Original Article

Optimal timing of reoperation for postoperatively diagnosed T2 gallbladder cancer: a retrospective multicenter cohort study

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Background: Although the frequency of incidental diagnosis of gallbladder cancer (GBC) after cholecystectomy is increasing and further resection is necessary for stage T2 GBC or higher, the optimal timing of reoperation remains debated. The objective of the current study was to compare short- and long-term outcomes according to the interval between initial cholecystectomy and reoperation.

Methods: Among 802 patients who underwent extended cholecystectomy for T2 GBC between November 2004 and October 2022 at five tertiary referral centers in Korea, 148 underwent reoperation after initial cholecystectomy and were included in this study. Patient outcomes were compared according to the interval between initial cholecystectomy and reoperation.

Results: Patients were divided into three groups according to the interval between initial cholecystectomy and reoperation: <4 weeks (group A), 4–8 weeks (group B), and >8 weeks (group C). Operation time (A *vs.* B *vs.* C: 225.3±124.7 *vs.* 179.4±85.6 *vs.* 169.3±56.4 min, P<0.001) and estimated blood loss {median (interquartile range), 100 [100–300] *vs.* 100 [100–100] *vs.* 100 [87.5–100] cc, P=0.03} were greater in group A. The median follow-up duration was 52 months. Five-year recurrence-free survival was worst in group C (64.0% *vs.* 83.6% *vs.* 58.9%, P=0.02). In multivariable analysis, long interval [hazard ratio (HR) 5.74, P=0.002] and residual disease (HR 5.42, P<0.001) were independent risk factors for recurrence.

Conclusions: The optimal interval between initial cholecystectomy and reoperation for postoperatively diagnosed T2 GBC is 4–8 weeks. Early reoperation is associated with worse intraoperative outcomes, and delayed reoperation is associated with higher risk of recurrence.

Keywords: Gallbladder cancer (GBC); laparoscopic cholecystectomy; extended cholecystectomy; reoperation

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Introduction

Gallbladder cancer (GBC) is a rare malignancy that is insidious and commonly progresses to an advanced stage before detection (1). Despite its grim prognosis, the increasing frequency of incidentally discovered GBC during or after cholecystectomy for benign indications offers an opportunity for earlier diagnosis and improved survival following effective treatment (2,3). For tumors of T1a stage, no further re-resection is recommended (4). Evidence from the literature is conflicting regarding the role of re-resection in T1b GBC, as some studies report no survival benefit due to the low incidence of residual disease (RD) (4-8). For postoperatively diagnosed T2 GBC, which is the most frequently detected stage, current guidelines recommend oncological extended re-resection, including lymph node dissection and partial liver resection unless disseminated disease or the patient's poor performance status contraindicate surgical management (4,5). However, evidence concerning the optimal timing of reoperation is scarce and contradictory.

The initial cholecystectomy can induce adhesion and fibrosis around the gallbladder bed and hepatoduodenal ligament that prompt most surgeons to avoid intervening during the peak phase of the inflammatory process (9,10). However, delaying radical reoperation for too long might lead to an inoperable state due to progression of the residual tumor (11). Therefore, it is extremely challenging to balance the decision on when to reoperate for postoperatively diagnosed GBC because technical aspects and tumor biology should both be considered.

Although a recent large multicenter study showed that a 4–8-week interval between cholecystectomy and reoperation was associated with favorable outcomes, contradictory results were obtained in other studies (12-14). In the present study, we specifically focus on postoperatively diagnosed GBC of stage T2, the most commonly diagnosed pathological tumor stage (pT) category, to compare the short- and long-term outcomes according to the interval between initial cholecystectomy and reoperation. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2024-713/rc) (15).

Highlight box

Key findings

- The optimal timing for reoperation for postoperatively diagnosed T2 gallbladder cancer (GBC) is 4 to 8 weeks after the initial cholecystectomy.

What is known and what is new?

- While the prognostic impact of the interval between initial cholecystectomy and reoperation in postoperatively diagnosed GBC has been reported in various studies, no conclusion has been reached.
- This is one of the largest series focusing specifically on T2 stage tumors that shows that a 4- to 8-week interval seems ideal for reoperation in terms of perioperative and oncologic outcomes.

What is the implication, and what should change now?

- In the early postoperative period, reoperation should be carefully planned due to the risk of perioperative morbidity.
- For patients with delayed referral after the initial cholecystectomy, restaging procedures to identify residual disease or interval development of metastasis should be considered before proceeding to reoperation.

Methods

Patients

We constructed a retrospective multicenter cohort of patients who underwent reoperation for postoperatively diagnosed T2 GBC at five tertiary referral centers in Korea (Seoul National University Bundang Hospital, Asan Medical Center, Severance Hospital, Gyeongsang National University Hospital, and Korea University Guro Hospital) between November 2004 and October 2022. Patients were eligible for this study if they met the following criteria: (I) GBC incidentally found after cholecystectomy for a presumed benign diagnosis; (II) stage pT2 confirmed by the pathology report after initial surgery; and (III) reoperation with a curative intent. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-2211-795-101). All participating institutions (Seoul National University Bundang Hospital, Asan Medical Center, Severance Hospital, Gyeongsang National University Hospital, and Korea University Guro Hospital) were informed and agreed to the study. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

There was no specific protocol regarding the timing of reoperation. Instead, the decision was made at the surgeon's discretion at each institution based on factors such as the patient's recovery status, the duration of preoperative evaluation, operating room availability, and the timing of the patient's visit for reoperation, particularly when initial operation was performed at a different hospital. Before the

reoperation, follow-up imaging studies including abdominal computed tomography (CT) and, if necessary, chest CT or positron emission tomography were obtained to evaluate local disease progression or distant metastasis.

Study design

The patients were divided into three groups according to a previous study based on the United States Extrahepatic Biliary Malignancy Consortium, employing the interval between cholecystectomy and reoperation: <4 weeks (group A), 4–8 weeks (group B), and >8 weeks (group C) (12). We compared operative parameters, including operation time, estimated blood loss, transfusion rate, and postoperative morbidity, as well as the long-term survival outcomes, among the three groups.

Data collection and definitions

Information on patient demographics, operative data regarding the initial cholecystectomy, pathological features of the primary tumor, operative data regarding the reoperation, pathological evaluation of RD, and survival data were retrieved from the medical records at each institution.

Operative data regarding the initial cholecystectomy included the initial suspected diagnosis, location of initial operation (same or different hospital), date of initial operation, operative approach, completeness of cholecystectomy (partial versus complete), percutaneous drainage before cholecystectomy, and perforation during operation. In many cases referred from an outside hospital, information regarding the initial cholecystectomy could only be retrieved from the available records at the participating institution. Only parameters without missing data were included in the analysis.

The pathological T stage was defined in accordance with the eighth edition of the American Joint Committee on Cancer (AJCC) guidelines (16). T2 GBC was subdivided by location into T2a (peritoneal side) and T2b (hepatic side). The initial pathology report for early cases (November 2004 to December 2016, n=65) did not specify the T2 substage because the pathologists followed prior editions of the AJCC guidelines; in such cases, the preoperative images and operation records were further reviewed to determine the tumor location. Postoperative complications were defined according to the Clavien-Dindo classification, and clinically relevant complications were defined as Clavien-Dindo grade IIIa or higher (17).

Patients were scheduled for regular follow-up visits with tumor markers and abdominal CT scans. Recurrence included newly noted lesions in the gallbladder bed, regional lymph node stations, intrahepatic metastasis, and distant metastasis. Recurrence-free survival was defined as the interval between the date of surgery and the date at which recurrence was first recognized. In patients without recurrence, recurrence-free survival was calculated between the date of surgery and the date of last follow-up. Disease-specific survival was calculated from the date of surgery to the date of cancer-related death or the date of last follow-up.

Statistical analyses

All categorical data are expressed as the frequency (percentage), and continuous variables are expressed as the mean ± standard deviation for normally distributed variables or as the median (interquartile range) for non-normally distributed variables. Continuous variables were compared using the one-way analysis of variance (ANOVA) or the Kruskal-Wallis rank sum test according to the distribution and variance of the data. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Survival analysis was conducted using the Kaplan-Meier method with the log-rank test. Univariable and multivariable Cox regression analyses were performed to identify risk factors for recurrence. All P values were two-sided, and P<0.05 was considered statistically significant. Statistical analyses were performed using R Project for Statistical Computing (version 4.3.3).

Results

Baseline characteristics

During the study period, 802 patients underwent extended cholecystectomy for T2 GBC at the participating institutions. Of these, 147 (18.3%) were postoperatively diagnosed after simple cholecystectomy and underwent reoperation. Four (2.7%) patients received systemic therapy between the initial cholecystectomy and reoperation. The median time between initial cholecystectomy and reoperation was 29 days, and ranged from 5 to 299 days. Overall, 73 patients (49.7%) underwent reoperation within 4 weeks (group A), 58 patients (39.5%) underwent reoperation during 4–8 weeks (group B), and 16 patients (10.9%) underwent reoperation after more than 8 weeks (group C) from the initial cholecystectomy. The clinicopathological characteristics of these three groups of

Table 1 Baseline characteristics of patients according to the interval between initial cholecystectomy and reoperation

Characteristics	Group A (n=73)	Group B (n=58)	Group C (n=16)	P value
Age (years)	61.9±9.5	65.7±9.8	69.3±10.2	0.002**
Sex (male:female)	31:42	31:27	8:8	0.45
BMI (kg/m^2)	24.0 (21.7–25.5)	24.3 (22.1–25.8)	24.2 (21.9–26.4)	0.86
ASA class				<0.001***
1	23 (31.5)	5 (8.6)	0	
2	47 (64.4)	50 (86.2)	11 (68.8)	
3	3 (4.1)	3 (5.2)	5 (31.2)	
Initial cholecystectomy				
Location				0.01*
Same hospital	34 (46.6)	13 (22.4)	4 (25.0)	
Outside hospital	39 (53.4)	45 (77.6)	12 (75.0)	
Operative method				0.26
Laparoscopic	69 (94.5)	58 (100.0)	16 (100.0)	
Robotic	1 (1.4)	0	0	
Open	3 (4.1)	0	0	
Percutaneous cholecystostomy	1 (1.4)	2 (3.4)	0	0.71
Perforation during operation	3 (4.1)	3 (5.2)	0	0.61
Radical reoperation				
Time interval to re-resection (weeks)	3.0 (2.1–3.6)	5.1 (4.6–6.3)	10.1 (8.4–14.0)	<0.001***
Operative method				0.31
Laparoscopic	16 (21.9)	19 (32.8)	3 (18.8)	
Open	57 (78.1)	39 (67.2)	13 (81.2)	
Liver resection	62 (84.9)	48 (82.8)	11 (68.8)	0.30
Type of liver resection				0.001**
Gallbladder bed resection	43 (69.4)	21 (43.8)	3 (27.3)	
Segment IVb/V bisegmentectomy	19 (30.6)	27 (56.2)	7 (63.6)	
Right hemihepatectomy	0	0	1 (9.1)	
Cystic duct re-excision	45 (61.6)	30 (51.7)	7 (43.8)	0.31
Bile duct resection	11 (15.1)	7 (12.1)	3 (18.8)	0.77

Values are mean ± SD or median (interquartile range) or n (%). *, P<0.05; **, P<0.01; ***, P<0.001. Group A: <4 weeks; group B: 4–8 weeks; group C: >8 weeks. ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

patients are summarised in *Table 1*. Longer interval between the initial cholecystectomy and reoperation was associated with older age (A *vs.* B *vs.* C: 61.9±9.5 *vs.* 65.7±9.8 *vs.* 69.3±10.2 years, P=0.002) and higher American Society of Anesthesiologists (ASA) class (P<0.001).

Operative parameters

Patients in group A more frequently underwent initial cholecystectomy and reoperation at the same hospital [A *vs.* B *vs.* C: 34 (46.6%) *vs.* 13 (22.4%) *vs.* 4 (25.0%), P=0.01]. The type of operative method for the initial cholecystectomy

and the frequencies of percutaneous cholecystostomy and gallbladder perforation during operation, did not differ among the three groups. Furthermore, the type of operative method for the reoperation and the extent of resection did not differ among the three groups, and most patients in each group underwent lymph node dissection with liver resection, as recommended in the guidelines [A *vs.* B *vs.* C: 62 (84.9%) *vs.* 48 (82.8%) *vs.* 11 (68.8%), P=0.30]. Among 121 patients who underwent liver resection, gallbladder bed wedge resection was performed in 67 (55.4%) patients, segment IVb/V bisegmentectomy in 53 (43.8%) patients, and right hemihepatectomy in one (0.8%) patient. Longer interval between the initial cholecystectomy and reoperation was associated with wider extent of liver resection (P=0.001). In the study population, 82 (55.8%) patients underwent re-excision of the cystic duct, and extrahepatic bile duct resection with reconstruction was performed in 21 (14.3%) patients. There was no difference among the three groups in cystic duct re-excision (P=0.31) or bile duct reconstruction rates (P=0.77).

Postoperative short- and long-term outcomes

The frequencies of T stage, N stage, tumor differentiation, and margin status were similar in each group (*Table 2*). The number of retrieved lymph nodes was sufficient, with a mean number exceeding six in all three groups (A *vs.* B *vs.* C: 9.1±7.2 *vs.* 8.1±5.3 *vs.* 9.3±5.1, P=0.73). RD was noted in 23.8% (35/147) of the total cohort. The most common location of RD was lymph nodes (30/35, 85.7%), followed by cystic or bile duct (6/35, 17.1%), and the liver (3/35, 8.6%). Although the overall frequency of RD did not differ, RD in the liver was more frequent in group C [A *vs.* B *vs.* C: 1 (1.4%) *vs.* 0 *vs.* 2 (12.5%), P=0.03].

During reoperation, operation time (A *vs.* B *vs.* C: 225.3±124.7 *vs.* 179.4±85.6 *vs.* 169.3±56.4 min, P<0.001) and estimated blood loss {median (interquartile range), 100 [100–300] *vs.* 100 [100–100] *vs.* 100 [87.5–100] cc, P=0.03} were significantly greater in group A than in the other groups. All patients with estimated blood loss greater than 1,000 cc were found in group A. The intraoperative red blood cell transfusion rate was highest in group A, although the difference was not statistically significant [10 (13.7%) *vs.* 4 (6.9%) *vs.* 0 (0%), P=0.21]. The incidence of postoperative complications, including clinically relevant complications, did not differ among the three groups. Postoperative hospital stay was longer in group A than in the other groups (A *vs.* B *vs.* C: 10.0±5.1 *vs.* 7.7±4.6 *vs.* 7.7±2.0 days, P=0.004). Similar proportions of patients received adjuvant treatment in each group.

Survival outcomes

The median follow-up duration was 52 months. The recurrence rate was higher in group A and group C compared to group B [A *vs.* B *vs.* C: 22 (30.1%) *vs.* 7 (12.1%) *vs.* 6 (37.5%), P=0.02]. The 5-year recurrence-free survival rate was significantly better in group B (87.2%) than in group A (68.2%) and group C (61.9%) (log-rank P=0.02; Bonferroni-corrected comparisons: A *vs.* B, P=0.03; B *vs.* C, P=0.03; *Figure 1A*). Disease-specific survival was not significantly different among the three groups (A *vs.* B *vs.* C: 77.3% *vs.* 86.1% *vs.* 80.4%, P=0.62; *Figure 1B*).

Univariable and multivariable Cox regression analyses of recurrence and cancer-related death were performed (*Table 3*). In the univariable analysis of recurrence, a short (<4 weeks) [hazard ratio (HR) 2.63, P=0.03] or long interval (>8 weeks) between cholecystectomy and reoperation (HR 3.93, P=0.01), RD (HR 5.41, P<0.001) and lymphovascular invasion (HR 2.63, P=0.007) were significant predictors of recurrence. In the multivariable analysis performed with these three factors, a long interval (>8 weeks) between cholecystectomy and reoperation (HR 4.68, P=0.008) and RD (HR 5.35, P<0.001) remained significant. In the univariable analysis of cancer-related deaths, RD (HR 5.58, P<0.001) and lymphovascular invasion (HR 2.53, P=0.02) were significant factors. In the multivariable analysis performed with these two factors, only RD remained significant (HR 5.24, P<0.001).

Subgroup analysis for T2a and T2b substage revealed that the recurrence-free survival rate was significantly lower in group A and group C compared to group B in T2a tumors, while disease-specific survival rates showed no statistically significant difference (*Figure 2*). In T2b tumors, the time interval between cholecystectomy and reoperation did not affect survival outcomes (*Figure 3*).

Discussion

In the current study, we evaluated the impact of the time interval between initial cholecystectomy and reoperation on the perioperative and long-term oncologic outcomes of patients with postoperatively diagnosed T2 GBC. Several multicenter studies have addressed the issue of reoperation timing of incidentally found GBC; however, most studies were based on a heterogeneous study population, including

Table 2 Comparison of short- and long-term outcomes after radical reoperation according to the interval between initial cholecystectomy and reoperation

Items	Group A (n=73)	Group B (n=58)	Group C (n=16)	P value
Residual disease	17 (23.3)	12 (20.7)	6 (37.5)	0.58
Liver	1 (1.4)	0	2 (12.5)	0.03*
Lymph node	15 (20.5)	11 (19.0)	5 (31.3)	0.54
Cystic duct/bile duct	3 (4.1)	3 (5.2)	0	>0.99
Diameter of tumor (cm)	3.0±2.1	2.0±1.6	2.8±1.5	0.11
Differentiation				0.77
Well	28 (39.4)	22 (37.9)	4 (25.0)	
Moderate	37 (52.1)	30 (51.7)	11 (68.8)	
Poor	6 (8.5)	4 (6.9)	0	
T stage				0.61
T2a	38 (52.1)	27 (46.6)	10 (62.5)	
T2b	35 (47.9)	31 (53.4)	6 (37.5)	
N stage				0.84
N0	57 (80.3)	48 (82.8)	12 (75.0)	
N1	12 (16.9)	9 (15.5)	4 (25.0)	
N2	2 (2.8)	1 (1.7)	0	
Number of retrieved lymph nodes	9.1±7.2	8.1±5.3	9.3±5.1	0.73
Resection status				0.67
R0	67 (93.1)	56 (96.6)	16 (100)	
R1	5 (6.9)	2 (3.4)	0	
Lymphovascular invasion	17 (23.3)	12 (20.7)	2 (12.5)	0.67
Perineural invasion	14 (19.2)	11 (19.0)	2 (12.5)	0.81
Operation time (min)	225.3±124.7	179.4±85.6	169.3±56.4	<0.001***
Estimated blood loss (cc)	100 [100–300]	100 [100–100]	100 [87.5–100]	0.03*
RBC transfusion	35 (47.9)	7 (12.1)	4 (25.0)	<0.001***
Postoperative stay (days)	10.0±5.1	7.7±4.6	7.7±2.0	0.004**
Complication	13 (17.8)	9 (15.5)	2 (12.5)	0.95
Complication ≥ CD grade IIIa	3 (4.1)	4 (6.9)	0	0.63
Adjuvant treatment				0.49
Chemotherapy	23 (31.5)	15 (25.9)	7 (43.8)	
RT	0	1 (1.7)	0	
CCRT	8 (11.0)	3 (5.2)	1 (6.3)	
Recurrence	22 (30.1)	7 (12.1)	6 (37.5)	0.02*
Liver bed	2 (2.7)	0	0	
Regional lymph node	1 (1.4)	0	0	
Intrahepatic metastasis	9 (12.3)	2 (3.4)	3 (18.8)	
Distant metastasis	9 (12.3)	4 (6.9)	0	
Cancer-related death	17 (23.3)	7 (12.1)	3 (18.8)	0.23
Follow-up (months)	52 [32–77]	54 [39–81]	44 [27–56]	0.33

Values are median [interquartile range], n (%), or mean ± standard deviation. *, P<0.05; **, P<0.01; ***, P<0.001. Group A: <4 weeks; group B: 4–8 weeks; group C: >8 weeks. CD, Clavien-Dindo; CCRT, concurrent chemoradiotherapy; N, node; RBC, red blood cell; RT, radiotherapy; T, tumor.

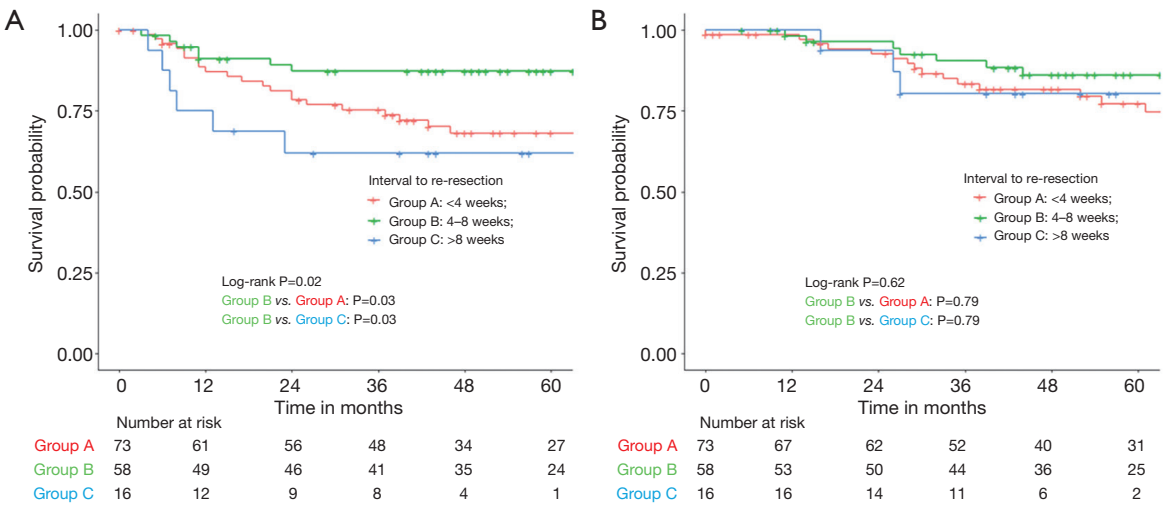

Figure 1 Comparison of survival outcomes according to the interval between initial cholecystectomy and reoperation. (A) Disease-free survival. (B) Disease-specific survival.

different T stages. By confining the study population to pT2 patients, we sought to control for the prognostic impact of T stage and determine the optimal timing for radical reoperation. Using this multicenter cohort of 148 patients with T2 GBC diagnosed after cholecystectomy, we found that early reoperation (<4 weeks after cholecystectomy) was associated with worse perioperative outcomes, whereas delayed reoperation (>8 weeks) was associated with a greater risk of recurrence. To our knowledge, this is one of the largest series focusing on the impact of the timing of reoperation in patients with postoperatively diagnosed T2 GBC.

It is notable that the median duration between the index cholecystectomy and reoperation varied greatly among individual studies. For example, Ethun *et al.* reported a median interval of 7.4 weeks, and only 12% of patients underwent reoperation within 4 weeks (12). By contrast, in a study by Patkar *et al.*, the interval was longer, with a median of 10 weeks; while 19.9% of patients underwent reoperation within 6 weeks, 24.3% underwent reoperation >14 weeks after cholecystectomy (13). In the current study, the median interval between initial cholecystectomy and reoperation was 4.1 weeks, and 49.3% of patients underwent reoperation within 4 weeks. This difference could be explained by the medical care and referral systems unique to each country, such that the timing of reoperation is not only determined by patient factors and the surgeon's decision, but also by physical and geographic barriers to reaching hepatobiliary centers and administrative factors such as long waitlists (18).

Despite the varied timing of reoperation, there is some controversy about the optimal timing of reoperation in terms of improving the survival outcomes of patients with postoperatively diagnosed GBC (19). Goetze *et al.* compared the survival outcomes between patients who did or did not undergo reoperation and found a significant survival benefit in patients who did undergo reoperation (20). In that study, all patients underwent reoperation following the German guidelines, within the first 45 days after initial cholecystectomy. By comparison, Tsirlis *et al.* advocated for delaying reoperation for ≥3 months from the index cholecystectomy because they found that "urgent" reoperation did little to increase the patient's chance of survival (14). In a US multicenter study involving 10 high-volume institutions that analyzed 207 patients with incidentally diagnosed GBC, the authors reported that reoperation at 4–8 weeks was associated with better overall survival than reoperation at <4 or >8 weeks after cholecystectomy (12). In a recent large propensity score-matched study in India, 322 patients who underwent reoperation were divided into four groups according to the interval: 0–6, 6–10, 10–14 , and >14 weeks (13). After matching for baseline T stage, reoperation at 10–14 weeks was associated with superior recurrence-free and overall survival rates.

There is general consensus that early reoperation within 4 weeks after cholecystectomy is associated with ongoing inflammation that could render further resection

Table 3 Cox regression analysis for risk factors of recurrence and cancer-related deaths

Items	Recurrence				Cancer-related death			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Initial CA 19-9								
<37 U/mL	Ref.				Ref.			
≥37 U/mL	1.62 (0.55–4.76)	0.38			1.15 (0.26–5.03)	0.85		
Percutaneous cholecystostomy								
No	Ref.							
Yes	0.05 (0.00–8,053.45)	0.62						
Gallbladder perforation								
No	Ref.				Ref.			
Yes	1.59 (0.38–6.66)	0.53			1.75 (0.41–7.42)	0.76		
Timing of reoperation								
4–8 weeks	Ref.		Ref.		Ref.			
<4 weeks	2.63 (1.12–6.15)	0.03*	2.15 (0.90–5.12)	0.08	1.99 (0.82–4.79)	0.13		
>8 weeks	3.93 (1.32–11.73)	0.01*	4.68 (1.50–14.58)	0.008**	1.82 (0.47–7.08)	0.39		
Operative approach								
Open	Ref.				Ref.			
Laparoscopic	0.87 (0.38–2.00)	0.75			1.04 (0.42–2.58)	0.93		
Liver resection								
No	Ref.				Ref.			
Yes	0.84 (0.36–1.92)	0.68			0.86 (0.33–2.28)	0.76		
Residual tumor								
No	Ref.		Ref.		Ref.		Ref.	
Yes	5.41 (2.77–10.57)	<0.001***	5.35 (2.52–11.35)	<0.001***	5.58 (2.61–11.95)	<0.001***	5.24 (2.25–12.22)	<0.001***
Tumor size								
≤2.0 cm	Ref.				Ref.			
>2.0 cm	0.84 (0.39–1.80)	0.66			0.72 (0.30–1.71)	0.45		
Differentiation								
Well/moderate	Ref.				Ref.			
Poor	1.03 (0.31–3.40)	0.96			1.64 (0.49–5.50)	0.42		
T stage								
T2a	Ref.				Ref.			
T2b	1.52 (0.78–2.96)	0.22			1.36 (0.63–2.95)	0.43		
Lymphovascular invasion								
No	Ref.		Ref.		Ref.		Ref.	
Yes	2.63 (1.30–5.33)	0.007**	1.69 (0.77–3.75)	0.194	2.53 (1.17–5.45)	0.02*	1.24 (0.53–2.92)	0.63
Perineural invasion								
No	Ref.				Ref.			
Yes	2.01 (0.93–4.34)	0.08			1.70 (0.71–4.04)	0.23		

*, P<0.05; **, P<0.01; ***, P<0.001. CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; Ref., reference, T, tumor.

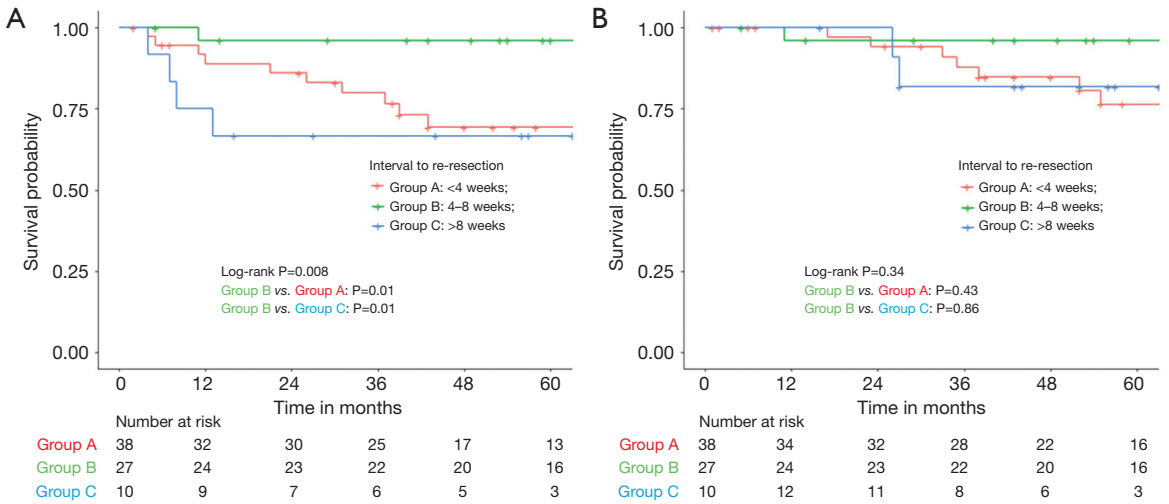

Figure 2 Comparison of survival outcomes according to the interval between initial cholecystectomy and reoperation in T2a patients. (A) Disease-free survival. (B) Disease-specific survival.

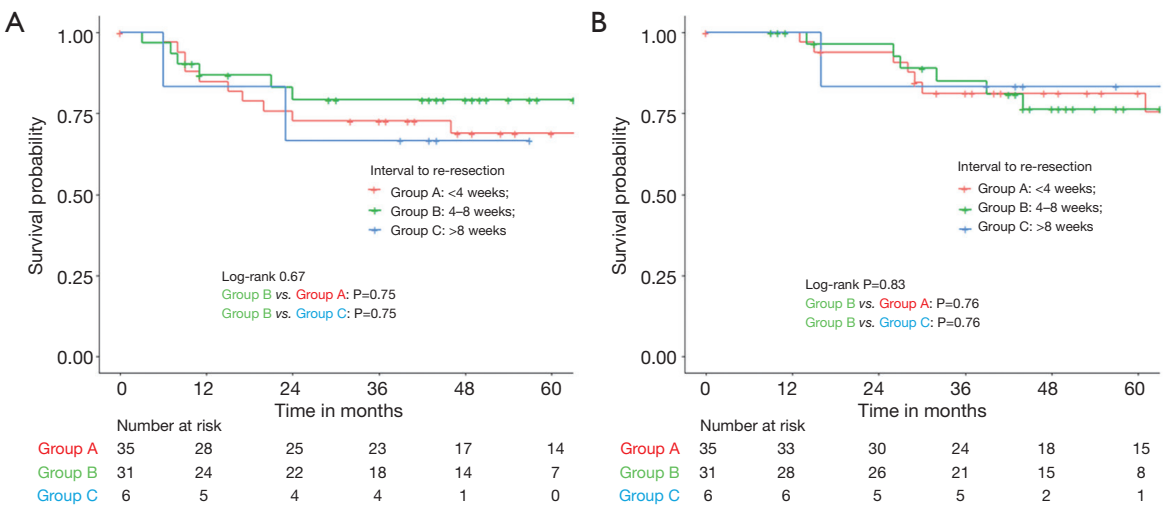

Figure 3 Comparison of survival outcomes according to the interval between initial cholecystectomy and reoperation in T2b patients. (A) Disease-free survival. (B) Disease-specific survival.

technically difficult (11). We found that early (<4 weeks) reoperation was associated with longer operative time, greater estimated blood loss during operation, and higher transfusion rates, which suggests that resection during this period was more challenging. Although we found no difference in complication rate among the three groups, the duration of postoperative hospital stay was significantly longer in the early reoperation group, although it was characterised by younger patients and lower ASA class compared with the other groups. This implies that technical difficulties translate into a greater burden of postoperative recovery on the patient. It is also important to note that earlier reoperation did not have a survival benefit in our study. Another essential aspect to consider is that a short interval between cholecystectomy and reoperation may not allow for complete evaluation of RD, potentially leading to misinterpretation and downstaging of the tumor. Subclinical disease that is already present but not visible might be overlooked during early reoperation, and underestimation of the patient's tumor status could increase the risk of futile

surgery and result in a lost opportunity for potentially beneficial systemic treatment (14).

We should also consider that delaying reoperation for too long might lead to dissemination of the disease beyond a resectable stage. In the current study, delayed (>8 weeks) reoperation was associated with an increased risk of recurrence, even though the three groups showed no differences in their tumor-related characteristics, including T stage, N stage, differentiation, and margin status. However, the percentage of patients with RD at the time of reoperation did not differ between the three groups, which is consistent with the results of other studies. In the US multicenter study, the percentages of patients with RD or distal metastasis at reoperation were similar between patients who underwent reoperation at 4–8 weeks and those who underwent late reoperation at >8 weeks (12). Patkar *et al.* also noted that patients who had RD or metastatic disease on the final pathology report showed similar survival rates irrespective of the timing of reoperation (13). Similarly, patients with RD noted on the final histopathology report after upfront revision surgery also had similar survival outcomes irrespective of the interval to reoperation. However, these findings might be the result of selection bias because only patients who did not develop systemic progression were eligible for reoperation at a delayed time point. Patients with postoperatively diagnosed T2 GBC who presented with unresectable disease were missing from the datasets of all studies, and the proportion of patients for whom a late decision for reoperation led to a lost opportunity of curative surgery remains largely unknown.

Current guidelines recommend reoperation for postoperatively diagnosed GBC based on the T stage, a known risk factor for patient survival (3-5,21). Advanced T stage is also associated with a greater risk of RD (18,22,23). The presence of RD at reoperation was reported to be one of the most critical prognosticators in patients with postoperatively diagnosed GBC (3,20). In the current study, we found that a long interval (>8 weeks) between index cholecystectomy and reoperation and the presence of RD were significant risk factors for recurrence in the multivariable regression analysis. Ultimately, the optimal interval before reoperation should be interpreted as the most effective timing to identify RD, provide accurate staging, and select patients who would benefit from adjuvant systemic treatment after reoperation.

The recurrence-free survival rates of patients with T2 GBC in previous studies varied considerably, ranging from 29% to 70% (24-26). Several studies have shown the survival benefit of extended cholecystectomy in T2 GBC; however, reports on the difference in survival between extended and simple cholecystectomy also vary (26-29). All three groups in the current study had 5-year disease-free survival rates exceeding 60%, which is comparable to the survival rate after extended cholecystectomy for T2 GBC in previous studies. Although this study shows that the interval between initial cholecystectomy and reoperation affects prognosis, it is important to note that reoperation at any time is more beneficial to the patient's outcome than not performing reoperation at all.

This study has some limitations. First, it was limited by its retrospective nature. No prospective studies have evaluated the effect of the interval to reoperation in patients with postoperatively diagnosed GBC, and this is clearly a subject that needs further research. Second, because we only collected data for patients who were eligible for reoperation, there is some selection bias regarding the rate of disease progression after the index cholecystectomy. Many patients are expected to show disseminated disease at restaging, and studies that consider these patients could be useful in terms of developing guidelines for the optimal timing of reoperation. Third, as half of the patients received reoperation within a month, the number of patients in group C was limited. The discrepancy in sample size between groups should be considered in interpreting the results of the current study. Lastly, the differences in overall survival rate did not reach statistical significance in this study, although the recurrence rates were significantly different among the groups. Because we did not fully account for potential confounding factors, including systemic treatment and performance status, the impact of reoperation timing on overall survival in postoperatively diagnosed T2 GBC should be further investigated in large-scale prospective studies.

Conclusions

The results of the current study support that reoperation should not be delayed by more than 8 weeks after the initial cholecystectomy in order to improve oncologic outcomes. Considering the technical difficulties related to early reoperation, a 4- to 8-week interval seems ideal for postoperatively diagnosed T2 GBC. For patients with delayed referral after the initial cholecystectomy, restaging procedures to evaluate the presence of RD and the possibility of disseminated metastasis could be beneficial in

predicting the prognostic value of reoperation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2024-713/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2024-713/coif). H.S.H. serves as an unpaid editorial board member of *HepatoBiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-2211-795-101). All participating institutions (Seoul National University Bundang Hospital, Asan Medical Center, Severance Hospital, Gyeongsang National University Hospital, and Korea University Guro Hospital) were informed and agreed to the study.

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