Effects of Surgical Methods and Tumor Location on Survival and Recurrence Patterns after Curative Resection in Patients with T2 Gallbladder Cancer

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Background/Aims: Extended cholecystectomy is generally recommended for patients with T2 gallbladder cancer. However, few studies have assessed the extent of resection relative to T2 gallbladder tumor location. This study analyzed the effects of surgical methods and tumor location on survival outcomes and tumor recurrence in patients with T2 gallbladder cancer. **Methods:** Clinicopathological characteristics, extent of resection, survival rates, and recurrence patterns were retrospectively analyzed in 88 patients with pathologically confirmed T2 gallbladder cancer. **Results:** The 5-year disease-free survival rate was 65.0%. Multivariate analysis showed that lymph node metastasis was the only independent risk factor for poor 5-year disease-free survival rate. Survival outcomes were not associated with tumor location. Survival tended to be better in patients who underwent extended cholecystectomy than in those who underwent simple cholecystectomy. Recurrence rate was not affected by surgical method or tumor location. Systemic recurrence was more frequent than local recurrence without distant recurrence. Gallbladder bed recurrence and liver recurrence were relatively rare, occurring only in patients with liver side tumors. **Conclusions:** Extended cholecystectomy is the most appropriate treatment for T2 gallbladder cancer. However, simple cholecystectomy with regional lymph node dissection may be appropriate for patients with serosal side tumors. **(Gut Liver 2016;10:140-146)**

INTRODUCTION

Gallbladder (GB) cancer traditionally has a dismal prognosis.[1,2] The only curative therapy is surgical resection. However, many patients are diagnosed too late due to the lack of specific symptoms, and GB cancer has a propensity for early dissemination, thus preventing curative surgery. Regular health examinations and laparoscopic surgery have increased the incidental diagnosis of early GB cancer, increasing the probability of curative resection and improving survival outcomes.

The extent of resection is mainly determined by the depth of tumor invasion. T2 GB cancer is defined as a tumor invading the perimuscular connective tissue or subserosal layer but not invading the serosa.[3] Extended cholecystectomy is generally recommended for patients with T2 GB cancer, a procedure that includes cholecystectomy, liver wedge resection around the GB bed and regional lymphadenectomy.[4] Previous studies have reported that extended surgery improves survival rates.[5-11] However, due to the rarity of GB cancer and its varied incidence in different countries, to date no well-designed randomized control study or prospective cohort study has assessed the effect of extent of surgery on outcomes in patients with T2 GB cancer. The recommendation of radical surgery for T2 GB cancer is based on low level of evidence.

Half of the GB is attached to the inferior surface of liver (liver side) and the other side faces the peritoneum (serosal side). Venous and lymphatic drainage of GB cancers differ according to the anatomic location of the tumor, especially for tumors located on the liver and serosal sides,[12] thus affecting the patterns of tumor spread.[13] Little is known, however, about the effects of tumor location on the outcomes of GB resection, and it remains unclear whether hepatic resection is necessary for T2 GB tumors located on the serosal side.

Therefore, this study analyzed the effects of tumor location and surgical methods on survival outcomes and recurrence patterns of T2 GB cancer after curative resection.

MATERIALS AND METHODS

Between April 1998 and December 2010, 144 patients with pathologically confirmed T2 stage GB cancer underwent surgery in Seoul National University Hospital. Patients who did not have preoperative computed tomography (CT) scans and pathologic slides for image and pathology review (n=38), those who had distant metastasis at the time of operation (n=13), and those who had GB cancer combined other malignancies (n=2), were excluded. Curative resection was defined as the absence of surgical margin involvement on pathologic reports and the absence of metastases to distant organs. Among the patients who underwent cholecystectomy without lymph node (LN) dissection, those with suspected LN metastasis on preoperative radiologic images and/or operative findings and confirmed as having metastasis by review of follow-up studies were defined as having undergone noncurative resection and excluded. Patients at high risk of dissemination, such as those with preoperative GB perforation (n=1) or who underwent percutaneous GB drainage with unsuspected GB cancer (n=2), were also excluded. Finally, the medical records and radiologic imaging results of 88 patients with T2 GB cancer who underwent curative resection were retrospectively reviewed. Patients' demographic and clinical characteristics, including age, gender, clinical history, preoperative radiologic image results and type of operation, were investigated. Preoperative CT images were reviewed to determine preoperative clinical stage. Tumor location was divided into two groups, such as serosal side and liver side, by preoperative CT and pathologic slide review. Serosal side tumors were defined as those with no contact point with the liver bed; all others with total or partial contact with liver were classified as liver side tumors (Fig. 1). Type of operation was categorized as simple or extended cholecystectomy. Laparoscopic cholecystectomy and open cholecystectomy without liver resection were categorized as simple cholecystectomy (SC). Cholecystectomy with hepatic wedge resection including regional LN dissection was categorized as extended cholecystectomy (EC). In our institution, cystic duct LN, common bile duct LN, hepatoduodenal ligament LN and posterior pancreatoduodenal LN were dissected routinely for regional LN dissection. Pathological staging was based on the seventh edition of the American Joint Committee on Cancer (AJCC) Manual.[3] Tumors were classified grossly as papillary, nodular and sclerosing types. Adjuvant therapy was reviewed. Adjuvant chemotherapy and radiation therapy was recommended for patients with T2 GB cancer, especially for patients with LN metastasis, if the patient's general condition was tolerable. Recurrence patterns, including time to recurrence, recurrence site and disease-free survival (DFS), were also investigated.

Statistical analyses were performed using IBM SPSS version 21.0 (IBM Co., Armonk, NY, USA). Categorical variables were compared using the Pearson chi-square or the Fisher exact test and continuous variables using the Student t-test or the Mann-Whitney U test. Cumulative survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression analysis included variables relatively associated with survival outcome on univariate analyses (p-values≤0.1). p-values ≤0.05 were considered statistically significant.

This study was approved by the Institutional Review Board of the Seoul National University Hospital (H-1401-063-550).

RESULTS

1. Clinicopathological characteristics

The clinicopathological characteristics of the patients are shown in Table 1. The 88 patients with pathologically confirmed, curatively resected T2 GB cancer included 36 men and 52 women, with mean age of 65.0 years and median follow-up duration of 66.5 months (range, 6.4 to 190.5 months). Sixteen patients underwent simple cholecystectomy and 72 underwent extended cholecystectomy. Combined common bile duct resection was done for five patients with suspicious cystic duct resection margin involvement (n=3) or presence of choledochal cyst (n=2). Tumors were located on the liver side of the GB in
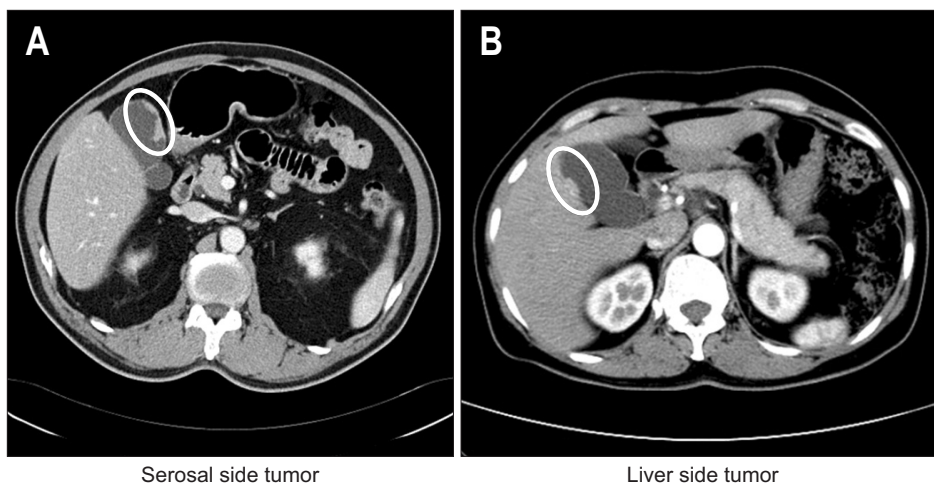

Serosal side tumor   Liver side tumor

Fig. 1. Computed tomography scans of tumors on the serosal (A) and liver side (B).

Table 1. Clinicopathological Characteristics according to Tumor Location

Characteristic	Total (n=88)	Liver side (n=62)	Serosal side (n=26)	p-value
Age, yr	65.0 (39–84)	65.1 (39–84)	63.8 (43–80)	0.572
Sex				0.484
Male	36 (40.9)	27 (43.5)	9 (34.6)	
Female	52 (59.1)	35 (56.5)	17 (65.4)	
Operation method				0.375
Extended cholecystectomy	72 (81.8)	49 (79.0)	23 (88.5)	
Simple cholecystectomy	16 (18.2)	13 (21.0)	3 (11.5)	
Gross type*				0.116
Papillary	41 (47.7)	30 (49.2)	11 (44.0)	
Nodular	33 (38.4)	20 (32.8)	13 (52.0)	
Sclerosing	12 (14.0)	11 (18.0)	1 (4.0)	
Lymph node metastasis				0.798
Positive	29 (33.0)	21 (38.9)	8 (32.0)	
Negative	50 (56.8)	33 (61.1)	17 (68.0)	
Lymphovascular invasion	27 (30.7)	19 (30.6)	8 (30.8)	0.590
Perineural invasion	13 (14.8)	11 (17.7)	2 (7.7)	0.191
Adjuvant chemotherapy	29 (33.0)	18 (29.0)	11 (42.3)	0.320
Adjuvant radiotherapy	27 (30.7)	15 (24.2)	12 (46.2)	0.074

Data are presented as mean (range) or number (%).
*Two cases were missing because of the lack of information about gross type on operation record and pathologic report.
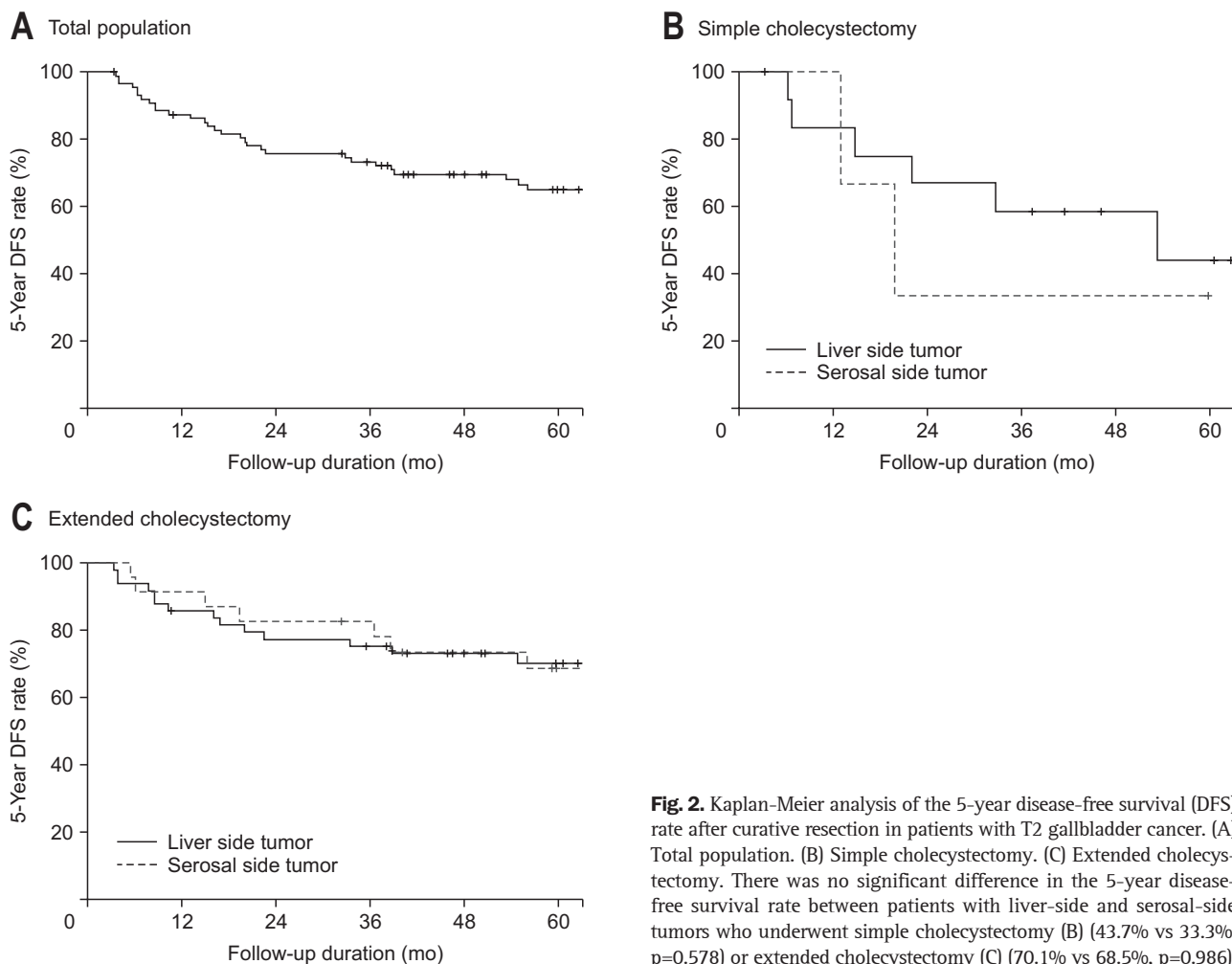

A Total population

B Simple cholecystectomy

C Extended cholecystectomy

Fig. 2. Kaplan-Meier analysis of the 5-year disease-free survival (DFS) rate after curative resection in patients with T2 gallbladder cancer. (A) Total population. (B) Simple cholecystectomy. (C) Extended cholecystectomy. There was no significant difference in the 5-year disease-free survival rate between patients with liver-side and serosal-side tumors who underwent simple cholecystectomy (B) (43.7% vs 33.3%, p=0.578) or extended cholecystectomy (C) (70.1% vs 68.5%, p=0.986).

62 patients (70.5%) and on the serosal side in 26 (29.5%). Gross morphologic analysis showed that 41 tumors (47.7%) were papillary type, 33 (38.4%) were nodular type and 12 (14.0%) were sclerosing type. The mean number of acquired lymph nodes was 7.5 of 79 patients who underwent LN dissection. LN metastases were found in 29 patients (33.0%), and no LN metastases in 50 (56.8%); the remaining nine patients did not undergo LN dissection, thus preventing evaluation of LN metastasis status. Among 29 patients with LN metastases, 27 patients had metastatic LN in group 1 regional LN according to seventh AJCC manual and two patients had posterior pancreatoduodenal LN metastases. Lymphovascular invasion was observed in 27 patients (30.7%) and perineural invasion in 13 (14.8%). Twenty-nine patients (33.0%) received adjuvant chemotherapy, and 27 (30.7%) received adjuvant radiotherapy. There were no significant differences in gender, age, extent of resection, rates of LN metastasis, lymphovascular invasion, perineural invasion and adjuvant therapy between patients with liver side and serosal side tumors.

2. Survival outcome

The 5-year overall survival (OS) rate of the 88 patients was 69.4% and their 5-year DFS rate was 65.0% (Fig. 2A). Univariate and multivariate analyses of the associations between clinico-pathological factors and 5-year DFS rate are shown in Table 2. Only LN metastasis (relative risk [RR], 2.573; 95% confidence interval [CI], 1.103 to 6.000; p=0.029) was identified as an independent risk factor for poor 5-year DFS. Survival was relatively better in patients who underwent EC than SC, but the difference

Table 2. Risk Factors for Disease-Free Survival in Patients with T2 Gallbladder Cancer

Risk factor	5-Year DFS, %	p-value	Relative risk	95% CI	p-value
Age, yr		0.443			
≤70	63.1		–	–	–
>70	69.3				
Sex		0.576			
Male	61.2		–	–	–
Female	67.8				
Tumor location		0.983			
Liver side	65.2		–	–	–
Serosal side	64.5				
Operation method*		0.053			
Extended cholecystectomy	69.5				
Simple cholecystectomy	42.7		2.526	0.918–6.953	0.073
Gross type		0.511			
Papillary	66.1		–	–	–
Nodular	67.5				
Sclerosing	57.1				
Lymph node metastasis*		<0.001			
Positive	44.6		2.573	1.103–6.000	0.029
Negative	80.2				
Lymphovascular invasion		0.194			
Positive	59.3		–	–	–
Negative	68.5				
Perineural invasion*		0.031			
Positive	46.2		1.525	0.607–3.831	0.369
Negative	68.5				
Adjuvant chemotherapy		0.120			
Yes	52.4				
No	71.2				
Adjuvant radiotherapy*		0.018			
Yes	45.5		1.798	0.877–4.470	0.181
No	73.7				

DFS, disease-free survival; CI, confidence interval.
*Variables included in multivariate analysis.

was not statistically significant (RR, 2.526; 95% CI, 0.918 to 6.953; p=0.073). Tumor location was not associated with DFS rate. Subgroup analyses according to tumor location and extent of resection showed no differences in 5-year survival rates between patients with liver side and serosal side tumors who underwent SC (43.7% vs 33.3%, p=0.578) or EC (70.1% vs 68.5%, p=0.986) (Fig. 2B and C).

3. Recurrence pattern

The overall recurrence rate was 18.2% after a median follow-up of 66.5 months. The recurrence rate was similar in patients who had undergone SC or EC (25.0% vs 16.7%, p=0.322) and in patients with liver or serosal side tumors (17.7% vs 19.2%, p=0.544). Recurrence patterns are summarized in Fig. 3. LN was the most frequent site of recurrence (8.5%). Five patients experienced regional and four experienced paraaortic LN recurrences. There was no statistically significant difference in regional LN recurrence rate between the SC and EC groups (12.5% vs 4.2%, p=0.223). Only one patient experienced regional LN recurrence without distant recurrence, with this patient undergoing EC for a serosal side tumor. Systemic recurrence was more frequent than locoregional without distant recurrence. Of the 88 patients, 14 (15.9%) had distant recurrence with or without locoregional recurrence, whereas only two (2.3%) had locoregional recurrence without distant recurrence. Local recurrence occurred significantly more frequently after SC than EC (25.0% vs 5.6%, p=0.034). The four (of 16) patients with recurrences after SC all had locoregional recurrence with or without distant recurrence. Focusing on anatomic location of tumor, local (8.1% vs 11.5%,

p=0.438) and distant (17.7% vs 11.5%, p=0.353) recurrence rates were similar in patients with liver and serosal side tumors. Recurrences in the GB bed (n=2) and liver (n=3) were observed only in patients with liver side tumors but they were not affected by type of surgery. There was no GB bed and liver recurrence in patients with serosal side tumors.

DISCUSSION

Various studies have reported survival outcomes in patients with T2 GB cancer after surgical resection, with 5-year OS rates reported to range from 24% to 77.8%.[7,11,14-24] Most of these studies, however, were retrospective in design and included about 30 to 40 patients. Although other studies were based on national registry data, their survival results were poorer than those from individual institutions.[17,19,24] National registry data may have included patients who underwent noncurative resection or with inconsistent pathologic reports. Indeed, we found that the 5-year OS rate in 16 patients noncuratively resected for T2 GB cancer, including those with preoperative perforation, percutaneous GB drainage or distant metastatic lesions, was much poorer (12.5%) than in those who underwent curative resection (69.4%).

The optimal extent of surgical resection for T2 GB cancer has not been clearly determined, although several clinical guidelines recommend radical resection. The National Comprehensive Cancer Network Guidelines recommend that patients with T1b and more advanced GB cancer undergo cholecystectomy, *en bloc* hepatic resection of segments IV B and V and clearing all LNs
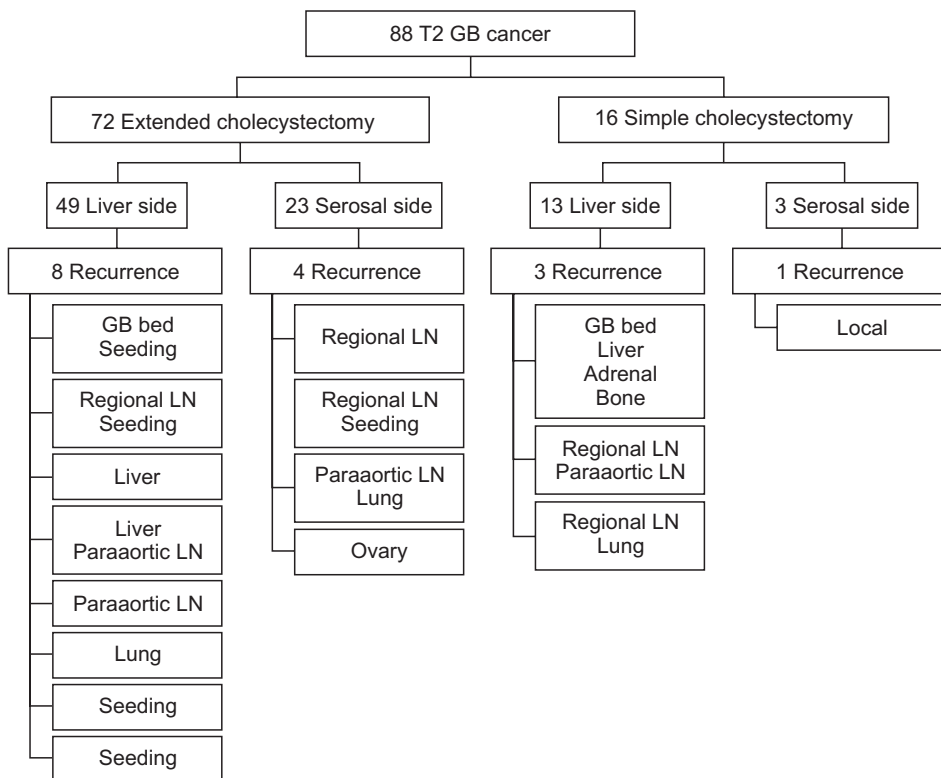

Fig. 3. Recurrence pattern after curative resection in patients with T2 gallbladder (GB) cancer.
LN, lymph node.

in the porta hepatis.[4] Similarly, German guidelines recommend that patients with T2 and more advanced tumors undergo cholecystectomy, hepatic wedge resection around the GB bed with 3 cm margins or bisegmentectomy of segment IV B and regional LN dissection along the hepatoduodenal ligament.[25] In Japan, open, not laparoscopic, cholecystectomy is recommended for patients with suspected GB cancer, with additional hepatectomy and lymphadenectomy recommended for patients with T2 GB cancer.[26] According to the Korean guideline published in 2014, EC is generally recommended for patients with GB cancer at stage T2 or above.[27] All of these recommendations, however, are based on retrospective data of small numbers of patients, with a low level of evidence.

We observed a 5-year DFS rate of 65.0% in patients curatively resected for T2 GB cancer. Multivariate analysis found that LN metastasis, observed in 31.9% of patients, was the only factor prognostic of survival. Previous studies have reported LN metastasis rates of 37% to 50%, with LN metastasis being prognostic of survival.[5-11] LN recurrence was the most common, observed in eight of 16 patients with tumor recurrence. EC tended to show a better 5-year DFS rate than SC, on both univariate (69.5% vs 42.7%, p=0.053) and multivariate (RR, 2.526; 95% CI, 0.918 to 6.953; p=0.073) analyses. This result is comparable to previous studies, which reported that 5-year DFS rates were higher after EC (61% to 90%) than SC (19% to 40%).[5,28-34]

Assessments of tumor location showed no significant difference in clinicopathological factors, such as operation type, gross tumor type, lymphovascular invasion, perineural invasion and LN metastasis between patients with liver side and serosal side tumors. Their 5-year DFS rates were similar, and subgroup analysis showed that the extent of surgery for both liver side and serosal side tumors was not associated with survival outcomes. A recent multicenter study showed that rates of vascular invasion (51% vs 19%, p<0.01), neural invasion (33% vs 8%, p<0.01), and LN metastasis (40% vs 17%, p<0.01) were significantly higher in patients with liver side than serosal side tumors.[35] The 5-year OS rates were also significantly higher in patients with serosal side than liver side tumors (64.7% vs 42.6%, p=0.0006), with liver side tumors independently associated with poor survival outcome (RR, 2.7; 95% CI, 1.7 to 4.2; p<0.001). The discrepancies between that study and the present work may be due to differences between the clinicopathologic features of liver side tumors in the two studies.

Analysis of recurrence patterns after curative resection is important in understanding disease characteristics and the effects of treatment. Although we found that recurrence rates were not affected by tumor location, GB bed recurrences were observed only in two patients with liver side tumors, and liver recurrences were observed only in three patients with liver side tumors, with neither observed in patients with serosal side tumors. In contrast, regional LN recurrences were frequently observed in patients with serosal side tumors. Similar results were obtained in the earlier multicenter study, with liver recurrences

more frequent in patients with liver than serosal side tumors (23% vs 3%, p=0.003).[35] These findings indicate that EC including liver resection should be performed in all patients with liver side T2 GB cancers. However, SC with regional LN dissection, without liver resection around the GB bed, may be sufficient for patients with serosal side T2 GB cancer. This hypothesis could be supported by the previous study that reported laparoscopic cholecystectomy with LN dissection for early GB cancer without liver invasion could feasible option with comparable outcome. Eighteen patients with T1 (n=8) or T2 (n=10) GB cancer had undergone laparoscopic cholecystectomy with LN dissection and survived without recurrence after a median follow-up of 27 months.[36] However, there was only limited result about this issue and in our study, only two patients with serosal side tumor underwent SC with LN dissection. It was too small a number to analyze. Subsequent studies with large cohort or prospective design about this issue will be needed to confirm the hypothesis.

This study had limitations. First, as it was based on retrospective data it may be subject to selection and information bias. Second, the small subgroup sizes and large proportion of patients lost to follow up may have altered the results.

LN metastasis was the most important prognostic factor in patients curatively resected for T2 GB cancer, with extended cholecystectomy tending to improve 5-year DFS rate. Tumor location did not affect survival outcome or recurrence patterns. However, no patient with serosal side tumors experienced GB bed or liver recurrence even after SC.

EC is the preferred surgical treatment for T2 GB cancer overall; however, the rarity of GB bed recurrence in patients with serosal side T2 GB cancer suggests that SC with regional LN dissection may be sufficient for these patients, if curative resection could be achieved.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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