORC group, respectively ($P=.641$) (Fig. 4B). There was no reported trocar site tumor recurrence or tumor dissemination among the LRC group.

***3.2.2. Liver resection vs no liver resection.*** Since most patients in this cohort underwent simple cholecystectomy only, particularly those patients in the LRC, we investigated the oncologic long-term benefit of liver resection in patients with T2 GBC. Figure 5 illustrates the long-term oncologic outcomes between patients who underwent liver resection and no liver resection. There was no 5-year OS advantage in liver resection and no liver resection (51.8 vs 57.2 months, $P=.154$).Similarly, there was no 5-year DFS advantage between patients who underwent liver resection and no liver resection (51.3 vs 52.2 months, $P=.730$). Among patients who underwent no liver resection, there was no evidence of residual tumor on the liver bed and on final pathology report. In addition, no evidence of tumor recurrence on the gallbladder bed on patients who had no liver resection. In fact, the 2 liver recurrences in this cohort were observed on 2 patients who had wedge resection and segment 4b/5 resection in segment 8 and 3, respectively. The presence of micro metastasis was also not observed on the final pathology of the resected liver.

Moreover, among 58 (67.4%) patients with tumor located in the liver side, 16 (27.8%) underwent liver resection while 42

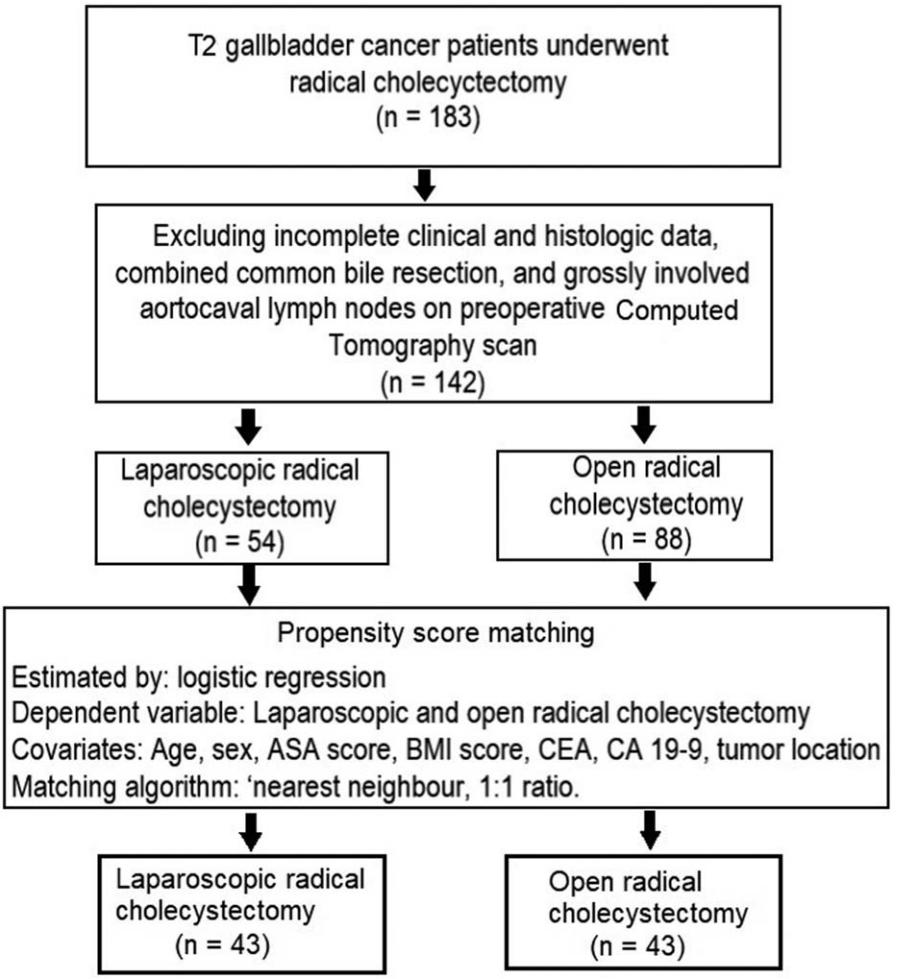


**Figure 3.** Flowchart of patients with T2 gallbladder cancer included in the study and propensity score matching process.

(72.4%) patients did not undergo liver resection. However, liver resection was not associated with improved 5-year DFS (50.4 vs 48.2 months, $P=.865$) and 5-year OS (51.8 vs 55.4 months, $P=.254$) (Fig. 5C and D), respectively.

***3.2.3. RLND vs ELND.*** We also evaluated the long-term survival advantage of ELND compared to RLND. Among 86 patients, 31 (40.7%) underwent ELND in this cohort. The mean 5-year DFS of patients with RLND is comparable to those patients with ELND (50.8 vs 53.0 months, $P=.665$) (Fig. 6A). Likewise, there was no 5-year OS advantage between ELND and RLND (52.1 vs 54.6 months, $P=.951$) (Fig. 6B). The incidence of tumor recurrence in the aortocaval area (station 16A and B lymph nodes) was also not statistically different in patients with only RLND (2/6, 25%) and in those with ELND (3/3, 50%) ($P=.334$). As such, ELND has no survival advantaged compared to RLND alone.

### *3.3. Secondary endpoints: short-term outcomes*

***3.3.1. Pathologic outcome.*** According to the AJCC 8th edition, there were no significant differences between the laparoscopic and open surgery groups according to pN0, pN1, and pN2 status in the final pathology report ($P=.518$). Although significantly more lymph nodes were harvested during ORC than during LRC group ($6.12\pm5.78$ vs $11.93\pm7.03$, $P=.0001$), the metastatic lymph node to retrieved lymph node ratio was not statistically significantly different between the LRC group and ORC group (15.7% vs 8.13%, $P=.208$). Notably, among 35 (40.7%) patients (7 in the LRC, and 28 in the ORC) who underwent ELND, none of them had tumor metastasis on the aortocaval lymph nodes (station 16A and 16B). Moreover, the presence of microscopic residual disease (R1 resection) was not significantly different between the 2 groups (ORC, 3 vs LRC, 2, $P=1.000$). All the microscopic residual disease was noted at the resection margin of the cystic duct on the final pathology.

***3.3.2. Perioperative outcome.*** The mean operative time was significantly shorter, blood loss was less, the length of hospital stay was shorter, and adjuvant therapy was started earlier in the LRC group than in the ORC group ($P=<.05$). There were also more complications, on the basis of the Clavien-Dindo classification, in the ORC group, including chyle leak and intra-abdominal infections, than in the laparoscopic surgery group ($P=.050$) (Table 2). There was no reported 30 days mortality.

### *3.4. Literature review about LRC in T2 GBC*

Table 3 summarizes the long-term outcome of patients with GBC treated with LRC from single-institution experienced. Although different methods were used to achieve a negative liver bed

**Table 1**

**Clinicopathologic characteristics between the laparoscopic surgery and open surgery groups before propensity score matching.**

| Clinicopathologic characteristics | Pre-matched | | | Post-matched | | |
|---|---|---|---|---|---|---|
| | LRC (n=54) | ORC (n=88) | *P* | LRC (n=43) | ORC (n=43) | *P* |
| | 66.5±10.5 | 64.7±8.08 | .253 | 66.7±10.3 | 65.4±7.6 | .669 |
| Gender | | | | | | |
| Male | 30 | 51 | .799 | 25 | 28 | .506 |
| Female | 24 | 37 | | 18 | 15 | |
| Incidental | | | | | | |
| No | 44 | 63 | .184 | 37 | 32 | .279 |
| Yes | 10 | 25 | | 6 | 11 | |
| ASA score | | | | | | |
| 1 | 15 | 25 | .292 | 14 | 16 | .804 |
| 2 | 32 | 46 | | 25 | 22 | |
| 3 | 5 | 17 | | 4 | 5 | |
| BMI, kg/m$^2$ (mean) | | | | | | |
| <18 | 3 | 4 | .063 | 2 | 3 | .898 |
| 18–25 | 40 | 54 | | 34 | 33 | |
| 25–30 | 11 | 24 | | 7 | 7 | |
| >30 | 0 | 6 | | 0 | 0 | |
| CA 19-9, U/mL (mean) | 19.6±22.8 | 27.2±51.9 | .345 | 20.3±23.5 | 22.9±37.7 | .707 |
| CEA, ng/mL (mean) | 2.2±1.2 | 3.4±11.9 | .211 | 2.2±1.2 | 1.9±1.0 | .212 |
| Tumor location | | | | | | |
| Hepatic side | 33 | 63 | .195 | 27 | 31 | .357 |
| Peritoneal side | 21 | 25 | | 16 | 12 | |
| Tumor size, cm (mean) | 4.5±3.1 | 4.5±2.9 | .940 | 4.8±3.1 | 4.9±2.9 | .801 |
| PNI | | | | | | |
| No | 35 | 56 | .443 | 28 | 25 | 1.000 |
| Yes | 6 | 6 | | 3 | 2 | |
| LVI | | | | | | |
| No | 31 | 55 | .303 | 27 | 22 | .286 |
| Yes | 11 | 12 | | 5 | 8 | |
| Grade | | | | | | |
| Well/moderately differentiated | 48 | 74 | .652 | 38 | 34 | .675 |
| Poorly/undifferentiated | 5 | 10 | | 4 | 6 | |
| Residual disease | | | | | | |
| No | 50 | 85 | .293 | 40 | 41 | 1.000 |
| Yes | 4 | 3 | | 3 | 2 | |
| Adjuvant chemotherapy | | | | | | |
| No | 35 | 66 | .157 | 27 | 30 | .494 |
| Yes | 19 | 21 | | 16 | 13 | |
| Surgical approach | | | | | | |
| Liver resection | | | | | | |
| No | 47 | 41 | .0001 | 38 | 23 | .001 |
| Wedge | 7 | 32 | | 5 | 12 | |
| 4b/5 | 0 | 15 | | 0 | 8 | |
| Extent of LND | | | | | | |
| Regional | 44 | 26 | .0001 | 36 | 15 | .0001 |
| Aortocaval | 10 | 62 | | 7 | 28 | |

AJCC=American Joint Committee on Cancer, ASA=American Society of Anesthesiologists, BMI=body mass index, CA=cancer antigen, CEA=carcinoembryonic antigen, LND=lymph node dissection, LRC=laparoscopic radical cholecystectomy, ORC=open radical cholecystectomy.

margin, the reported 5-year OS rates for T2 gallbladder cancer ranged from 50% to 90%.[13–18] Our laparoscopic approach (either simple cholecystectomy or liver resection and regional lymphadenectomy), however, had comparable long-term outcomes with other studies.

## 4. Discussion

The standard of care for the treatment of T2 GBC is still ORC, which includes en bloc liver resection (wedge or segment 4b and 5), and regional lymphadenectomy. However, with increasing expertise and advances in instrumentation in minimally invasive surgery, surgeons have now been exploring the efficacy and safety of the laparoscopic approach in the treatment of GBC.[19–21] Nevertheless, because of the innate complexity of the procedure and the concern for potential tumor dissemination during the procedure,[22] LRC was only performed in high volume centers with expert hepatobiliary surgeons.[23]

In our center, we employ laparoscopic approach in suspected T1 and T2 GBC. A proper preoperative imaging, including CT scan, magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) to assess the extent of the tumor invasion is of paramount importance in the decision making whether or not to do extended cholecystectomy. Notably, 61 (71%) patients in

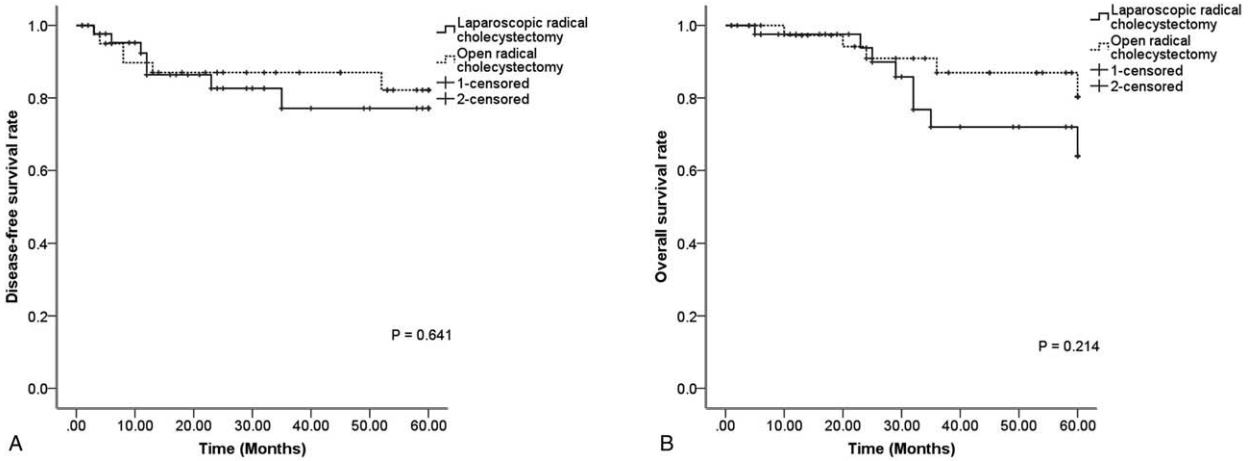


**Figure 4.** Kaplan–Meier survival curves of patients with T2 gallbladder carcinoma after curative-intent radical resection. (A) Comparison of 5-year disease-free survival between laparoscopic and open radical cholecystectomy group. (B) Comparison of overall 5-year survival between laparoscopic and open radical cholecystectomy group.

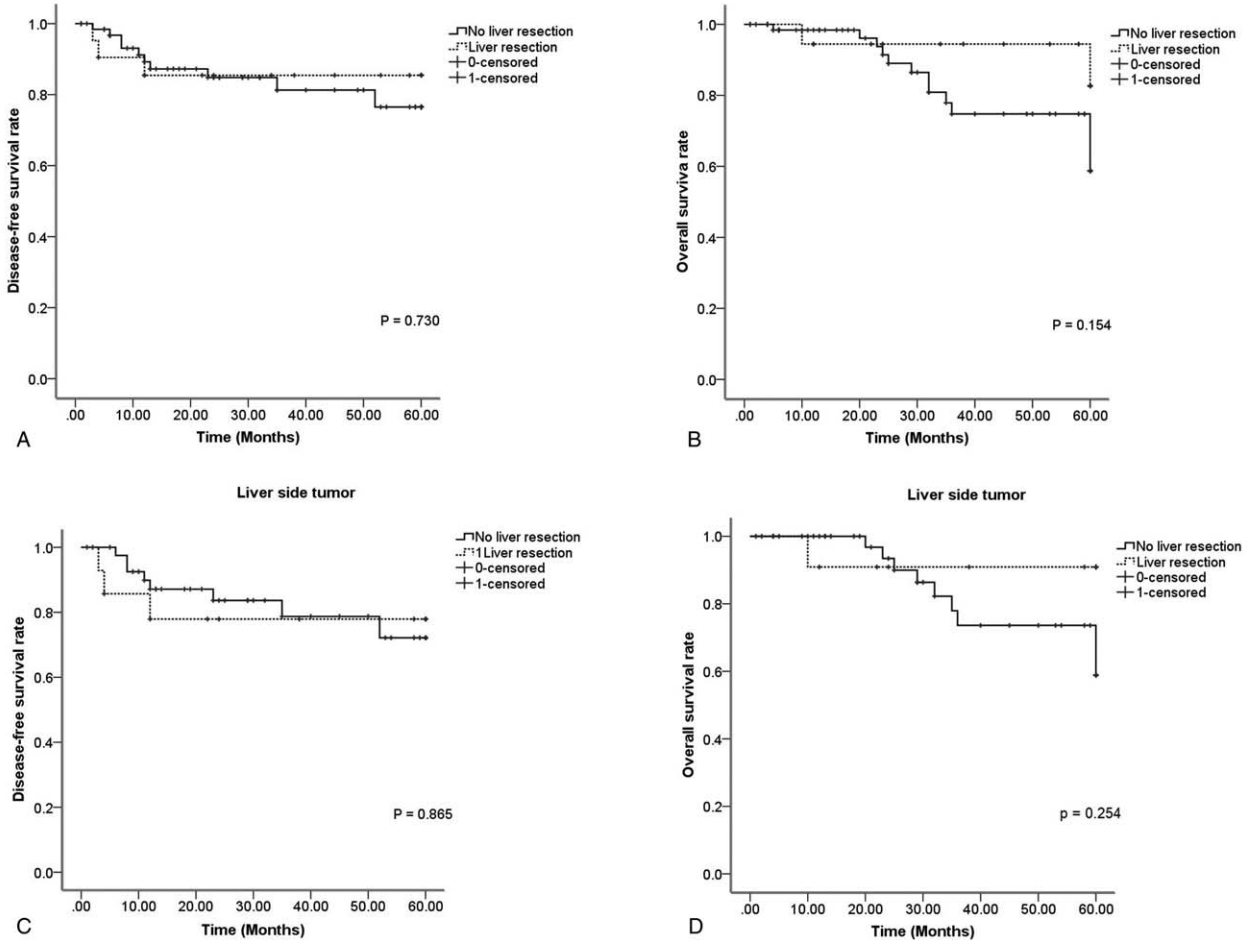


**Figure 5.** Comparison between liver resection and no liver resection in T2 gallbladder carcinoma according to tumor location. (A) 5-year disease-free survival between liver resection and no liver resection in patients with liver-side tumors. (B) 5-year overall survival between liver resection and no liver resection in patients with liver-side tumor. (C) Disease-free survival between liver resection and no liver resection in patients with liver-side tumor. (D) 5-year overall survival between liver resection and no liver resection in patients with liver-side tumor.

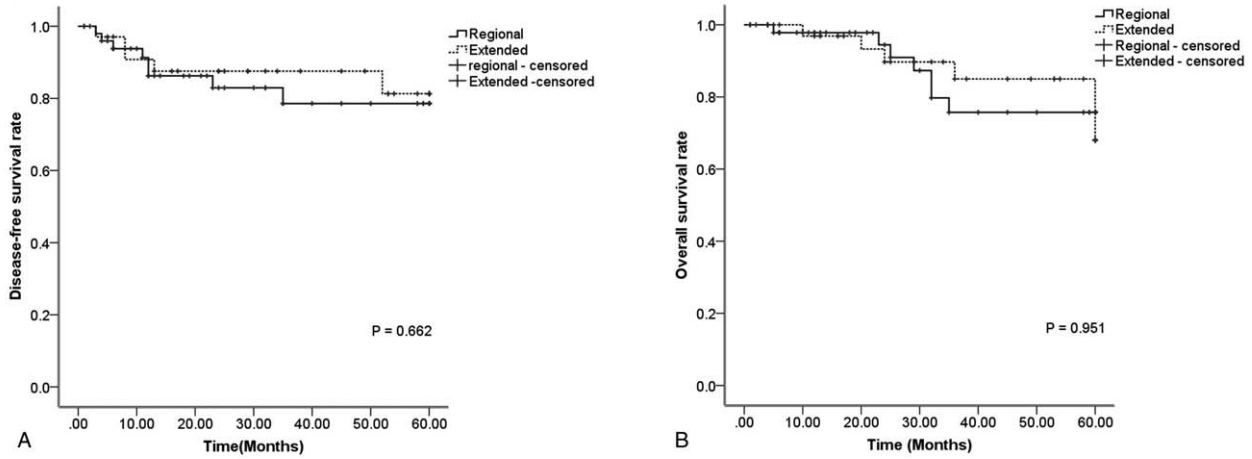


**Figure 6.** Kaplan–Meier survival curves of patients with T2 gallbladder carcinoma according to extent of lymph node dissection. (A) Comparison of 5-year disease-free survival between regional and extended lymph node dissection. (B) Comparison of 5-year overall survival between regional extended lymph node dissection.

this cohort underwent only cholecystectomy with lymph node dissection, and only 25 of 47 patients (29%) underwent liver wedge resection with at least a 1-cm margin. Previously, Kim et al[24] reported that reported that simple cholecystectomy and lymph node dissection without liver resection in patients with T2 GBC had the same OS as well as recurrence pattern compared to extended cholecystectomy (wedge or segment 4b/5 resection). There were several reports of various laparoscopic approaches in establishing a negative margin on the liver bed with acceptable oncologic outcomes. These included simple cholecystectomy

**Table 2**

**Operative, postoperative, and pathologic outcomes in patients with T2 gallbladder cancer after laparoscopic or open radical cholecystectomy.**

| Clinicopathologic characteristics | Laparoscopic radical cholecystectomy (n = 43) | Open radical cholecystectomy (n = 43) | *P* |
|---|---|---|---|
| Operative outcome | | | |
| Operative time, minutes (mean) | 139.05 ± 97.09 | 211.16 ± 91.36 | .001 |
| Blood loss, mL (mean) | 71.63 ± 178.77 | 208.14 ± 242.165 | .004 |
| Blood transfusion | | | |
| No | 43 | 40 | .039 |
| Yes | 0 | 3 | |
| Post-operative outcome | | | |
| Length of hospital stay, days (mean) | 6.05 ± 9.846 | 12.58 ± 5.504 | .0001 |
| Days from operation to start the start of adjuvant chemotherapy, days (mean) | 25.28 ± 71.14 | 38.58 ± 15.57 | .014 |
| Complications (Clavien–Dindo classification) | | | |
| No | 41 | 38 | .050 |
| I | 2 | 1 | |
| II | 0 | 4 | |
| III | 0 | | |
| Pathologic outcome | | | |
| Retrieved lymph nodes (mean) | 6.12 ± 5.78 | 11.93 ± 7.03 | .0001 |
| Lymph node ratio (%) | 15.7% | 8.13% | .208 |
| AJCC 8th pN | | | |
| 0 | 32 | 29 | .518 |
| 1 | 11 | 13 | |
| 2 | 0 | 1 | |
| AJCC 8th TNM stage | | | |
| IIA | 17 | 19 | .682 |
| IIB | 14 | 11 | |
| IIIB | 11 | 12 | |
| IVB | 0 | 1 | |
| Residual disease | | | |
| No | 40 | 41 | 1.000 |
| Yes | 3 | 2 | |

AJCC = American Joint Committee on Cancer.

**Table 3**

**Overall survival after laparoscopic radical cholecystectomy.**

| Author | Studies | Patients (n) | Operation | Liver resection | Lymph node dissection | T stages (n) | 5-year OS (%) |
|---|---|---|---|---|---|---|---|
| Shirobe and Maruyama[13] | Retrospective | 11 | LRC | Yes (n = 6) | Regional | T2 (8) | 83 |
| | | | | | | T1b (3) | 100 |
| Castro et al[14] | Retrospective | 18 | LRC | Yes | Regional | T1b (7) | 80 |
| | | | | | | T2 (10) | |
| | | | | | | T3 (1) | |
| Palanisamy et al[15] | Retrospective | 12 | LRC | Yes | Regional | T2 (11) | 68.75 |
| | | | | | | T3 (1) | |
| Yoon et al[16] | Prospective | 32 | LRC | Yes | Regional | T1(7) | 100 |
| | | | | | | T2(25) | 90.2 |
| Susuki et al[17] | Retrospective | 20 | ORC | Yes | Regional | T1b (15) | 77 |
| | | | | | | T2 (5) | |
| Choi et al[17] | Retrospective | 32* | ORC | Not specify | Regional | T2 | 51.8 |
| Our study | Retrospective | 183 | LRC | No | Regional | T2 (43) | 64.0 |
| | | | ORC | | | T2 (43) | 80.4 |

LRC = laparoscopic radical cholecystectomy, ORC = open radical cholecystectomy, OS = overall survival.

only, whole-layer cholecystectomy,[25] 2-mm thickness liver resection margin,[18] >1 cm liver bed margin,[26] and segment 4b/5 resections.[27] Until recently, there remains no consensus about the extent of liver resection (wedge resection vs segment 4b/5 resection).[28]

Interestingly, our results showed that there was no significant difference in the DFS and OS between patients with liver resection and those with no liver resection. In addition, patients with a liver-side tumor who underwent liver resection (wedge or segment 4b/5) either through a laparoscopic approach or open surgery had no survival advantage over patients who did not undergo liver resection. This is contrary to the findings of other recent studies demonstrating that liver-side tumors portend worse survival compared with peritoneal-side tumors[29,30] and may benefit from liver resection.[30] However, the present study may suggests that a simple cholecystectomy with lymphadenectomy can be oncologically safe and effective in well-selected patients, as survival may not be affected by the tumor location.[31]

Although the optimal extent of lymphadenectomy for radical cholecystectomy is still controversial,[28] several studies had suggested that an adequate lymphadenectomy includes a RLND, which includes the cystic duct, pericholedochal, posterosuperior pancreaticoduodenal, retroportal, right celiac, and hepatic artery node groups.[32–35] It was observed in our study that ELND was commonly performed among those who underwent ORC. Thus, more lymph nodes were harvested in the open group than in the laparoscopic group. Nevertheless, the mean number of lymph nodes harvested in the laparoscopic group was 6.12, which is equal to the recommended number (at least 6 lymph nodes) for adequate staging and prognostication.[36,37] In addition, our results showed no survival benefit of ELND over RLND.

Our analysis was based on a retrospective review of data, with unavoidable bias. First, patients in the ORC group underwent extensive surgery (liver resection and ELND) compared to LRC group. This selection bias undoubtedly affects the short-term outcomes in this cohort. As such, patients who underwent LRC had a shorter length of hospital stay and fewer postoperative complications. Moreover, patients in the LRC group started with adjuvant therapy earlier than patients who underwent ORC. Nevertheless, our findings emphasized that this extensive surgery is not necessary for T2 GBC for the following reasons: first, using the more extensive approach provides no long-term survival benefit; second, although more lymph nodes were harvested in the ORC, our laparoscopic approach provided adequate lymph nodes harvested for proper prognostication. In the recent British Phase III BILCAP study, adjuvant capecitabine has been shown to significantly improve survival on patients with biliary tract cancer and should be offered after surgery.[38] Thus, an early start of adjuvant chemotherapy would be the fundamental advantage of our minimally invasive surgery approach over open surgery. Second, the sample size was small and the selection of patients who underwent either laparoscopic surgery or open surgery was not randomized. Thus, to properly assess the efficacy, safety, and oncologic significance of LRC, a further randomized study should be conducted. However, when considering the rarity of gallbladder cancer, to our knowledge, this study included the largest number of patients with T2 GBC who underwent LRC.

## 5. Conclusion

Our laparoscopic approach allows for a shorter length of hospital stay, results in fewer postoperative complications, and an earlier start of adjuvant chemotherapy. The 5-years OS and DFS of patients with T2 GBC after LRC is comparable to those of patients treated with ORC. In addition, extensive surgery has no survival advantage over simple cholecystectomy plus RLND for T2 GBC. Further studies are needed to validate these findings.

## Author contributions

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## References


[1] Hari DM, Howard JH, Leung AM, et al. A 21-year analysis of stage I gallbladder carcinoma: is cholecystectomy alone adequate? HPB (Oxford) 2013;15:40–8.
[2] Lee SE, Kim KS, Kim WB, et al. Practical guidelines for the surgical treatment of gallbladder cancer. J Korean Med Sci 2014;29:1333–40.
[3] Sternby Eilard M, Lundgren L, Cahlin C, et al. Surgical treatment for gallbladder cancer—a systematic literature review. Scand J Gastroenterol 2017;52:505–14.
[4] Kondo S, Takada T, Miyazaki M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. J Hepatobiliary Pancreat Surg 2008;15:41–54.
[5] Bencini L, Bernini M, Farsi M. Laparoscopic approach to gastrointestinal malignancies: toward the future with caution. World J Gastroenterol 2014;20:1777–89.
[6] Cheng Y, Zhang L, Li H, et al. Laparoscopic versus open liver resection for colorectal liver metastases: a systematic review. J Surg Res 2017;220:234–46.
[7] Sharma B, Baxter N, Grantcharov T. Outcomes after laparoscopic techniques in major gastrointestinal surgery. Curr Opin Crit Care 2010;16:371–6.
[8] Lundberg O, Kristoffersson A. Open versus laparoscopic cholecystectomy for gallbladder carcinoma. J Hepatobiliary Pancreat Surg 2001;8:525–9.
[9] Fong Y, Brennan MF, Turnbull A, et al. Gallbladder cancer discovered during laparoscopic surgery: potential for latrogenic tumor dissemination. Arch Surg 1993;128:1054–6.
[10] Paolucci V. Port site recurrences after laparoscopic cholecystectomy. J Hepatobiliary Pancreat Surg 2001;8:535–43.
[11] Zimmitti G, Manzoni A, Guerini F, et al. Current role of minimally invasive radical cholecystectomy for gallbladder cancer. Gastroenterol Res Pract 2016;2016:7684915.
[12] Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual. 8 edNew York: Springer International Publishing; 2017.
[13] Shirobe T, Maruyama S. Laparoscopic radical cholecystectomy with lymph node dissection for gallbladder carcinoma. Surg Endosc 2015;29:2244–50.
[14] Castro CM, Santibanez SP, Rivas TC, et al. Totally laparoscopic radical resection of gallbladder cancer: technical aspects and long-term results. World J Surg 2018;42:2592–8.
[15] Palanisamy S, Patel N, Sabnis S, et al. Laparoscopic radical cholecystectomy for suspected early gall bladder carcinoma: thinking beyond convention. Surg Endosc 2016;30:2442–8.
[16] Yoon YS, Han HS, Cho JY, et al. Is laparoscopy contraindicated for gallbladder cancer? A 10-year prospective cohort study. J Am Coll Surg 2015;221:847–53.
[17] Suzuki S, Yokoi Y, Kurachi K, et al. Appraisal of surgical treatment for pT2 gallbladder carcinomas. World J Surg 2004;28:160–5.
[18] Choi SB, Han HJ, Kim CY, et al. Surgical outcomes and prognostic factors for T2 gallbladder cancer following surgical resection. J Gastrointest Surg 2010;14:668–78.
[19] Gumbs AA, Hoffman JP. Laparoscopic radical cholecystectomy and Roux-en-Y choledochojejunostomy for gallbladder cancer. Surg Endosc 2010;24:1766–8.
[20] Gumbs AA, Hoffman JP. Laparoscopic completion radical cholecystectomy for T2 gallbladder cancer. Surg Endosc 2010;24:3221–3.
[21] de Aretxabala X, Leon J, Hepp J, et al. Gallbladder cancer: role of laparoscopy in the management of potentially resectable tumors. Surg Endosc 2010;24:2192–6.
[22] Berger-Richardson D, Chesney TR, Englesakis M, et al. Trends in port-site metastasis after laparoscopic resection of incidental gallbladder cancer: a systematic review. Surgery 2017;161:618–27.
[23] Yoon YS, Han HS, Agarwal A, et al. Survey results of the expert meeting on laparoscopic surgery for gallbladder cancer and a review of relevant literature. Dig Surg 2019;36:7–12.
[24] Kim DH, Kim SH, Choi GH, et al. Role of cholecystectomy and lymph node dissection in patients with T2 gallbladder cancer. World J Surg 2013;37:2635–40.
[25] Ome Y, Hashida K, Yokota M, et al. Laparoscopic approach to suspected T1 and T2 gallbladder carcinoma. World J Gastroenterol 2017;23:2556–65.
[26] Itano O, Oshima G, Minagawa T, et al. Novel strategy for laparoscopic treatment of pT2 gallbladder carcinoma. Surg Endosc 2015;29:3600–7.
[27] Agarwal AK, Javed A, Kalayarasan R, et al. Minimally invasive versus the conventional open surgical approach of a radical cholecystectomy for gallbladder cancer: a retrospective comparative study. HPB (Oxford) 2015;17:536–41.
[28] Han HS, Yoon YS, Agarwal AK, et al. Laparoscopic surgery for gallbladder cancer: an expert consensus statement. Dig Surg 2019;36:1–6.
[29] Shindoh J, de Aretxabala X, Aloia TA, et al. Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: an international multicenter study. Ann Surg 2015;261:733–9.
[30] Lee H, Choi DW, Park JY, et al. Surgical strategy for T2 gallbladder cancer according to tumor location. Ann Surg Oncol 2015;22:2779–86.
[31] Jung W, Jang JY, Kang MJ, et al. Effects of surgical methods and tumor location on survival and recurrence patterns after curative resection in patients with T2 gallbladder cancer. Gut Liver 2016;10:140–6.
[32] Shirai Y, Sakata J, Wakai T, et al. "Extended" radical cholecystectomy for gallbladder cancer: Long-term outcomes, indications and limitations. World J Gastroenterol 2012;18:4736–43.
[33] Birnbaum DJ, Viganò L, Russolillo N, et al. Lymph node metastases in patients undergoing surgery for a gallbladder cancer. Extension of the lymph node dissection and prognostic value of the lymph node ratio. Ann Surg Oncol 2015;22:811–8.
[34] Shirai Y, Wakai T, Sakata J, et al. Regional lymphadenectomy for gallbladder cancer: rational extent, technical details, and patient outcomes. World J Gastroenterol 2012;18:2775–83.
[35] Kishi Y, Nara S, Esaki M, et al. Extent of lymph node dissection in patients with gallbladder cancer. Br J Surg 2018;105:1658–64.
[36] Ito H, Ito K, D'Angelica M, et al. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. Ann Surg 2011;254:320–5.
[37] Liu GJ, Li XH, Chen YX, et al. Radical lymph node dissection and assessment: Impact on gallbladder cancer prognosis. World J Gastroenterol 2013;19:5150–8.
[38] Primrose JN, Fox R, Palmer DH, et al. Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study. J Clin Oncol 2017;35 (15_suppl):4006.