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Original Article

# The appropriate surgical strategy for T1b gallbladder cancer incidentally diagnosed after a simple cholecystectomy

Byoung-Hyoung Kim, Seok-Hwan Kim, In-Sang Song, and Gwang-Sik Chun

*Department of Surgery, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Korea*

**Backgrounds/Aims:** The appropriate surgical treatment was investigated for T1b gallbladder (GB) cancer through a retrospective analysis of the clinical outcomes of patients with incidental T1 GB cancer. **Methods:** Patients with T1 GB cancer who were incidentally diagnosed while undergoing a simple cholecystectomy at Chungnam University Hospital from January 2004 to December 2017 were enrolled. Overall, 39 patients with T1 GB cancer, 17 patients with T1a, and 22 patients with T1b were included. We retrospectively analyzed the patients' clinical and pathologic findings and follow-up results. **Results:** Among the 6490 patients who underwent cholecystectomy during the study period, 165 patients were diagnosed with GB cancer (T1=42 [25.5%]). The risk factor associated with recurrence and cancer-related death in patients with T1 GB cancer was lymphovascular invasion (recurrence, $p$=0.028; death, $p$=0.004). In the T1b group, the 5-year disease-free survival (DFS) rate showed a statistical difference between patients with and without lymphovascular invasion (45.7% vs. 83.6%, $p$=0.048). There was no statistically significant difference in 5-year DFS and overall survival rate between simple cholecystectomy and extended cholecystectomy in T1b GB cancer with lymphovasular invasion ($p$=0.054 and $p$=0.091, respectively). **Conclusions:** In incidental T1b GB cancer, extended cholecystectomy was not superior to simple cholecystectomy in terms of the 5-year DFS rate and nor in overall survival rate or recurrence rate, even when lymphovascular invasion was identified after simple cholecystectomy. Therefore, simple cholecystectomy may be recommended as a primary surgical strategy for T1b GB cancer. **(Ann Hepatobiliary Pancreat Surg 2019;23:327-333)**

**Key Words:** Gallbladder; Cancer; Cholecystectomy

## INTRODUCTION

Gallbladder carcinoma is one of the most common malignant tumors of the biliary tract. However, it remains debated whether curative resection is the most beneficial treatment for improving long-term survival in patients with this malignancy. GB cancer that is limited to the mucosa (T1a) or the muscularis (T1b) is classified as early cancer.[1-3] Many studies recommend simple cholecystectomy as the surgical procedure of choice for T1a GB cancer, as it is a local disease. However, in the case of T1b GB cancer, several guidelines, including the National Comprehensive Cancer Network (NCCN) guidelines, recommend extended cholecystectomy as the initial treatment.[4-6] It may be premature to conclude that extended cholecystectomy should be the surgical treatment of choice for T1b GB cancer because there remain controversies such as tumor spreading. Some studies considered T1b GB cancer as a local disease and therefore suggested simple cholecystectomy as the treatment method.[7-10]

Recent studies have reported increased incidences of incidental diagnoses of T1 GB cancer, reaching up to 50-58%.[11-14] Therefore, it is necessary to consider whether the surgical strategy will benefit the future recurrence rate and survival rate of simple cholecystectomy and extended cholecystectomy for these patients. In this retrospective study, we analyzed the clinicopathologic features of GB cancer to determine the predictive risk factors that affect recurrence and survival. This study aimed to establish the surgical criteria for patients with early GB cancer.

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**Corresponding author:** Seok-Hwan Kim
Department of Surgery, Chungnam National University Hospital, Chungnam National University School of Medicine, 282 Munhwa-ro, Jung-gu, Daejeon 35015, Korea
Tel: +82-42-280-8385 (7175), Fax: +82-42-257-8024, E-mail: kjxh7@cnuh.co.kr

## MATERIALS AND METHODS

From January 2004 to December 2017, a total of 6490 patients underwent cholecystectomy at a single center (Chungnam National University Hospital), excluding cases of cholecystectomy performed as an additional resection during surgery for other primary cancers (common bile duct cancer, hepatocellular carcinoma, pancreatic head cancer, etc.) and cases of preoperatively confirmed GB cancer. Our study protocol was approved by the institutional review board of our institution. Of the 6490 patients, 165 had an incidental diagnosis of GB cancer (T1= 42 [25.5%], T2=88 [53.3%], T3=34 [34%], T4=1 [0.6%]), 42 cases of which were staged as T1. Because 3 cases had no pathology records, they were excluded, and a total of 39 cases (17 cases of T1a and 22 cases of T1b) were enrolled in the study (Fig. 1). The clinicopathologic findings and results of long-term follow-up observation in these patients were analyzed.

The staging was performed according to the TNM (tumor, node, metastasis) system of the American Joint Committee on Cancer (AJCC) 8th edition.[15,16] T1a GB cancer was defined as an invasion to the mucosa and T1b as an invasion to the muscular layer. The degree of lymph node extension was divided into N0 and N1. Concerning the surgical methods, simple cholecystectomy was defined as cholecystectomy alone, and extended cholecystectomy was defined as cholecystectomy with dissection of the surrounding lymph nodes with or without hepatic resection. Lymph node dissection was defined as resection involving the lymph nodes around the gallbladder and the hepatoduodenal ligament.

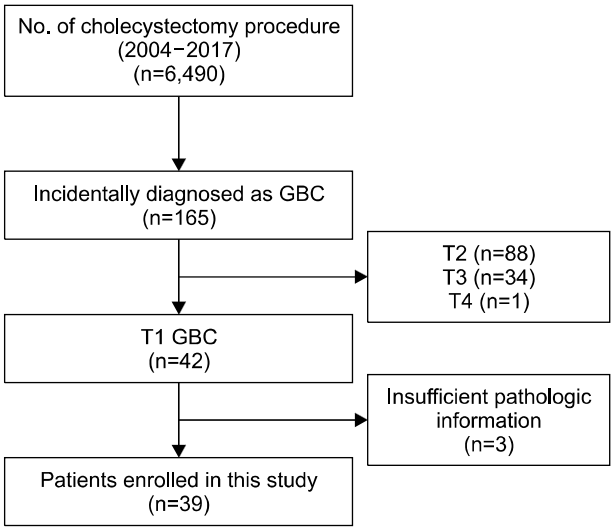


**Fig. 1.** Flowchart of patients registered in this study. GBC, gallbladder cancer.

The mean follow-up period was 54.2 months (range, 1-181 months), and recurrence was confirmed using abdominopelvic computed tomography. Medical records and survival data were obtained through chart reviews and direct communication with the patients. Multivariate regression analysis was performed using Cox proportional hazard models to identify the independent prognostic factors for recurrence and survival. Statistically significant factors based on the results of the univariate analysis were entered into the multivariate analysis. Categorical data were compared using the chi-square test. Values of $p < 0.05$ were considered statistically significant.

## RESULTS

### Characteristics of the study population

A total of 39 patients were included in this study, comprising 22 men (56.4%) and 17 women (43.6%). Of these, 17 patients (43.6%) had T1a tumor, and 22 patients (56.4%) had T1b tumor. The average age at the time of diagnosis was 66.8 years (range, 45-84 years), and the average follow-up period was 54.2 months (range, 1-181 months) (Table 1).

### Types of surgical intervention

The surgical outcomes according to the surgical method are summarized in Table 2. Of the 27 patients who underwent simple cholecystectomy, 13 (76.47%) and 14 (63.63%) had T1a and T1b tumor, respectively ($p$=0.791). Among the 27 simple cholecystectomies, 26 (96.3%) were laparoscopic surgeries. In the remaining case, conversion to open simple cholecystectomy was needed owing to severe adhesions from previous operations.

Extended cholecystectomy was performed in 4 patients (23.5%) and 8 patients (36.3%) with T1a and T1b tumor, respectively ($p$=0.003). None of the extended cholecystectomy cases were laparoscopic surgeries (all were open surgeries). Among the 12 cases of extended cholecystectomy, 7 cases involved liver resections (wedge resection in 3 cases and segmental resection in 4 cases). In the 2 cases of secondary operations, which were performed af-

**Table 1.** Clinical outcome and analysis of prognostic factors in T1 gallbladder cancer

| Variables | No. of patients | | Recurrence | | GBC-related death | |
|---|---|---|---|---|---|---|
| | T1a (%) (n=17) | T1b (%) (n=22) | Univariate | Multivariate | Univariate | Multivariate |
| | | | *p*-value | *p*-value | *p*-value | *p*-value |
| Age (years) | | | 0.060 | | 0.103 | |
| ＜60 | 6 (35.3) | 6 (27.3) | | | | |
| ＞60 | 11 (64.7) | 16 (72.2) | | | | |
| Gender | | | 0.679 | | 0.602 | |
| Male | 9 (52.9) | 13 (59.1) | | | | |
| Female | 8 (47.1) | 9 (40.9) | | | | |
| N stage | | | 0.313 | | 0.867 | |
| Nx | 11 (64.7) | 12 (54.5) | | | | |
| N0 | 5 (29.4) | 10 (45.5) | | | | |
| N1 | 1 (5.9) | 0 (0.0) | | | | |
| Operation | | | 0.348 | | 0.855 | |
| Simple | 13 (76.5) | 14 (63.6) | | | | |
| Extended | 4 (23.5) | 8 (36.4) | | | | |
| Histology | | | 0.003 | 0.847 | 0.453 | |
| Well | 2 (11.8) | 4 (18.2) | | | | |
| Moderate | 14 (82.3) | 16 (72.7) | | | | |
| Poor | 1 (5.9) | 2 (9.1) | | | | |
| LV invasion | | | 0.028 | 0.976 | 0.004 | 0.531 |
| Positive | 2 (11.8) | 8 (36.4) | | | | |
| Negative | 15 (88.2) | 14 (63.6) | | | | |
| LN dissection | | | 0.636 | | 0.814 | |
| Yes | 4 (23.5) | 6 (27.3) | | | | |
| No | 13 (76.5) | 16 (72.2) | | | | |
| Tumor location | | | 0.552 | | 0.192 | |
| Peritoneal | 13 (76.5) | 10 (45.5) | | | | |
| Liver | 4 (23.5) | 12 (54.5) | | | | |
| Recurrence | | | 1.000 | | 0.003 | 0.000 |
| Yes | 1 (6.3) | 5 (22.7) | | | | |
| No | 16 (93.7) | 17 (77.3) | | | | |
| GBC-related death | | | 0.003 | | 1.000 | |
| Yes | 0 (0.0) | 3 (13.6) | | | | |
| No | 17 (100) | 19 (86.4) | | | | |

GBC, gallbladder cancer; LV, lymphovascular; LN, lymph node

**Table 2.** Surgical outcomes of T1 gallbladder cancer

| | T1a (n=17) | T1b (n=22) | *p*-value | Total (n=39) |
|---|---|---|---|---|
| Simple cholecystectomy (%) | 13 (76.47) | 14 (63.63) | 0.791 | 27 (69.23) |
| Open (%) | 0 (0.00) | 1 (7.14) | | 9 (33.33) |
| Laparoscopic (%) | 13 (100) | 13 (92.86) | | 24 (66.67) |
| Extended cholecystectomy (%) | 4 (23.52) | 8 (36.37) | 0.003 | 12 (30.77) |
| Open conversion (%) | 0 (0.00) | 2 (25.00) | | 2 (16.67) |
| 2nd operation (%) | 0 (0.00) | 2 (25.00) | | 2 (16.67) |
| Major hepatectomy (%) | 0 (0.00) | 7 (31.81) | 0.012 | 7 (17.95) |

ter the diagnosis of GB cancer, both involved T1b tumor and 1 case involved liver wedge resection.

### Pathologic outcomes

On histopathologic analysis, there were 6 cases (15.4%) of well-differentiated, 30 cases (76.9%) of moderately dif-

ferentiated, and 3 cases (7.7%) of poorly differentiated T1 GB cancer. The histologic grade was a statistically valid risk factor for recurrence in univariate analysis ($p$=0.003) (Table 1). The T1b group included 4 cases (18.2%), 16 cases (72.7%), and 2 cases (9.1%) of well-differentiated, moderately differentiated, and poorly differentiated gallbladder cancer, respectively.

### Lymphovascular invasion

Initially, we considered that lymph node metastasis would be the primary prognostic factor; however, among our patient population (n=39), none showed lymph node metastasis on the final pathology findings. Therefore, we proceeded to investigate lymphovascular invasion, which was pathologically observed in 2 cases (11.8%) in the T1a group and 8 cases (36.4%) in the T1b group (Table 3). Tumor recurrence and gallbladder cancer-related deaths seemed to be associated with lymphovascular invasion based on the univariate analysis ($p$=0.028 and $p$=0.004, respectively).

### Tumor location

In our investigation, we wanted to consider various prognostic factors. We, therefore, stratified the patients according to the tumor location (peritoneal or hepatic side). The AJCC 8th edition uses tumor location as a distinguishing factor between T2a and T2b disease.[15] In the T1a group, 13 cases (76.5%) were in the peritoneal side, and 4 cases (23.5%) were in the hepatic side. In the T1b group, 10 cases (45.5%) were in the peritoneal side, and 12 cases (54.5%) were in the hepatic side. Our univariate analysis showed that tumor location was not a significant prognostic factor of recurrence and DFS in T1 GB cancer ($p$=0.552 and $p$=0.192, respectively).

**Table 3.** Recurrence pattern of T1b gallbladder cancer after surgical treatment

| | Simple cholecystectomy (n=14) | Extended cholecystectomy (n=8) |
|---|---|---|
| Loco-regional recurrence (%) | 2 (14.28) | 1 (12.50) |
| CBD (%) | 1 (50.00) | 1 (100) |
| Lymph node (%) | 1 (7.7) | 0 |
| Port site (%) | 0 | 0 |
| Systemic recurrence (%) | 1 (7.14) | 1 (12.50) |
| Liver (%) | 1 (100) | 0 |
| Peritoneal seeding (%) | 0 | 0 |
| Lung (%) | 0 | 0 |
| Paraaortic LN (%) | 0 | 1 (100) |
| Total (%) | 3 (21.42) | 2 (25.00) |

CBD, common bile duct; LN, lymph node

### Recurrence

Recurrence was noted during the follow-up period in 6 patients with T1 GB cancer, including 1 case (6.3%) with T1a tumor and 5 cases (22.7%) with T1b tumor (Table 1). Of the 5 cases of T1b GB cancer recurrence, locoregional recurrence was present in 3 cases, and systemic recurrence occurred in 2 cases (Table 3). When categorized according to the surgical method, locoregional recurrence was noted in 2 cases (14.28%), and systemic recurrence was noted in 1 case (7.14%) in the simple cholecystectomy group. In the extended cholecystectomy group, one patient (12.5%) had a locoregional recurrence, and one patient (12.5%) had a systemic recurrence. Among the five recurrent T1b tumors, 3 (60%) were in the peritoneal side, and 2 (40%) were in the hepatic side. For the two hepatic side cases, hepatectomy was performed in 1 case but not in the other. There was no statistically significant correlation between tumor location and recurrence rate ($p$=0.552).

### Survival rate

In T1b cases, the 1-, 3-, and 5-year DFS rates were 92.3%, 84.6%, and 72.5%, respectively, in the simple cholecystectomy group, and 100%, 57.1%, and 57.1%, respectively, in the extended cholecystectomy group ($p$=0.332); however, the differences were not statistically significant (Fig. 2A). In the T1b group, the 5-year DFS rate was statistically significantly different between patients with and without lymphovascular invasion (83.6% in patients without invasion, 45.7% in patients with invasion; $p$=0.048) (Fig. 2B). According to the surgical method, the 5-year DFS rate was 64.3% for simple cholecystectomy and 0% for extended cholecystectomy in patients with lymphovascular invasion ($p$=0.054), whereas the overall 5-year survival rate was 70.0% for simple cholecystectomy and 100% for extended cholecystectomy, with both showing no statistically significant differences ($p$=0.091) (Fig. 3).

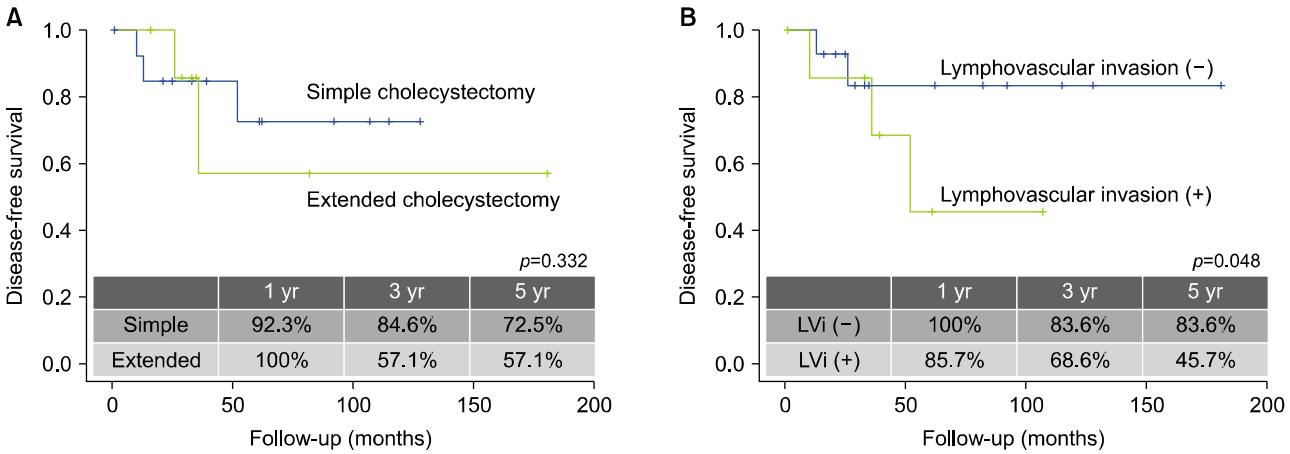


**Fig. 2.** Disease-free survival curves of patients with T1b gallbladder cancer compared between simple and extended cholecystectomy (A), and between negative and positive lymphovascular invasion (B). LVi, lymphovascular invasion.

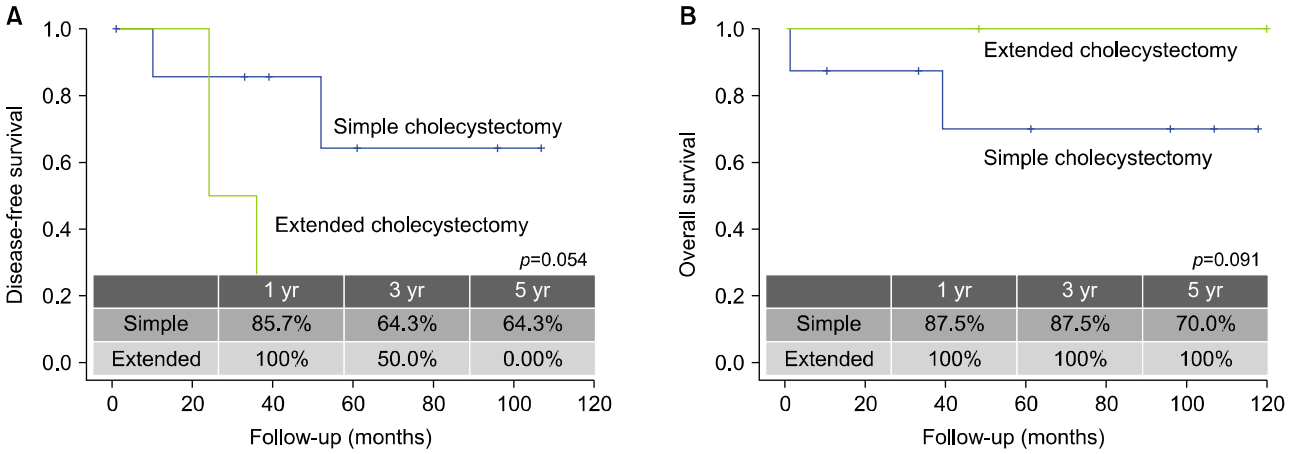


**Fig. 3.** Disease-free (A) and overall survival (B) curves of patients with lymphovascular invasion of T1b gallbladder cancer compared between simple and extended cholecystectomy.

## DISCUSSION

Incidental gallbladder cancer is defined as GB cancer that is histologically diagnosed after cholecystectomy for gallstone, cholecystitis, or gallbladder polyps, and its rate of detection ranges from 0.2% to 2.9%.[12,17,18] In the present study, incidental gallbladder cancer was diagnosed in 2.46% of our patients. When early GB cancer is confirmed on frozen biopsy during surgery or histologically diagnosed after the operation, there is no definitive clinical guideline on whether extended cholecystectomy or revision of the initially planned simple cholecystectomy should be performed, or if the type of surgery is beneficial to survival.

In general, the rate of diagnosis of advanced-stage GB cancer is high.[2,3] In our study, 123 of the 165 patients (75%) with an incidental diagnosis of GB cancer were confirmed to have stage T2 disease or higher at the time of diagnosis. Therefore, the level of research or evidence on the treatment of early GB cancer is, in fact, insufficient. Because the incidence of early gallbladder carcinoma has increased with the increasing use of laparoscopic cholecystectomy,[13,14,19] there is a growing need for surgical guidelines for early GB cancer. In Korea, a large-scale multicenter retrospective study was previously conducted to suggest the appropriate surgical method for T1 GB cancer.[20] That nationwide study concluded that simple cholecystectomy is an appropriate treatment for T1a GB cancer, and there was no evidence of the superiority of extended cholecystectomy for T1b GB cancer

over simple cholecystectomy. Therefore, the above study serves as a basis for recommending simple cholecystectomy for T1b GB cancer.[8,20]

For T1a GB cancer, which is limited to the mucosa, simple cholecystectomy including the resection margin has been considered the optimal treatment. This is a part of the NCCN guideline and has also been recommended at the highest level in the Korean domestic guidelines.[4-6,21] However, for T1b GB cancer, extended cholecystectomy is primarily recommended in the NCCN guideline, whereas other studies have shown that extended cholecystectomy was not more advantageous than simple cholecystectomy.[4-6,8] Furthermore, we did not find a relationship between extended cholecystectomy of T1b GB cancer and improvement in survival rate, and we did not obtain evidence that lymph node dissection has a therapeutic effect.[20,22-26] In other words, extended cholecystectomy was not superior to simple cholecystectomy in terms of survival rate and recurrence rate, and lymph node resection also did not improve the survival rate in T1b GB cancer. Based on these findings, simple cholecystectomy is being recommended as the appropriate surgical therapy for T1b GB cancer. Other guidelines also recommend simple cholecystectomy for the treatment of T1b GB cancer.[8,20,21,27,28]

Presence of lymph node metastasis is a well known prognostic factor in cancer and lymph node dissection is thought to be of benefit in raising survival rates. Although there is no definite guideline for the number of nodes to remove and the extent of resection in lymph node dissection in cholecystectomy, the 6th edition of the AJCC Staging Manual states, that removal of $>3$ lymph nodes is required to accurately determine the N stage.[15,16] The mean number of lymph nodes removed in this study was 8.2 (range, 2-19) in a total of 10 patients. In 2 cases, we removed $<3$ lymph nodes; however, both cases did not show recurrence. In this study, lymph node dissection in T1b cases did not significantly improve the survival or recurrence rate (27.3% vs. 72.2%, $p$=0.636). Initially, we considered lymph node metastasis as a general prognostic factor in this study. However, in the 39 total cases of incidental T1 GB cancer, none showed lymph node metastasis in final pathology findings.

T2 GB cancer was classified as T2a and T2b in the AJCC 8th edition, and it has been reported that patients with GB cancer in the hepatic side have a low survival rate.[15,29] In the T1b GB cancer cases in this study, the initial tumor location was the peritoneal side in 10 cases and the hepatic side in 12 cases. However, none of the 5 cases of gallbladder cancer recurrence were in the hepatic side or a local recurrence in the liver bed. In addition, we have previously mentioned that extended cholecystectomy in T1b cases did not improve the overall survival. Therefore, early GB cancer most likely does not require liver resection.

In this study, laparoscopic cholecystectomy was performed in 96.3% of T1 GB cancer cases treated with simple cholecystectomy and in 92.36% of patients with T1b tumor. We concluded that laparoscopic cholecystectomy might be a safe surgical procedure for T1 GB cancer because there was no significant difference in the survival rate and recurrence rate between simple cholecystectomy and extended cholecystectomy.

In patients with T1b tumor, the absence of lymphovascular invasion had a significant benefit in terms of the 5-year DFS rate and recurrence rate (Table 1) In T1b cases with lymphovascular invasion, the 5-year DFS rate was increased in patients treated with extended cholecystectomy, but not statistically significant ($p$=0.054), and there was no statistically significant difference in overall survival ($p$=0.091) (Fig. 3).

Given that extended cholecystectomy does not show a superiority in survival or recurrent rates, although NCCN guidelines recommend extended cholecystectomy in T1b cancer patients but there are realistic difficulties in domestic application Moreover, the results of our institution are also consistent with the domestic trend, and the simple cholecystectomy in T1b GB cancer can be considered as an appropriate surgical approach.[4,21]

This study has some limitations. The number of patients with incidental gallbladder cancer was relatively small. Moreover, the retrospective design of this study is also a limitation (a randomized controlled trial would have been ideal). Further investigations through large-scale randomized controlled trials are needed in the future.

In conclusion, extended cholecystectomy in T1 GB cancer does not offer an advantage in terms of the survival and recurrence rates. In T1b GB cancer, it seems questionable whether the recommendation for initially extended cholecystectomy including lymph node dissection is still valid. Therefore, when T1b GB cancer is inci-

dentally diagnosed after a simple cholecystectomy, we believe that simple cholecystectomy may be recommended as the primary surgical strategy.

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