


Prediction of Early Recurrence After R0 Resection for Gallbladder Carcinoma of Stage T1b–T3

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Purpose: The time-to-tumor recurrence can predict the prognosis of hepatobiliary cancers following curative-intent resection. Therefore, for patients with gallbladder carcinoma (GBC) of stage T1b–T3 who had undergone R0 resection, we investigated the risk factors for early recurrence of GBC and their prognosis.

Patients and Methods: A total of 260 patients with GBC with T1b–T3 disease and an R0 margin were identified. Their clinicopathologic characteristics, perioperative details and prognostic data were reviewed. Survival analyses were carried out using the Kaplan–Meier method. Logistic regression models were used to identify the risk factors for early recurrence.

Results: The optimal cutoff for early recurrence was 29 months. Early recurrence tended to result in relapse far from the primary tumor, and such patients tended to have significantly worse overall survival. Multivariate analysis revealed that T3 disease, N1/N2 stage, poor differentiation of tumor, and lymphovascular invasion (LI) were associated with a greater risk of early recurrence. Patients diagnosed as having GBC incidentally and who had the risk factors of early recurrence were more likely to benefit from re-resection 2–4 weeks after a cholecystectomy.

Conclusion: T3 stage, N1–N2 stage, poor differentiation, and LI were independent risk factors associated with early recurrence for patients with GBC with stage T1b–T3 disease after R0 resection.

Keywords: gallbladder carcinoma, early recurrence, prognosis, re-resection

Introduction

Gallbladder carcinoma (GBC) constitutes 80–95% of all biliary-tract tumors worldwide and is the most prevalent malignancy of the biliary tract.¹ A lack of effective screening and early symptoms have resulted in GBC being discovered incidentally in many patients during or after cholecystectomy for a presumed benign disease [ie, incidental gallbladder carcinoma (IGBC)].^{2–4} The mainstay of curative-intent therapy for GBC is radical resection aimed at achieving an R0 margin. This strategy might involve an extended hepatectomy combined with an adequate lymphadenectomy.^{5,6} However, GBC is a highly malignant tumor characterized by early involvement of lymph nodes and distant metastases. Such aggressiveness results in high prevalence of postoperative recurrence and a dismal prognosis, even after R0 resection.^{7,8}

The timing of recurrence tends to be associated with the long-term survival of GBC cases. Several studies have revealed the impact of early recurrence on the prognosis of numerous hepatobiliary cancers, such as hepatocellular carcinoma, cholangiocarcinoma,

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and pancreatic carcinoma.^{9–11} Sahara et al¹² reported that early recurrence impaired the prognosis of patients with GBC with stage T1–T4 after R0/R1 resection. Kota et al proposed a scoring system incorporating the T stage, margin status, differentiation, and type of liver resection for recurrence prediction. In comparison, only GBCs at stage T1b–T3 necessitating hepatectomy were included in this research, whereas T1a tumors are adequately treated with cholecystectomy alone, and the extent of primary resection is controversial for T4 lesions.^{13,14} Moreover, patients with GBC who had undergone R1 resection were excluded in the current cohort because the R0 margin is of the utmost priority in curative-intent surgery.¹⁵

We aimed to identify the best cutoff period to define early recurrence for patients with GBC with T1b–T3 disease who have undergone R0 resection. In addition, the clinicopathological variables associated with early recurrence were studied. We also investigated if the time interval of re-resection for IGBC affected the prognosis of patients with the risk factors for early recurrence.

Methods

Patient Selection

Data for 260 patients who underwent R0 resection for GBC of stage T1b–T3 between 2004 and 2018 at the West China

Hospital of Sichuan University were analyzed. The exclusion criteria comprised patients: (i) with macroscopically/microscopically positive margins; (ii) with T1a disease or metastatic disease; or (iii) who died <30 days after surgery (Figure 1). Ethical approval for this retrospective research was obtained from the institutional review board of West China Hospital of Sichuan University. Written informed consent was waived because of the retrospective design of the study. This study was conducted in accordance with the Declaration of Helsinki, and all patient data were kept confidential.

Preoperative Workup and Treatments

Systematic assessment and in-depth imaging were conducted in patients suspected of having GBC preoperatively. Surgical management was determined considering the preoperative and intraoperative findings. According to established consensus guidelines, the standard surgical procedure for GBC of stage T1b–T3 in our institute is cholecystectomy and wedge resection of the gallbladder bed or hepatectomy of segments IVb/V.^{16–18} Additional procedures, such as major hepatectomy or pancreatoduodenectomy, were undertaken in cases of tumor invasion of neighboring organs (liver parenchyma, pancreas, and duodenum). Dissection of lymph nodes near the cystic duct, portal vein in the hepatoduodenal

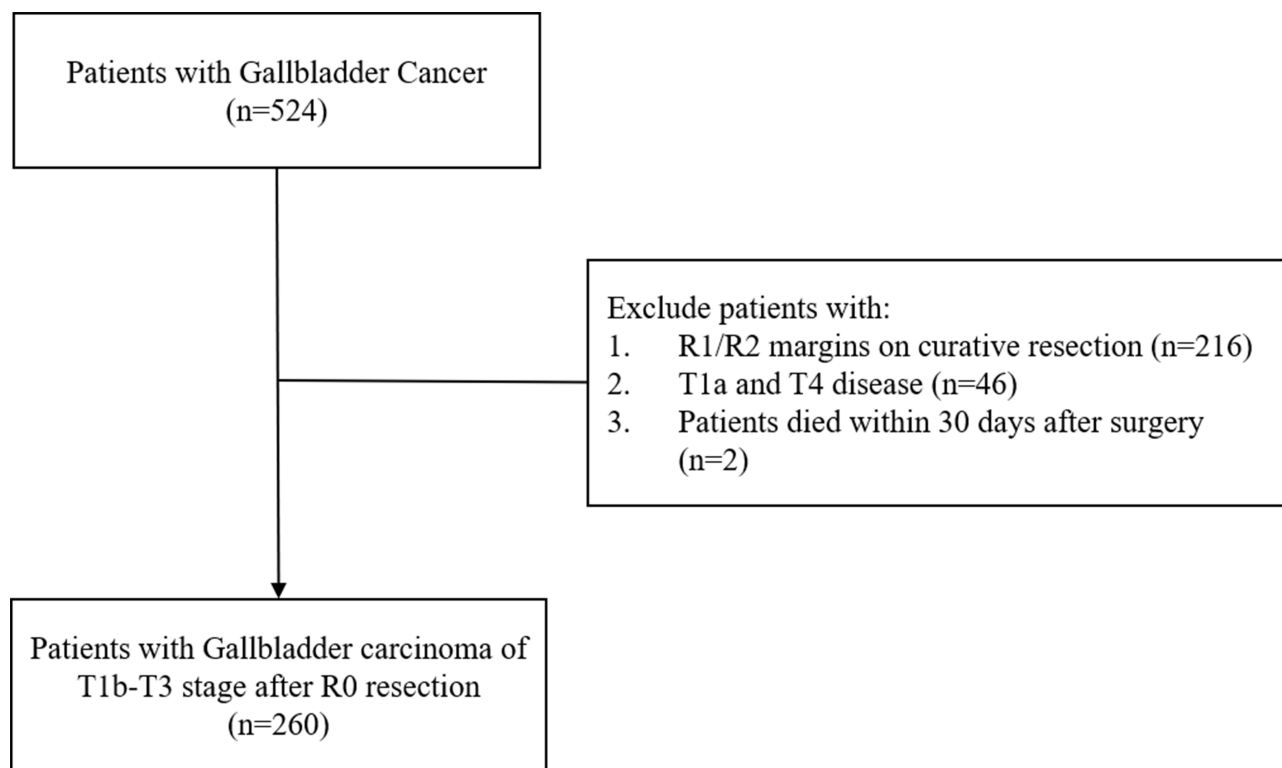


Figure 1 Derivation of the final study cohort.

ligament, and the hilum of the liver has been part of the standard approach for patients with GBC in our hospital for some time. Postoperative complications within 90 days after radical surgery were graded using the Clavien–Dindo classification system.¹⁹ Patients with more than one postoperative complication were determined to have the highest grade of severity.¹⁹

Follow-Up Protocol

Patients were followed up routinely every 3 months for the first 12 months after hospital discharge, and every 6 months beyond the first year.²⁰ Surveillance (liver function, tumor markers, and hepatic ultrasonography) was conducted regularly for all patients in the outpatient department. Imaging (computed tomography, magnetic resonance imaging, and positron emission tomography) and pathology (histology) were undertaken for a definitive diagnosis in patients with suspected tumor recurrence. Recurrence in the surgical bed, porta hepatis, and regional lymph nodes was defined as regional recurrence. Distant recurrence was defined as the discovery of metastasis in the discontinuous liver parenchyma, peritoneum, and other organs.

Data Collection

Details of the demographic features, imaging findings, surgical records, pathology data, and survival outcome of patients after radical surgery were collected and reviewed retrospectively. GBC in resected tumor samples was determined using histopathology reports. Tumor stage was classified according to the eighth edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system. Upon pathology, complete removal of any tumor lesions with microscopically negative margins was defined as a curative resection (R0). Overall survival (OS) was defined as the time from the date of radical surgery to the date of death from any cause or the date of the last follow-up. Disease-free survival (DFS) was measured from the date of curative resection to the date of recurrence or last follow-up.

Statistical Analyses

Continuous variables are described by the median [interquartile range (IQR)] and categorical variables by the frequency (%). Comparisons of continuous variables between two groups were undertaken using Student's *t*-test or Wilcoxon test. Comparisons of categorical factors were carried out using the chi-squared test or Fisher's

exact test. Survival was estimated using the Kaplan–Meier method. Differences were compared between groups using the log-rank test. Univariate and multivariate logistic regression models were used to identify independent factors that were associated with early recurrence. *P* < 0.05 (two-tailed) was considered significant. Data analyses were carried out using SPSS 19.0 (IBM, Armonk, NY, USA).

Results

Characteristics of the Study Population

The characteristics of the entire cohort are provided in Table 1. A total of 260 patients (79 males and 181 females) with a median age of 64 (IQR, 53–70) years underwent R0 resection for GBC of grade T1b–T3. The median body mass index was 23.5 (IQR, 20.2–25.3) kg/m². The preoperative

Table 1 Characteristics of the Entire Cohort (n = 260)

Variable	Value
Age (years)	64 (53–70)
Sex	
Male	79 (30.4%)
Female	181 (69.6%)
Body mass index (kg/m ²)	23.5 (20.2–25.3)
ASA score	
≤2	118 (45.4%)
>2	142 (54.6%)
Preoperative bilirubin (mg/dL)	0.8 (0.5–1.3)
Preoperative albumin (g/L)	40.4 (36.8–43.1)
Preoperative CA19-9 (U/mL)	16.7 (8.2–45.5)
Preoperative CEA (ng/mL)	3.2 (2.3–5.7)
Second surgical procedure	65 (25.0%)
Type of liver resection	
Partial hepatectomy *	245 (94.2%)
Major hepatectomy	15 (5.8%)
Total number of lymph nodes evaluated ^a	5 (1–19)
Number of positive lymph nodes ^a	0 (0–9)
Tumor diameter (cm)	3.2 (1.2–4.3)
AJCC stage	
I/II	172 (66.2%)
III/IV	88 (33.9%)
Duration of surgical procedure (min)	200 (155–270)
Estimated blood loss (mL)	380 (180–580)
Blood transfusion	42 (16.2%)
Any complication	54 (20.8%)
Severe complication (Clavien–Dindo class >II)	30 (11.5%)
Duration of hospital stay (days)	11 (10–14)
Duration of postoperative hospital stay (days)	7 (6–9)

Note: *Wedge resection of the gallbladder fossa or resection of IVb/V segments; ^aMedian (range).

Abbreviations: ASA, American Society of Anesthesiologist; AJCC, American Joint Committee on Cancer; CA19-9, cancer antigen 19–9; CEA, carcinoembryonic antigen.

albumin level was 40.4 (IQR, 36.8–43.1) g/L. A subset of cases underwent re-resection (n = 65, 25.0%). At the time of radical surgery, the type of resection consisted primarily of cholecystectomy with partial hepatic resection (n = 245, 94.2%). Resection of regional lymph nodes was performed routinely in all patients. The median number of harvested lymph nodes and positive lymph nodes was 5 (range, 1–19) and 0 (range, 0–9), respectively. Pathologically, most patients had tumors at stage I/II according to the AJCC classification (n = 172, 66.2%), with a median tumor diameter of 3.2 (IQR, 1.2–4.3) cm. Postoperatively, 54 patients had at least one complication, and the overall morbidity was 20.8%; 30 individuals (11.5%) developed major complications (Clavien–Dindo class > II).

Survival Outcomes and Definition of Early Recurrence

Median OS for the entire cohort was 45.5 months. OS at 1, 3, and 5 years was 91.9%, 63.5%, and 33.8%, respectively. At a median follow-up of 50.5 months, 84 (32.3%) patients experienced tumor recurrence after treatment; among them, 35.7% (n = 30) developed a local recurrence alone, while 40.5% (n = 34) and 23.8% (n = 20) experienced either a distant recurrence alone or both local and distant recurrence, respectively. The liver parenchyma (n = 22, 26.2%) was the most prevalent site of relapse. To determine the optimal cutoff point for early recurrence and late recurrence, recurrence prevalence was calculated at 6-month intervals. According to the intercept value of the two curves identified by linear regression, 29 months was defined as the cutoff to distinguish early recurrence from late recurrence for GBC (Figure 2A). The majority (n = 69, 82.1%) of recurrence occurred within 29 months after surgery (early recurrence), with the remaining (n = 15, 17.9%) cases were discovered beyond 29 months (late recurrence). OS of patients with GBC who experienced early recurrence was markedly lower than that of patients who experienced late recurrence (P < 0.001) (Figure 2B). Moreover, patients who experienced early recurrence were more likely to have distant metastasis than those who had late recurrence (P = 0.022) (Figure 2C).

Risk Factors Associated with Early Recurrence of GBC

The results of univariate and multivariate analysis for early recurrence are summarized in Table 2. Univariate analysis revealed the positive predictors of early recurrence to be cancer antigen 19–9 > 40 U/mL, high T category, high N category,

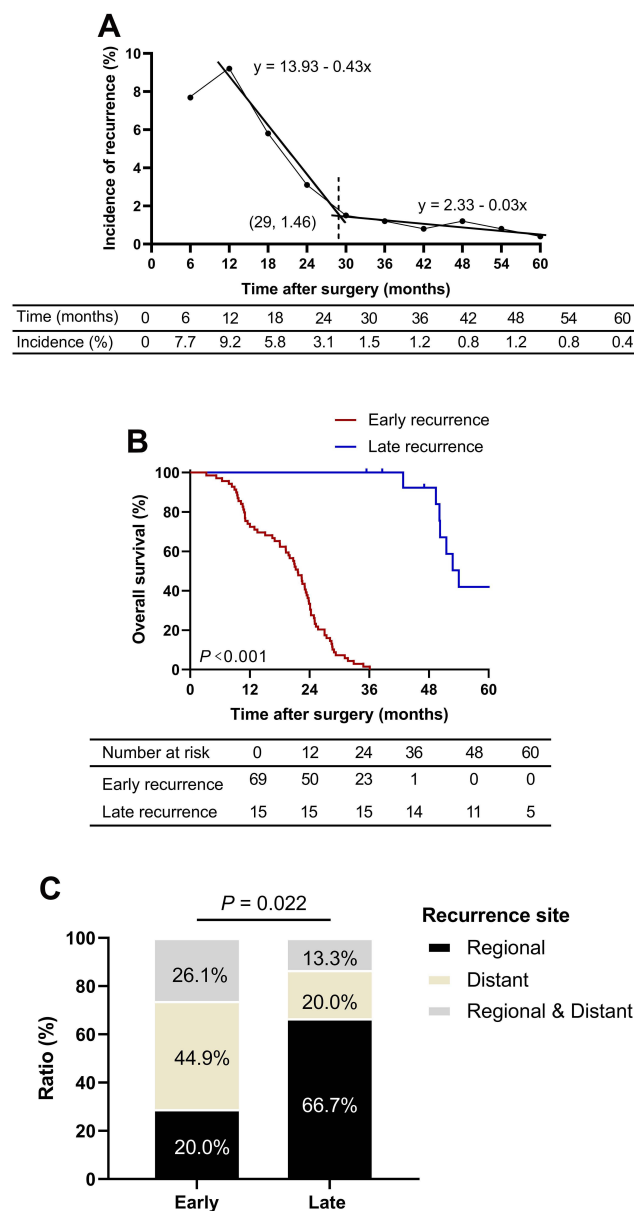


Figure 2 (A) Recurrence prevalence after R0 resection for GBC patients at 6-month intervals; (B) overall survival of an early-recurrence group and late-recurrence group of GBC patients who underwent R0 resection; (C) sites of recurrence stratified by early versus late recurrence.

poor differentiation, lymphovascular invasion (LI) and perineural invasion. Multivariate analyses of the logistic regression model revealed T3 stage, N1–N2 stage, poor differentiation, and LI as independent risk factors associated with early recurrence following R0 resection of GBC of stage T1b–T3.

Subgrouping of Patients with IGBC

Patients with IGBC who underwent re-resection were separated into three subgroups according to the time interval from the date of initial cholecystectomy to the date of radical resection: A (<2 weeks), B (2–4 weeks), and C (>4 weeks).

Table 2 Analysis of the Factors Associated with Early Recurrence Among Patients Undergoing R0 Resection for Gallbladder Carcinoma of Stage T1b–T3

Variable	Univariate Analysis			Multivariate Analysis	
	Early Recurrence Group	29-Month Recurrence-Free Group	P	HR (95% CI)	P
Age (years)			0.656		
≤60	30	89			
>60	39	102			
Sex			0.534		
Male	23	56			
Female	46	135			
CA19-9 (U/mL)			0.048	Reference	
<40	37	128			
≥40	32	63		1.446 (0.750–2.785)	0.271
CEA (ng/mL)			0.553		
<5	48	140			
≥5	21	51			
Second resection			0.168		
Yes	13	52			
No	56	139			
Tumor diameter (cm)			0.569		
<2	23	71			
≥2	46	120			
T category (AJCC)			<0.001	Reference	
T1b	10	35			
T2	28	127		1.212 (0.478–3.072)	0.686
T3	31	29		3.162 (1.014–7.852)	0.047
N category (AJCC)			<0.001	Reference	
N0	31	162			
N1/N2	38	29		3.699 (1.712–7.995)	0.001
Histology grade			0.015	Reference	
Well/moderate	47	157			
Poor	22	34		2.432 (1.180–5.012)	0.016
Lymphovascular Invasion			<0.001	Reference	
Negative	41	155			
Positive	28	36		2.796 (1.409–5.546)	0.003
Perineural Invasion			0.054	Reference	
Negative	56	172			
Positive	13	19		1.686 (0.670–4.242)	0.267
Type of liver resection			0.224		
Partial hepatectomy *	63	182			
Major hepatectomy	6	9			

Note: *Wedge resection of the gallbladder fossa or resection of hepatic segments IVb/V.

Abbreviations: HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen.

Table 3 shows the comparative analyses of clinicopathological factors across these three subgroups. There was no difference in baseline demographics or tumor-related factors

between the three subgroups ($P > 0.05$ for all). The 5-year OS was comparable among groups A, B, and C ($P > 0.05$ for all) (Figure 3A), as was DFS ($P > 0.05$ for all) (Figure 3B).

Table 3 Clinicopathologic Features of Patients with Incidental Gallbladder Carcinoma Stratified by Time Interval of Treatment After Initial Resection

Variable	Group A (<2 Weeks)	Group B (2–4 Weeks)	Group C (>4 Weeks)	P
Age (years)				0.449
≤60	10	15	9	
>60	12	9	10	
Sex				0.763
Male	7	8	8	
Female	15	16	11	
Body mass index (kg/m ²)				0.709
≤25	14	15	14	
>25	8	9	5	
ASA score				0.489
≤2	9	14	9	
>2	13	10	10	
Residual disease				0.412
Positive	6	9	9	
Negative	16	15	10	
Type of liver resection				0.243
Partial hepatectomy*	22	21	17	
Major hepatectomy	0	3	2	
T category (AJCC)				0.296
T1b	4	1	5	
T2	15	17	10	
T3	3	6	4	
N category (AJCC)				0.332
N0	18	19	12	
N1/N2	4	5	7	
Tumor diameter (cm)				0.169
<2	6	12	5	
≥2	16	12	14	
Histology grade				0.440
Well/moderate	19	17	15	
Poor	3	7	4	
Lymphovascular invasion				0.848
Positive	7	6	6	
Negative	15	18	13	
Perineural invasion				0.487
Positive	3	2	4	
Negative	19	22	15	

Note: *Wedge resection of the gallbladder fossa or resection of hepatic segments IVb/V.

Abbreviations: ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on Cancer.

Patients with IGBC were further divided into two groups based on the presence or absence of the risk factors associated with early recurrence. For patients with IGBC with risk factors, the 5-year OS of group B was significantly higher than that of the groups A and C ($P < 0.05$) (Figure 4A), and the 5-year DFS in group B was significantly higher than that in groups A and C ($P < 0.05$ for both) (Figure 4B). For patients with IGBC without the risk factors associated with early

recurrence, OS and DFS were not significantly different among the groups ($P > 0.05$ for all) (Figure 4C and D).

Discussion

Radical surgery aiming to achieve R0 resection is the only curative treatment for GBC. However, because of its aggressive local infiltration and early metastasis, the prevalence of postoperative recurrence of GBC has been

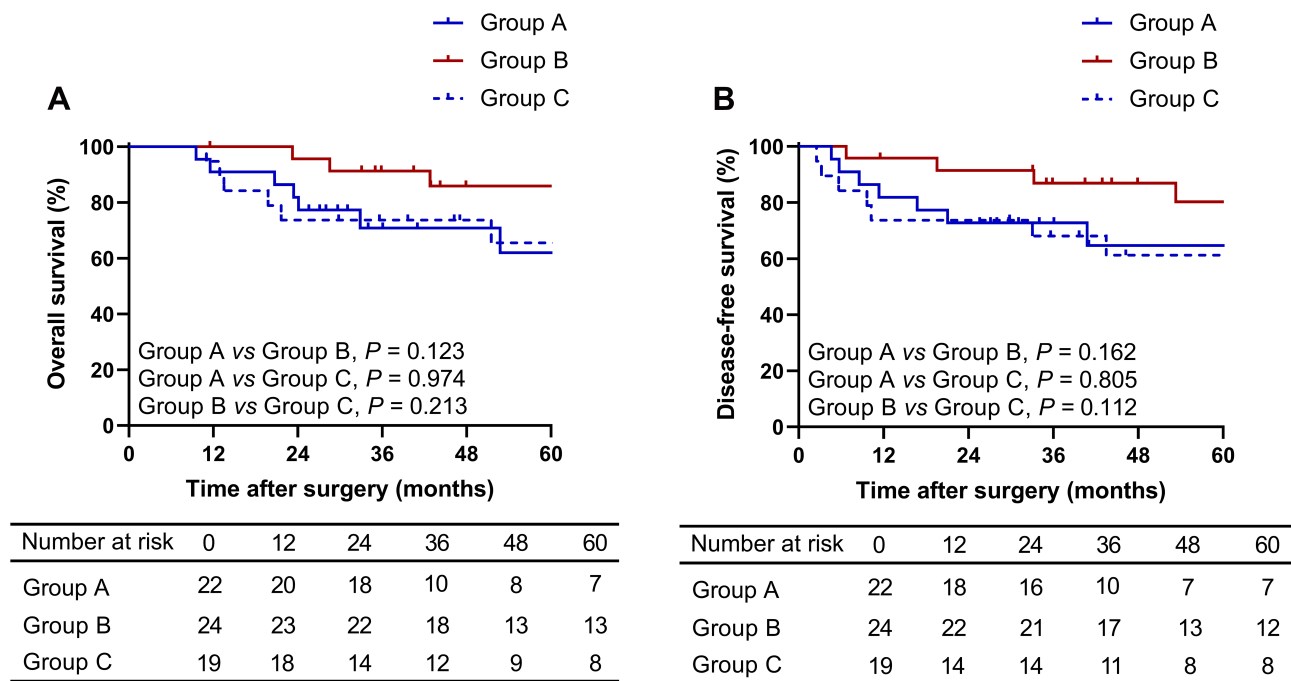


Figure 3 (A) Overall survival of IGBC patients stratified by the time interval of repeat resection; **(B)** disease-free survival of IGBC patients stratified by the time interval of repeat resection.

reported to be 25–65%.^{7,21} Several studies have demonstrated the association between early recurrence and poor prognosis for patients with hepatobiliary carcinoma.^{9–11} Although the recurrence patterns of patients with GBCs after R0 resection have been revealed in some studies, little is known about the predictive factors of early recurrence.

Our cohort comprised patients with GBC with T1b–T3 disease who had undergone R0 resection. We calculated 29 months as being the optimal cutoff to distinguish early recurrence from late recurrence. Perhaps unsurprisingly, the 5-year OS of patients in the early recurrence group was significantly shorter than that of patients in the late recurrence group. In addition, early recurrence tended to occur in a location distal to the primary tumor, whereas regional recurrence was more prevalent in the late recurrence group. This phenomenon has been demonstrated in other cancer types, but until now, it has not been reported for GBC.^{10,22}

Sahara et al evaluated patients with GBC with T1–T4 disease and found that major hepatectomy was a prognostic factor for early recurrence when compared with minor hepatectomy involving segments IVB/V.¹² In our cohort, however, major hepatectomy failed to remain a risk factor of early recurrence for patients with GBC with T1b–T3 disease. This inconsistency could reflect the

variation in patient selection. As mentioned above, cholecystectomy alone is sufficient for GBC of stage T1a, whereas radical resection for a T4 lesion is controversial,²³ thus neither of these two stages were included in our cohort. Besides, a subset of patients with stage T1b–T2 disease underwent hepatic wedge resection in our institute, whereas in the study by Sahara et al, minor hepatectomy referred solely to resection of IVB/V segments.¹² Kwon et al²⁴ demonstrated that patients with T2 lesions who had wedge resection of liver tissue around the gallbladder bed had comparable long-term survival to those who underwent resection of hepatic IVB/V segments. Therefore, wedge resection and resection of IVB/V segments were classified as “partial hepatectomy” in our study, and patients who underwent partial hepatectomy had a similar prevalence of early recurrence as those who had major hepatectomy. The scope of liver resection for GBC should be performed according to the T stage. We hypothesized that it is the T stage, rather than the scope of liver resection, that affects the risk of early recurrence in patients with GBC. We also discovered that the tumors in the early-recurrence group had more advanced T categories than those in the non-early-recurrence group. This result emphasized the importance of an adequate scope of resection to achieve long-term survival of patients with GBC.

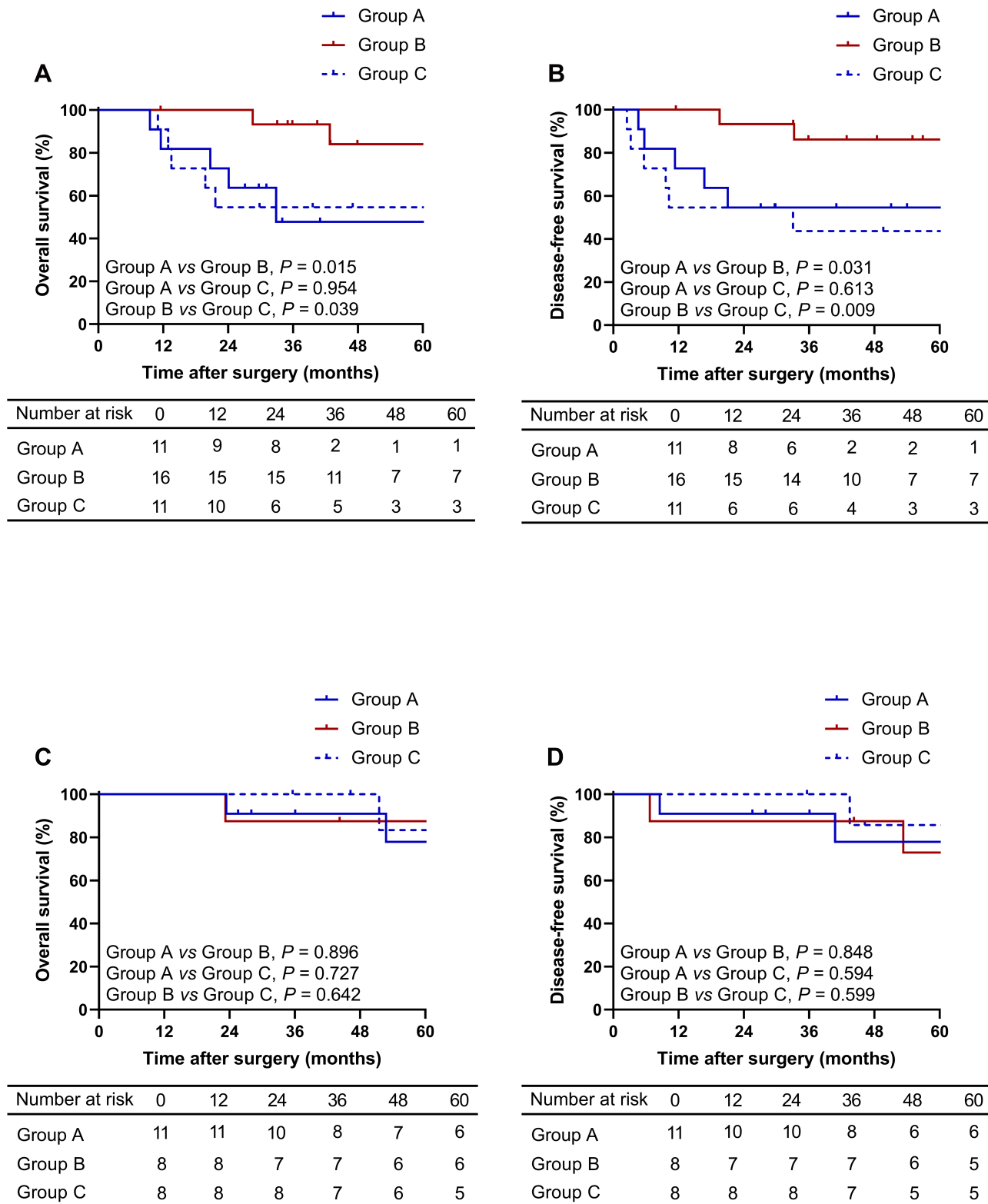


Figure 4 (A) Overall survival of IGBC patients with the risk factors of early recurrence stratified by the time interval of repeat resection; (B) disease-free survival of IGBC patients with the risk factors of early recurrence stratified by the time interval of repeat resection; (C) overall survival of IGBC patients without the risk factors of early recurrence stratified by the time interval of repeat resection; (D) disease-free survival of IGBC patients without the risk factors of early recurrence stratified by the time interval of repeat resection.

To date, most guidelines for GBC have recommended routine follow-up with a 3-month interval during the first 2 years after curative-intent therapy, and a 6-month interval thereafter, up to 5 years.^{25,26} However, there is no research supporting a specific surveillance schedule for patients with GBC nor has there been any study focusing on the impact of regular follow-up on prognosis. The present study demonstrated that more than 80% of recurrence occurred within 29 months after resection (early recurrence), typically in a location distant from the primary tumor site. Therefore, a more intense follow-up schedule in the first 2.5 years after surgery might be required for patients with T1–T3 stage GBC with early-recurrence-related risk factors, namely T3 stage, N1/N2 stage, positive LI, and poor differentiation.

GBC that is diagnosed by pathology during or after resection for a presumed benign disease is defined as IGBC and accounts for about 50–70% of all cases of GBC.^{27,28} Avoidance of a secondary surgical procedure requires frozen-section histopathology during cholecystectomy; however, this is not feasible for all hospitals in view of the increased medical expenditure and operative time.²⁹ For IGBC diagnosed postoperatively, few studies have focused on the timing of repeat resection. For example, the timing of radical resection after initial treatment has been studied in cancers of the esophagus and rectum, yet the primary focus has been on the timing between resection and neoadjuvant therapy.^{30,31} A multicenter study suggested that the optimal time interval for IGBC diagnosed postoperatively is 4–8 weeks.³² He et al³³ showed that patients with IGBC diagnosed postoperatively at an interval of 2–4 weeks had a longer OS than those with an interval of <2 weeks or >4 weeks. However, in our study, there was no significant difference between groups A, B, and C. Notably, important risk factors, such as T stage, N stage, differentiation, and LI, were also similar among the subgroups. When excluding patients without the risk factors of early recurrence, patients with IGBC in group B had longer survival than those in group A and group C. We assumed that for IGBC with the risk factors of early recurrence, a time interval <2 weeks might not be sufficient to evaluate and stage the tumors due to misinterpretation of frozen section analysis and imaging analysis in the setting of acute inflammation, whereas IGBC with time interval >4 weeks might carry a higher risk of tumor dissemination. The two aspects mentioned above might have contributed to early recurrence and resulted in a worse prognosis. For patients with IGBC without any

of the risk factors of early recurrence, the prognoses of patients in groups A, B, and C were comparable. Hence, these patients did not benefit from preoperative imaging or a timely secondary surgical procedure to the same extent as those with risk factors. In brief, this finding emphasizes the gravity of complete preoperative tumor evaluation and timely performance of radical resection, especially for those with potential risk factors. However, a significant bias might have been present in the survival analyses of the time interval because the number of patients in the three subgroups was small. A better definition of the correct timing of a secondary surgical procedure following cholecystectomy requires additional research.

Our study had three main limitations. First, it had a retrospective design, comprising data from a single tertiary center, whereas data from a multi-institution analysis would be less biased and more reliable. Second, some vital clinicopathological information was not recorded and analyzed in our study. The location of a T2 tumor, for instance, has been shown to be an important prognostic factor;³⁴ however, this was absent from our histology reports. Third, only 39 patients with IGBC had the risk factors for early recurrence; therefore, a larger scale study is needed to identify the variables that determine the optimal timing of a secondary surgical procedure.

Conclusions

T3 stage, N1–N2 stage, poor differentiation, and LI were identified as independent risk factors associated with early recurrence in patients with GBC with stage T1b–T3 disease after R0 resection. IGBC patients with risk factors undergoing re-resection between 2 and 4 weeks after the initial cholecystectomy had superior survival compared with those within 2 weeks or beyond 4 weeks. Moreover, intense follow-up schedule might be recommended for those with early-recurrence-related risk factors in the first 2.5 years after surgery.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval Statement

Ethical approval for this retrospective research was obtained from the institutional review board of West China Hospital of Sichuan University. Written informed consent was waived because of the retrospective design of

the study. This study was conducted in accordance with the Declaration of Helsinki, and all patient data were kept confidential.

Consent for Publication

The authors confirm that the details of any images, videos, recordings, etc. can be published, and that the person(s) providing consent have been shown the article contents to be published.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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