Retrospective comparison of outcomes of laparoscopic and open surgery for T2 gallbladder cancer – Thirteen-year experience

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ABSTRACT

Background: The objective of this retrospective study is to compare the outcomes of laparoscopic and open surgery for T2 gallbladder cancer (GBC) performed at our hospital for last 13 years.
Methods: Of 247 GBC patients who were treated at our hospital between Apr 2004 and Apr 2017, 151 patients with pathologic stage T2 were reviewed. Patients were divided into laparoscopic surgery group (LS group) and open (OS group). Medical recordings were reviewed to check perioperative outcomes, overall survival rates, and disease free survival rates.
Results: Fifty-five patients in LS group and 44 in OS met the inclusion criteria. Incidences of postoperative complication were similar between two groups (12.7% vs 13.6%, p = 1.000). Average postoperative hospital stay was significantly shorter in LS group (5.8 vs 9.5 days, p < 0.001). LS group showed significantly higher disease free survival rate (p = 0.0171). There was no significant difference in terms of disease free survival between T2N0 (p = 0.107) and T2N1 patients (p = 0.969) of LS group and OS group. In terms of overall survival rate there was no significant difference (p = 0.116). Overall survival rate was also not significantly different between T2N0 (p = 0.0941) and T2N1 (p = 0.579) patients of LS group and OS group.
Conclusions: Laparoscopic approach for treatment of T2 GBC was comparable to open approach in terms of disease free survival, overall survival and complication rate. Further prospective study with higher number of patients should be done to confirm this result in the future.

1. Introduction

With accumulation of experience and development of advanced devices, laparoscopic surgery has proved its oncologic safety and feasibility in many surgical fields, including colon and gastric surgery [1–3]. For gallbladder cancer (GBC), however, open surgery is still considered a standard treatment when this disease is suspected [4], except for incidentally diagnosed T1a cases in which laparoscopic cholecystectomy is accepted as oncologically safe treatment [5–8].

Lymph node dissection is mandatory for treatment of T2 GBC [9,10] and resection of liver and/or extrahepatic bile duct may be necessary to achieve negative margins [9–12]. Because these procedures have been considered to be difficult to perform laparoscopically, oncologic safety of laparoscopic approach for this lesion is still debatable. Recently, however, there are studies that showed no difference in number of harvested LNs between laparoscopic and open approach for malignant

diseases of rectum, which proves the effectiveness of the laparoscopic lymph node dissection in difficult area [13]. And the application of laparoscopic liver resection is being expanded even to the living donor hepatectomy, which also showed the safety of laparoscopic liver resection [14].

Previously we have reported encouraging long-term outcomes of intentional laparoscopic approach for early GBC [15,16]. However, these studies are only one-arm study of case series, that comparative studies are necessary to know the safety of laparoscopic approach for GB cancer. And the study focused on T2 GBC is also necessary, as this stage is no longer considered as early lesions. Early lesion like T1a GB cancer can be regarded as the indication of laparoscopic surgery, although there is controversy on application of laparoscopy for T1b or more advanced GB cancer.

In these regards, comparative study between laparoscopic vs. open treatment on T2 GBC is very necessary to evaluate new approach for GB

Table 1
Clinicopathological characteristics of the patients.

Group	LS (N = 55)	OS (N = 44)	Total (N = 99)	p
Sex				0.100
- Female	36 (65.5%)	21 (47.7%)	57 (57.6%)	
- Male	19 (34.5%)	23 (52.3%)	42 (42.4%)	
Age, year	70.1 ± 8.1	65.5 ± 10.5	68.0 ± 9.8	0.012
Median follow-up duration, months	35.2 (3–139)	38.6 (4–160)	36.2 (3–160)	0.454
Stage				0.005
- T2N0	42 (76.4%)	23 (52.3%)	65 (65.7%)	
- T2N1	10 (18.2%)	20 (45.5%)	30 (30.3%)	
- T2Nx	3 (5.4%)	1 (2.2%)	4 (4.0%)	

Table 3
Comparison of operative outcomes.

	LS group (N = 55)	OS group (N = 44)	p
Operation time, min	231.0 ± 95.2	252.5 ± 76.1	0.226
EBL, ml	225.1 ± 328.6	310.5 ± 260.9	0.163
Transfusion rate	4 (7.3%)	4 (9.1%)	1.000
Number of LNs collected	7.6 ± 3.4	9.9 ± 6.8	0.095
Postoperative hospital stay, day	5.8 ± 5.3	9.5 ± 4.8	0.000
Complications	7 (12.7%)	6 (13.6%)	1.000
Clavien-Dindo grade I	3		
Clavien-Dindo grade II		3	
Clavien-Dindo grade IIIa	4	3	

EBL: estimated blood loss, LN: lymph node.

cancer.

The objective of this retrospective study is to evaluate the feasibility, safety, and oncologic outcomes of laparoscopic operation for T2 GBC compared to open surgery, including 5-year disease free survival rates and overall survival rates, complication rates, and other perioperative outcomes.

2. Materials and methods

From Apr 2004 to Apr 2017, 247 GBC patients underwent an operation at our hospital (Seoul National University Bundang Hospital, Korea). Of these, 148 patients were diagnosed with pathologically T2 stage cancer after operation. Exclusion criteria were as follows: patients who had another primary malignancy or distant metastasis at the time of surgery, patients who were lost in follow up after discharge, patients who underwent simple cholecystectomy only, or patients who underwent complicated surgery such as right hemihepatectomy or pylorus preserving pancreaticoduodenectomy. We divided pathologically proven T2 GBC patients into two groups according to the type of operation they underwent, laparoscopic surgery group (LS group) and open surgery group (OS group).

T2 GBC was defined as the GBC which invades perimuscular connective tissue with no extension beyond serosa or into the liver, according to the 7th edition of the *Cancer Staging Manual* published by the American Joint Committee on Cancer [17].

Surgical procedure and decision on the extent of operation is described in our previous report [15]. We performed preoperative endoscopic ultrasonography and intraoperative specimen ultrasonography on resected gallbladder to predict the T stage as accurately as possible. When the results suggested T2 GBC, surgical approach (laparoscopic or open) was decided by the patient's preference after detailed explanation about the procedures. When the results suggested T3 or higher stage, we performed open procedure. Lymph node dissection was performed when intraoperative frozen biopsy confirmed presence of malignancy. Lymphadenectomy included resection of hepatoduodenal ligament nodes, common hepatic artery nodes, and peripancreatic head nodes.

When the cystic duct margin was involved by cancer, resection of extrahepatic bile duct and hepaticojejunostomy were performed. Wedge resection of the gallbladder bed was performed when the tumor was found to be located at the hepatic side in the operation room [18]. We also included patients who underwent open operation and were reported to have T2 GBC from the final pathology, and patients who were incidentally diagnosed to have T2 GBC and underwent additional radical procedures.

Electronic medical recordings were reviewed to check types of surgery, operation time, postoperative complications, duration of postoperative hospital stay, and disease-free survival rates, which have been recorded prospectively. Each patient's overall survival was confirmed by mortality record or by telephone survey. Each surgery-associated complication was classified according to the Clavien-Dindo classification.

Survival analysis was carried out with Kaplan-Meier method and log-rank test, using R version 3.2.1 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Patients were censored at the time of the last follow-up or death caused by non-GBC-related diseases. Wilcoxon Rank-Sum test was used to assess difference for continuous variables. Data were expressed as mean value and standard deviation. Differences between the two groups were considered statistically significant when p value was lower than 0.05.

3. Results

Of 148 patients who were diagnosed with pathologically T2 GBC, five who had another primary malignancy at the time of surgery, two who were lost to follow up after discharge, ten who had distant metastasis at the time of surgery, ten who underwent simple cholecystectomy only, and twenty-two who underwent complicated surgery were excluded. As a result there were 55 patients in LS group and 44 patients in OS group. Characteristics of the patients are described in Table 1. Mean age of the patients was 68, and mean age of LS group was

Table 2
Types of operation performed.

	LS group (N = 55)			OS group (N = 44)		
	T2Nx	T2N0	T2N1	T2Nx	T2N0	T2N1
	(N = 3)	(N = 42)	(N = 10)	(N = 1)	(N = 23)	(N = 20)
C + LND	2	30	6		4	5
C + LND + LWR	1	11	4	1	17	14
C + LND + EHBDR		1			2	1

C: Cholecystectomy.
LND: Lymph node dissection.
LWR: Liver wedge resection.
EHBDR: Extrahepatic bile duct resection with Roux-en-Y hepaticojejunostomy.

Overall Survival (LS vs OS)

Overall Survival (LS T2N0 vs OS T2N0)
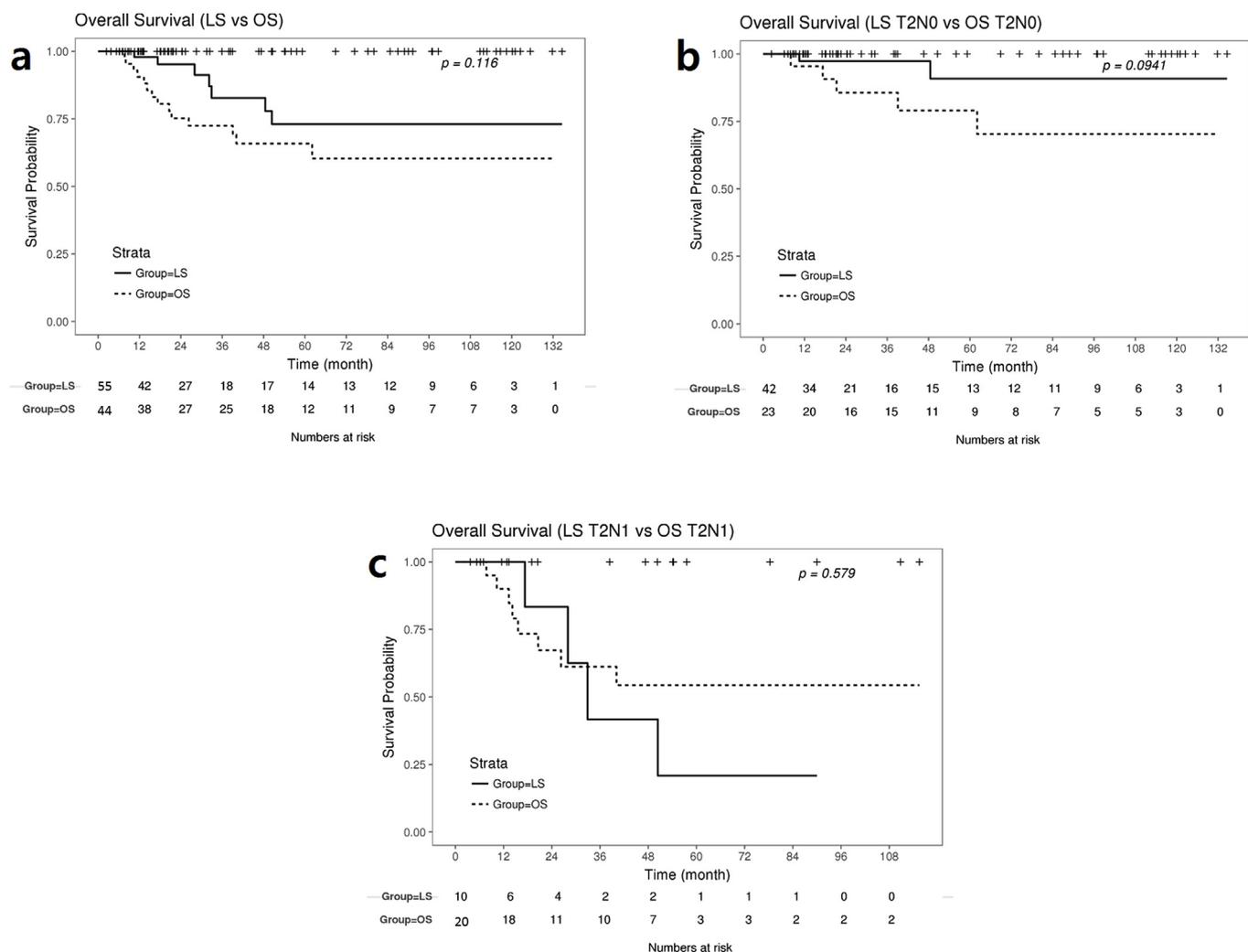
Overall Survival (LS T2N1 vs OS T2N1)

Fig. 1. a overall survival rate of LS group and OS group, b overall survival rate of T2N0 patients of OS group and LS group, and c overall survival rate of T2N1 patients of OS group and LS group.

5 years older than that of OS group. Median follow up time of LS group and OS group was 35.2 months and 38.6 months respectively.

OS group had more liver wedge resections than LS group (Table 2). The most frequently performed procedure in LS group was cholecystectomy with regional LN dissection (N = 38) while in OS group was cholecystectomy with regional LN dissection and liver wedge resection around the GB bed (N = 32).

Table 3 shows operation time, estimated blood loss (EBL), transfusion rate, postoperative hospital stay, and operation-related complication rate of each group. There were no significant differences between the two groups in terms of operation time (231.0 ± 95.2 vs 252.5 ± 76.1 min, $p = 0.226$), EBL (225.1 ± 328.6 vs 310.5 ± 260.9 cc, $p = 0.163$), and transfusion rate (7.3% vs 9.1%, $p = 1.000$). Mean number of lymph nodes collected was similar between the two groups (7.6 ± 3.4 vs 9.9 ± 6.8, $p = 0.095$). Postoperative hospital stay was significantly shorter in LS group (5.8 ± 5.3 vs 9.5 ± 4.8, $p < 0.001$). There were three Clavien-Dindo grade I and four grade IIIa complications in LS group (paralytic ileus and intraperitoneal complicated fluid collection, respectively), and three grade II, three grade IIIa complications in OS group (grade II: two urinary retention cases and one drain site infection, grade IIIa: wound dehiscence, hepaticojejunostomy site stricture, and bile leakage from liver resection site).

There was no statistically significant difference between the two groups in terms of overall survival rate (at 5 year LS vs OS = 73.1% vs 65.7%; $p = 0.116$, Fig. 1a). We subdivided each group into T2N0 patient group and T2N1 patient group to compare overall survival rate according to LN status. There was also no significant difference between LS T2N0 and OS T2N0 group (at 5 year LS vs OS = 90.8% vs 79.1%; $p = 0.0941$, Fig. 1b), and LS T2N1 and OS T2N1 group (at 5 year LS vs OS = 54.4% vs 21.0%; $p = 0.579$, Fig. 1c).

In terms of disease free survival rate, LS group showed significantly higher rate compared to OS group (at 5 year LS vs OS = 78.0% vs 62.4%; $p = 0.0171$, Fig. 2a). However, when compared according to LN status, there was no significant difference between LS T2N0 and OS T2N0 group (at 5 year LS vs OS = 91.1% vs 80.6%; $p = 0.107$, Fig. 2b), and LS T2N1 and OS T2N1 group (at 5 year LS vs OS = 47.1% vs 29.6%; $p = 0.969$, Fig. 2c).

No case of port-site metastasis was observed from the patients of LS group.

4. Discussion

GBC has been contraindicated for laparoscopic approach for a long time [19,20]. One reason is technical difficulty being encountered during operation. LN dissection should be performed during surgical treatment of T2 or more advanced GBC along with cholecystectomy. Laparoscopic LN dissection of hepatoduodenal ligament and around common hepatic artery requires experienced technique to be performed effectively and safely. Occasionally, liver resection or bile duct
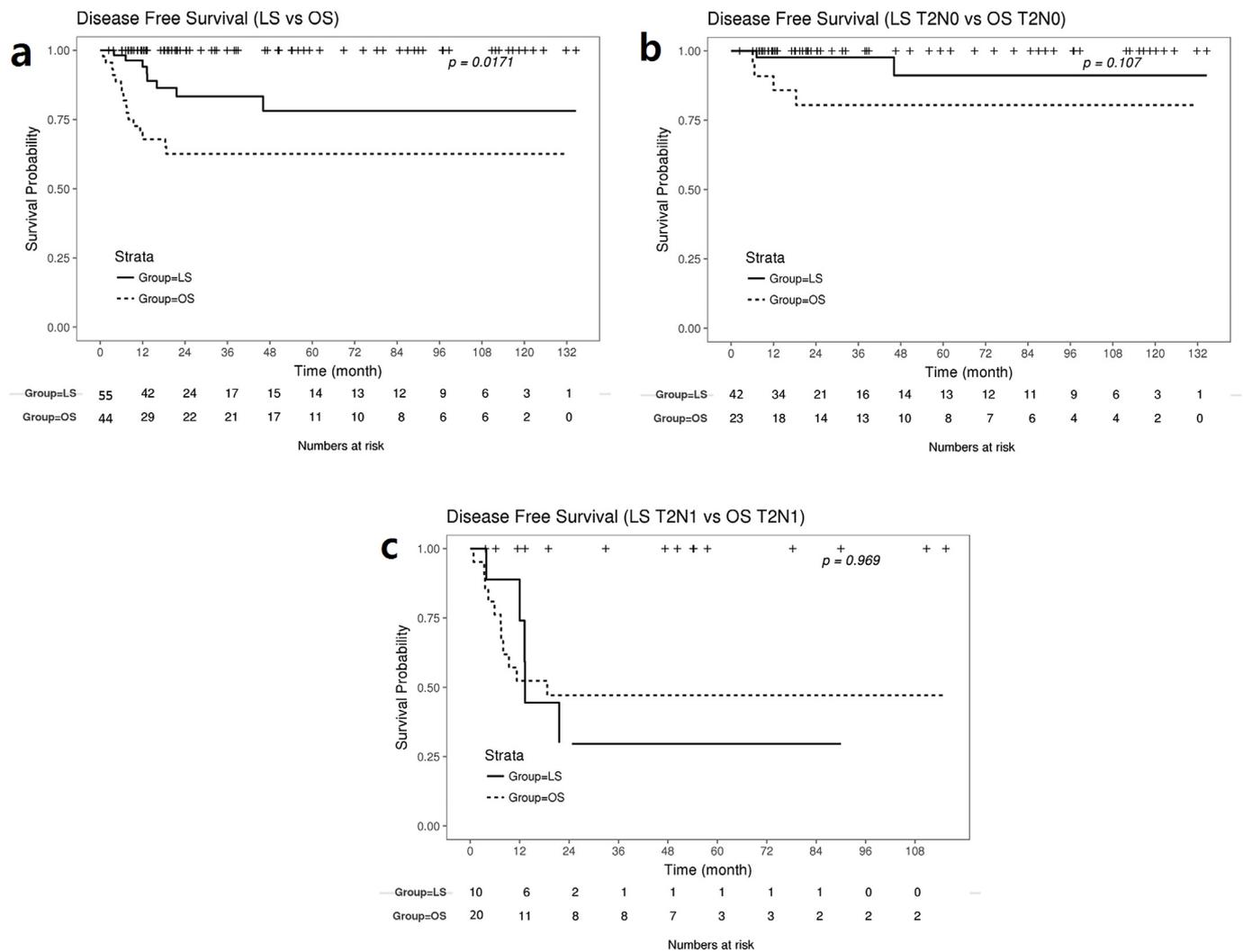
Fig. 2. **a** disease free survival rate of LS group and OS group, **b** disease free survival rate of T2N0 patients of OS group and LS group, and **c** disease free survival rate of T2N1 patients of OS group and LS group.

resection may be necessary which is also technically challenging to be performed laparoscopically. Another reason is lack of evidence on oncologic safety due to scarcity of studies. Only several small studies have been reported on surgical and oncological outcomes of laparoscopic approach for early GBC since 2010 [7,8,20–22]. Agarwal AK. et al. retrospectively compared outcomes of 24 cases of laparoscopic radical cholecystectomy and 46 cases of open radical cholecystectomy, and showed that there was no significant difference in terms of postoperative morbidity, mortality, number of lymph nodes collected, and recurrence rate [21]. Itano O. et al. reviewed 19 laparoscopic and 14 open cases of suspected T2 GBC, and also showed no significant difference in postoperative morbidity, mortality, number of lymph nodes collected, and recurrence rate [22]. In 2010 we have reported the results of our experience on laparoscopic treatment for early GBC patients [16]. In the study, all GBC patients who underwent laparoscopic cholecystectomy and LN dissection survived without any evidence of recurrence or metastasis during median follow-up of 27 months. After this first study, another report on the long-term outcomes of laparoscopic treatment of early GBC [15] was followed. In this subsequent report, 5-year disease-specific overall survival rate of twenty-five T2 GBC patients was 90.2%. These encouraging outcomes have opened the possibility of laparoscopic approach to be one of treatment modalities for early GBC. The results of a recent survey of experienced surgeons showed that laparoscopic surgery has an acceptable role for suspicious

or early GBC, and that laparoscopic extended cholecystectomy has a value comparable to that of open surgery in selected patients with GBC [23].

Another issue counting against laparoscopic approach for GBC is the possible risk of port-site metastasis. The first study on the port-site metastasis reported the incidence as 43% [24]. In the present study, however, there was no case of port-site metastasis, and a recent systematic review also showed that in the modern era (2000–2014) the incidence has decreased to 10.0% while the incidence of wound recurrence following open cholecystectomy remains approximately 7% [25]. Better preoperative recognition of malignancy, precautionary operative techniques, and use of improved modern trocars are probably attributable to this decline, hence concern about port-site metastasis doesn't seem to be an obstacle to laparoscopic approach for GBC anymore.

Purpose of this study is not only to analyze the results of laparoscopic surgery for T2 GBC itself but also to compare the results to those of open surgery. We reviewed data of patients whose final pathological diagnosis was T2. Mean values of EBL and transfusion rate were lower in LS group though the differences were not statistically significant. Postoperative hospital stay was significantly shorter in LS group, and complication rate was similar in both groups. Overall survival rate was also similar between the two groups. Disease free survival rate was significantly higher in LS group, though when subdivided the patients

into T2N0 and T2N1 subgroups there was no significant difference. The higher disease-free survival rate of LS group in this study can be explained by relatively higher number of T2N0 patients in LS group. To the best of our knowledge, the study which compares laparoscopic and open approach for T2 GBC is very scarce. However, the number of subjects in this study is still not enough to provide solid evidence on the safety and feasibility of laparoscopic approach.

Various types of surgical procedures were performed for each patient. Depending on general condition and intraoperative findings, simple cholecystectomy was performed deliberately for the patients who were considered to have high risk of surgery. We excluded those patients with simple procedure, which was more frequently performed in LS group to balance the extent of surgery between two groups and to minimize bias when comparing two different procedures. And the patients with extensive and complicated procedure were also excluded for this purpose as well. We decided not to perform resection of gallbladder bed when tumor was located at peritoneal side. Though still there is no high level of evidence on the extent of hepatic resection for T2 GBC, a recent study suggests better prognosis of peritoneal-sided GBC compared to that of hepatic-side GBC [18], and another study showed that survival rate was not significantly different between liver resection with lymph node dissection group and lymph node dissection only group in T2 GBC patients [26].

This study has limitations as follows. First, this is a single center study which has a relatively small number of patients to provide a high level of evidence. Second, patients in this study were enrolled based on their final pathologic results. Though we tried to predict T stage as accurately as possible by carrying out preoperative endoscopic ultrasonography and intraoperative specimen ultrasonography, the results were not always consistent with final pathology. Previously we investigated the accuracy of intraoperative specimen ultrasonography in diagnosis of T1b or more advanced GBC, and the sensitivity and specificity was 81% (95% CI, 54–96%) and 85% (65–96%), respectively [27]. Another study evaluated diagnostic accuracy of high resolution ultrasonography, endoscopic ultrasonography, and computed tomography for GBC, and when diagnosis was T2, rate of underestimation was 16.7% (1/6), 16.7% (1/6), and 20% (1/5), respectively [28]. Therefore, when planning laparoscopic surgery for suspected early GBC, precise preoperative workups should be done to exclude advanced cases which would merit an open approach.

Laparoscopic approach has potential advantages over open approach. Smaller incision size reduces incidence and severity of wound-related pain and complications. Less exposure of the internal organs to external environment leads to lower incidence of infectious complications and postoperative ileus [29,30]. Consequently postoperative recovery is faster and hospital stay is definitely shorter. Adhesion between internal organs is less severe that it may be less burdensome to perform secondary operation when necessary [30]. Feasibility and oncologic safety of laparoscopic treatment for advanced GBC is still unclear, but based on the results of the present study, we anticipate that laparoscopic approach will be accepted as an alternative treatment option for selected T2 GBC and patients will benefit from those advantages mentioned above.

5. Conclusion

Laparoscopic surgery for treatment of T2 GBC is technically feasible and its perioperative outcomes and oncologic results are comparable to those of open surgery. Future prospective studies with higher number of patients are necessary to confirm these results from our retrospective data.

Declarations of interest

None.

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