

ORIGINAL ARTICLE

Incidental gallbladder cancer after laparoscopic cholecystectomy: incidence, management, and prognosis

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Abstract

Aims: Although incidental gallbladder cancer (IGBC) diagnosed after laparoscopic cholecystectomy (LC) is not rare, its incidence, management, and prognosis are still unclear and controversial. The present study aimed to increase the understanding of IGBC after LC in the medical community.

Methods: Patients with IGBC treated at our institution between January 2001 and December 2018 were enrolled. Data collected included demographic characteristics, treatment pattern, pathological information, and prognoses. We compared the characteristics of patients with different prognoses and calculated the cumulative overall survival rate and mean survival period for IGBC.

Results: The cohort comprised 26 patients with a mean age of 66.4 ± 12.5 years. All patients were diagnosed with IGBC via postoperative pathology. Three patients underwent radical reoperation. As of June 2019, 26 patients were followed for a mean of 31.6 ± 29.6 months. Fourteen patients died during the follow-up period, and 12 survived without recurrence. The mean survival duration was 50.5 months. The 1-, 3-, and 5-year cumulative overall survival rates of the entire cohort were 79.8, 49.0, and 40.8%, respectively. IGBC patients with T1a stage had significantly longer survival than those with T1b or more advanced stages (96.1 vs 32.6 months, $P = .006$).

Conclusions: IGBC after LC is diagnosed in 0.2% of patients, accounting for 5.4% of all gallbladder cancer cases. IGBC patients with T1a stage had significantly longer survival than those with T1b or more advanced stages. Simple cholecystectomy is probably acceptable only in T1a lesions.

KEYWORDS

incidental gallbladder cancer, laparoscopic cholecystectomy, prognosis, reoperation, risk factor

1 | INTRODUCTION

Gallbladder cancer (GBC) is the most common neoplasm of the biliary tract and the third most common cancer of the gastrointestinal tract.^{1,2} Its incidence is particularly high in South America and Asia, where there are high rates of cholecystitis and salmonella infection, both of which are reported as risk factors for GBC.²⁻⁴ In China, more than 50 000 incident cases and more than 40 000 deaths due to GBC are reported each year.⁵ The 5-year survival rate of GBC is less than

5%.^{6,7} In addition to poor biological behavior, the low early diagnosis rate is also an important cause of poor prognosis. Because GBC is generally asymptomatic in the early and middle stage of disease, approximately 50 to 70% of GBC are diagnosed incidentally during or after elective cholecystectomy, which accounts for approximately 0.7% of all cholecystectomy specimens.⁸⁻¹⁰ This kind of GBC that is unsuspected preoperatively and diagnosed during or after cholecystectomy is called incidental gallbladder cancer (IGBC).¹¹

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Laparoscopic cholecystectomy (LC) has become the gold standard surgical procedure for cholecystectomy because of its convenience and safety. For patients diagnosed with benign disease before and during LC, postoperative pathological examination may still suggest IGBC. However, the exact incidence, proper management, and possible prognosis of IGBC after LC remain unclear and controversial. The present study aimed to clarify the incidence, management, and prognosis of IGBC after LC to ultimately increase its understanding and improve patient outcomes. Toward this goal, we retrospectively reported 26 patients with IGBC after LC treated at our facility. We analyzed their clinical features and explored the management methods and prognosis. Differences between patients with different prognoses were compared and analyzed. We also compared the differences between patients with IGBC after and during LC.

2 | METHODS

2.1 | Patients

The medical records of patients who underwent LC at our hospital between January 2001 and December 2018 were reviewed retrospectively. The inclusion criteria were: (1) benign disease was diagnosed via ultrasonography or computed tomography (CT) preoperatively, (2) the patient underwent LC at our facility, (3) IGBC was confirmed via postoperative pathology, and (4) the patient either underwent radical reoperation or consented to close follow-up at our hospital. Patients were excluded if they were preoperatively or intraoperatively suspected of having GBC. Clinical data were collected from both outpatient and inpatient medical records by two independent doctors. A retrospective database containing demographic features, laboratory and imaging tests, underlying diseases, operation information, pathological results, and prognoses was constructed and analyzed.

2.2 | Treatment and follow-up

All patients underwent ultrasonography or CT before surgery. No antibiotic or laxative was administered. Surgery was conducted under general anesthesia in all cases, and LC was executed using the three-trocar technique. An endopouch was routinely used when retrieving the gallbladder to protect portsite. Intraoperative frozen section was performed if suspicious lesion was found via macroscopic inspection and palpation of the gallbladder. All specimens were examined by two to three different pathologists.

For patients with IGBC after LC, radical reoperation was recommended for T1b and more advanced lesions except those with serious underlying disease. Both the benefits and risks of reoperation and close follow-up were explained to patients with T1a stage (ie, the tumor invading only the lamina propria), and the management strategy was decided according to the patients' preference. For patients who consented to radical reoperation, the revisional procedure included wedge resection of the gallbladder bed, regional lymph node dissection of

the hepatoduodenal ligament, and lymph node dissection around the pancreatic head and duodenum. Complications were defined as any abnormal event recorded within 30 days after surgery and classified according to the Clavien-Dindo classification of surgical complications.¹² Outpatient interviews and telephone calls were used for follow-up. All patients were followed up every 3 months during the first postoperative year, and every 6 months thereafter. Reexamination included ultrasonography, CT, and blood test.

2.3 | Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences software (version 25.0, IBM Corp., Armonk, NY, USA). Continuous variables had been confirmed as being normally distributed before presentation and were presented as mean \pm standard deviation. Categorical variables were shown as absolute number or frequency. Differences between groups were analyzed using Student's *t* test, χ^2 test, or Fisher's exact test as appropriate. Logistic multivariate regression analyses were performed to identify independent risk factors for poor prognosis of IGBC. Survival probability was estimated using the Kaplan-Meier method with log-rank test. A *P*-value of $<.05$ was considered statistically significant.

2.4 | Ethics

The present study was approved by the Peking Union Medical College Hospital Institutional Review Board (S-K951). All patients or their legal guardian provided written informed consent for the surgical procedures performed. The requirement of informed consent for publication of data was waived owing to the retrospective nature of the study.

3 | RESULTS

3.1 | Patient characteristics

Between January 2001 and December 2018, a total of 11 589 patients underwent LC at our hospital. Of these, 26 patients (0.2%) with IGBC after LC were included in this study (Figure 1). During the same period, a total of 480 patients with GBC were admitted to our hospital, and the 26 patients with IGBC after LC accounted for 5.4%. The demographic data and preoperative symptoms of the enrolled patients are presented in Table 1. The most common symptom was abdominal pain, occurring in 16 patients (61.5%). The age and sex distribution are presented in Figure 2. IGBC was more common among women and older patients.

3.2 | Preoperative findings

All patients underwent imaging examination and blood tests before surgery. Ultrasonography was performed in 26 patients (100%), CT in 11 (42.3%), magnetic resonance cholangiopancreatography in six (23.1%), and endoscopic retrograde cholangiopancreatography in one

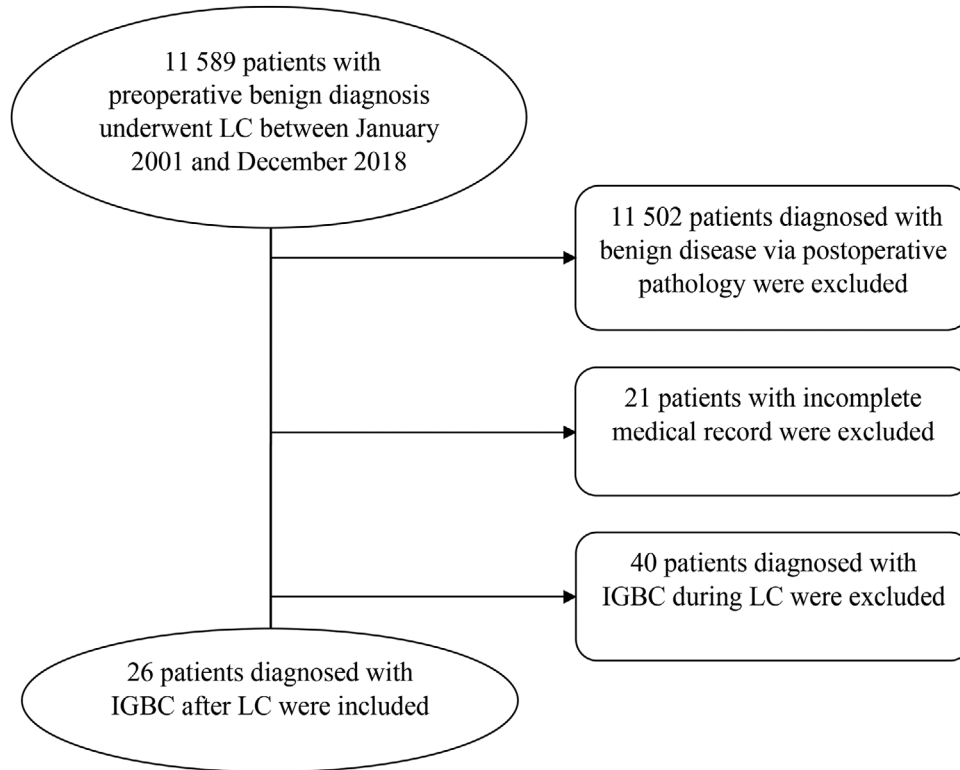


FIGURE 1 Flow diagram of patient selection. IGBC, incidental gallbladder cancer; LC, laparoscopic cholecystectomy

TABLE 1 Demographic data and preoperative symptoms in patients with IGBC after LC

Characteristic	Value
Gender	n (%)
Male	12 (46.2)
Female	14 (53.8)
Age (years)	66.4 ± 12.5
Range	49-89
BMI (kg/m ²)	23.4 ± 2.9
Symptoms	n (%)
Abdominal pain	16 (61.5)
Jaundice	2 (7.7)
None	10 (38.5)

BMI, body mass index; IGBC, incidental gallbladder cancer; LC, laparoscopic cholecystectomy.

(3.8%). All the imaging examinations revealed cholelithiasis, cholecystitis, or gallbladder polyp without blood flow. No preoperative malignancy was suspected. Carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were tested in 19 patients (73.1%). CA 19-9 levels were elevated in two patients (35.0 and 47.2 U/mL; reference range, 0-34.0 U/mL), while CEA levels were elevated in three patients (5.1, 5.2, and 6.6 ng/mL; reference range, 0-5.0 ng/mL). All patients with abnormal CA 19-9 or CEA levels underwent preoperative CT to rule out malignancies.

3.3 | Surgical outcomes

All LC procedures were successfully completed without conversion to laparotomy. Postoperative complications occurred in two patients. One patient had urinary retention, which was managed using catheterization. The other patient had fever and was treated with antipyretics. These complications were classified as grade I following the Clavien-Dindo classification of surgical complications. All patients were diagnosed with IGBC via postoperative pathology within a mean of 6.3 ± 2.8 days (range: 3 to 13 days) after LC. Three patients underwent radical reoperation, and the other 23 patients only consented to close follow-up. Of the 23 patients who did not undergo reoperation, 13 patients were classified to have T1b or more advanced disease, and 9, 2, and 2 patients of them refused reoperation due to advanced age (≥70 years), underlying disease, and fear of surgery risk, respectively. As of June 2019, 26 patients were followed for a mean of 31.6 ± 29.6 months (range: 3-107 months). Fourteen patients died during the follow-up period due to tumor-related diseases. The remaining 12 patients survived without recurrence. The treatment and prognosis of IGBC patients with different T-stages are summarized in Table 2.

3.4 | Risk factors of poor prognosis

To analyze potential risk factors associated with poor prognosis, the patients were divided into two groups for analysis: the survival group and the nonsurvivor group. The former included patients who were still alive at the last follow-up ($n = 12$). The latter included patients

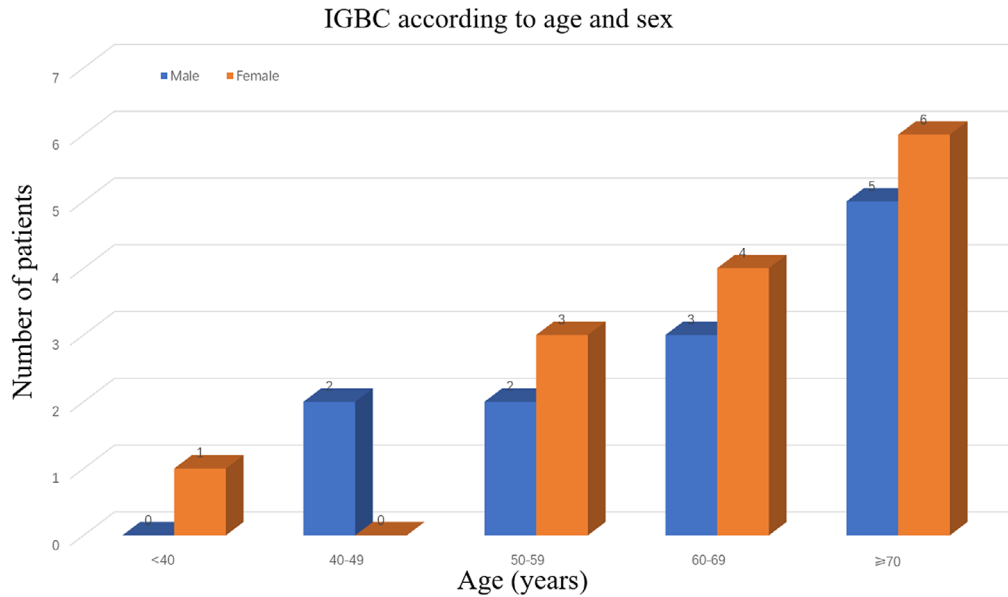


FIGURE 2 Incidence of IGBC according to age and sex. IGBC was more common among women and older patients. IGBC, incidental gallbladder cancer [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Treatment and prognosis of the IGBC patients according to T-stage

T-stage ^a	Total (n = 26)	Reoperation (n = 3)	Survival (n = 12)	Nonsurvivor (n = 14)
T1a	10	0	9	1
T1b	3	0	1	2
T2	4	1	1 ^b	3
T3	9	2	1	8 ^c

IGBC, incidental gallbladder cancer.

^aAccording to the AJCC 2018 TNM classification, 8th edition.

^bUnderwent reoperation.

^cIncluding the two patients who underwent reoperation.

who had died during the follow-up period ($n = 14$). Table 3 shows the comparison of the demographic characteristics, symptoms, underlying diseases, test results, follow-up information, and pathological results between the two groups. Elderly patients had significantly higher risk of poor prognosis. Meanwhile, IGBC patients with T1a stage disease had significantly better prognosis than patients with other stages. Multivariate logistic regression analysis was performed with those variables found significant in univariate analysis (Table 4). However, no variable proved to be independently associated with poor prognosis.

The cumulative overall survival rate for IGBC patients with any T-stage was shown in a Kaplan–Meier curve (Figure 3A). The 1-, 3-, and 5-year cumulative overall survival rates of the entire cohort were 79.8, 49.0, and 40.8%, respectively. The mean survival period was 50.5 months. The cumulative overall survival rates calculated separately according to T-stage are shown in Figure 3B. The mean survival periods of patients with T1a, T1b, T2, and T3 IGBC were 96.1, 32.5,

TABLE 3 Comparison of IGBC patients according to prognoses

	Survival (n = 12)	Nonsurvivor (n = 14)	P-value
Male/female (n)	5/7	7/7	.713
Age (years)	56.3 ± 8.3	75.1 ± 8.1	<.001
BMI (kg/m ²)	23.9 ± 2.1	22.9 ± 3.4	.377
Abdominal pain (n)	6	10	.422
Jaundice (n)	0	2	.483
Diabetes (n)	2	1	.580
Hypertension (n)	2	7	.110
CA 19-9 level >34.0 U/mL (n)	1	1	1.000
CEA level > 5.0 ng/mL (n)	0	3	.225
ASA grade ≥III (n)	0	3	.225
Hospital stay (days)	8.0 ± 4.9	10.4 ± 4.2	.200
Reoperation (n)	1	2	1.000
Follow-up time (m)	36.7 ± 32.8	27.2 ± 27.1	.428
T1a stage ^a	9	1	.001

ASA, American Society of Anesthesiologists; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; IGBC, incidental gallbladder cancer.

^aAccording to the AJCC 2018 TNM classification, 8th edition.

TABLE 4 Univariate and multivariate analysis for risk factors of poor prognosis

	Survival (n)	Nonsurvivor (n)	P-value	
			Univariate	Multivariate
Old age (≥70 years)	0	11	<.001	.999
T-stage (≥T1b)	3	13	.001	.199

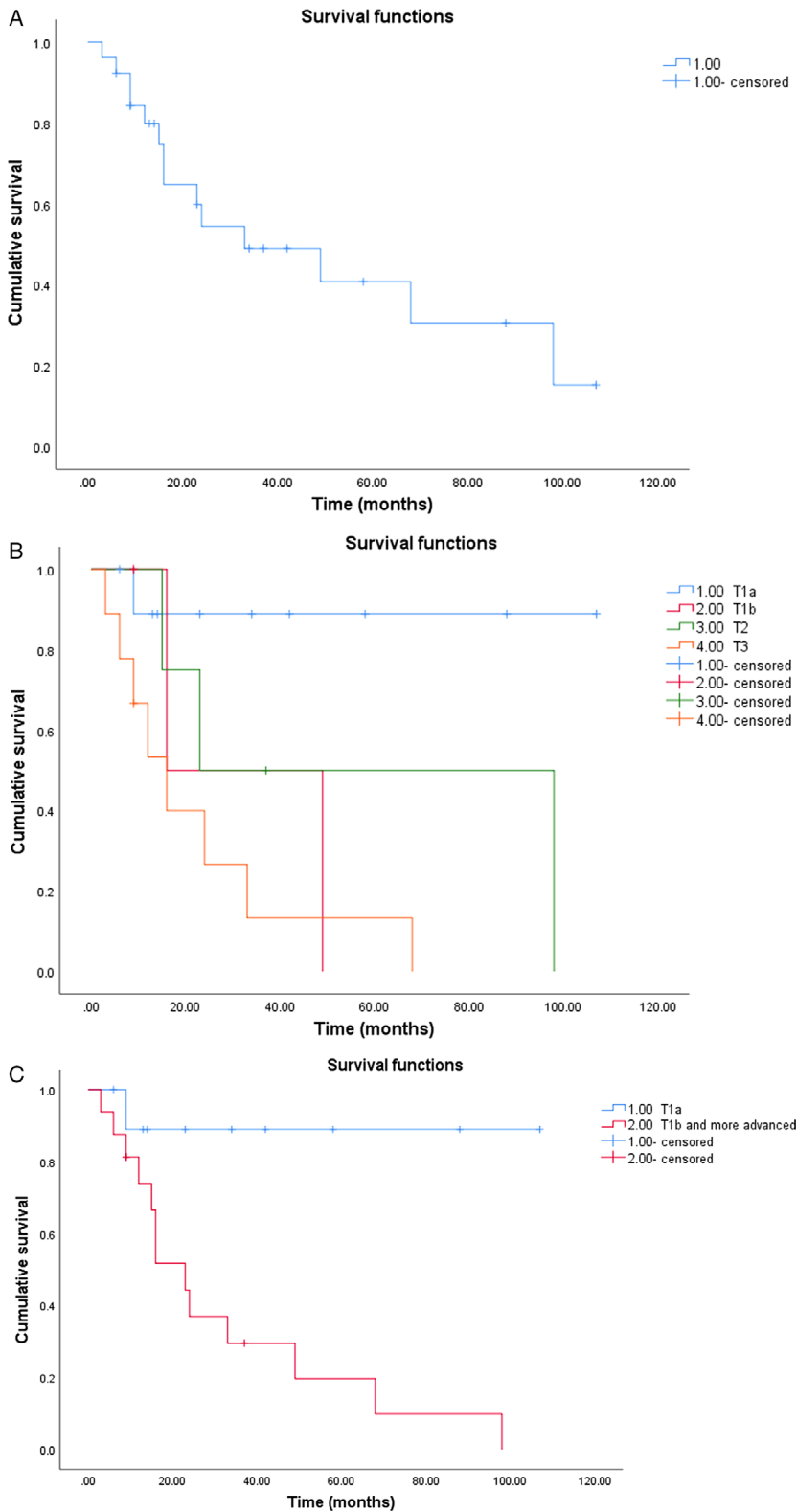


FIGURE 3 Kaplan–Meier survival curve for IGBC patients. The 1-, 3-, and 5-year cumulative overall survival rates of IGBC were 79.8, 49.0, and 40.8%, respectively (A). The mean survival period was 50.5 months for the entire cohort, and 96.1, 32.5, 58.5, and 22.4 months for patients with T1a, T1b, T2, and T3 stage disease, respectively (B). IGBC patients with T1a stage had significantly longer survival than those with T1b or more advanced stages (96.1 vs 32.6 months, $P = .006$) (C) [Colour figure can be viewed at wileyonlinelibrary.com]

58.5, and 22.4 months, respectively. Because the number of patients with T1b and T2 disease was too small and the curves in Figure 3B overlap, T1b, T2, and T3 stages were combined into one group and compared with T1a stage (Figure 3C). IGBC patients with T1a stage had significantly longer survival than those with T1b or more advanced stages (96.1 vs 32.6 months, $P = .006$).

3.5 | Differences between IGBC after and during LC

During the patient selection process, we also found 40 patients diagnosed with IGBC during LC. Thirteen of them underwent radical operation. As of June 2019, all 40 patients were followed for a mean of 45.4 ± 35.8 months (range: 6–149 months). Twenty-one patients died

TABLE 5 Comparison of IGBC patients discovered postoperatively and intraoperatively

	IGBC after LC (n = 26)	IGBC during LC (n = 40)	P-value
Male/female (n)	12/14	18/22	.927
Age (years)	66.4 ± 12.5	65.1 ± 11.7	.670
BMI (kg/m ²)	23.4 ± 2.9	24.5 ± 3.6	.183
Abdominal pain (n)	16	21	.470
Radical operation (n)	3	13	.052
Follow-up time (m)	31.6 ± 29.6	45.4 ± 35.8	.106
Survival/nonsurvivor (n)	12/14	19/21	.915
T-stage ^a			.107
T1a	10	6	
T1b	3	9	
T2	4	13	
T3	9	11	
T4	0	1	

BMI, body mass index; IGBC, incidental gallbladder cancer; LC, laparoscopic cholecystectomy.

^aAccording to the AJCC 2018 TNM classification, 8th edition.

during the follow-up period, and 19 patients survived without recurrence. The differences between patients with IGBC after and during LC are compared in Table 5. Patients with IGBC discovered intraoperatively were more likely to accept radical operation than those with IGBC discovered postoperatively (32.5, 13/40 vs 11.5, 3/26); however, the difference was not statistically significant ($P = .052$).

4 | DISCUSSION

GBC is an aggressive malignancy with poor prognosis. Due to the particularity of anatomic location and atypical symptoms, both the early diagnosis rate and preoperative diagnosis rate of GBC are not high, and IGBC is not uncommon. In the present study, the incidence of IGBC after LC is 0.2%, and that accounts for 5.4% of all GBC cases. These rates are lower than those in the literature⁸⁻¹⁰ and may be because we gave profound importance to preoperative imaging examination, intraoperative palpation, and frozen pathology when necessary. Compared with intraoperative IGBC, postoperative IGBC often causes greater psychological and physical trauma to patients because it involves reoperation.

Current guidelines recommend reoperation for IGBC after LC for T1b, T2, and T3 lesions.¹³ Yamaguchi et al reported that IGBC patients with T1b or T2 disease who underwent resection had significantly better 5-year disease-specific survival rate than those who did not undergo additional operation.¹⁴ Different researchers have reported various modalities for IGBC according to the tumor stage. Glauser et al suggested extended resection of the regional lymph nodes and gallbladder bed for IGBC patients after LC with T2 and T3 disease.¹⁵ Meanwhile, Tian et al recommended radical resection for IGBC patients with T1b or more advanced stage.¹⁶ In the

present study, radical reoperation was recommended for T1b or more advanced lesions, unless contraindicated by poor performance status or advanced underlying disease. However, only 3 of 16 patients consented to reoperations. The patients refused reoperation primarily due to advanced age (9/13, 69.2%), and this may be related to the old mean age in this study (66.4 ± 12.5 years).

In the analysis of possible risk factors associated with poor prognosis, old age and advanced T-stage were found significant in univariate analysis. Older patients generally have worse health conditions, recover more slowly after surgery, and are more likely to choose a more conservative treatment. However, neither proved to be independently associated with poor prognosis in multivariate analysis, and this may be related to the limited number of patients in this study. Nevertheless, Kaplan–Meier analysis with log-rank test to calculate the mean expected survival period of IGBC patients according to T-stage showed significant differences. The T-stage is crucial in the prognosis of GBC as it directly indicates tumor prognosis.^{2,6,17,18} Patients with T1a lesion survived significantly longer than those with T1b or more advanced lesions. Several previous studies reported that patients with T1a IGBC could achieve long-term survival via simple cholecystectomy.^{1,19-21} Similarly, in the present study, all the 10 T1a patients underwent LC only, and 9 of them (90.0%) survived without recurrence.

In the present study, the mean survival period of all IGBC patients was 50.5 months, and the 1-, 3-, and 5-year cumulative overall survival rates were 79.8, 49.0, and 40.8%, respectively, and these rates are markedly better than those reported for GBC in the literature^{6,7,22-25} As mentioned above, the T-stage is directly related to the prognosis of GBC. Higher-stage tumors, particularly T3 or T4 tumors, are easier to be detected on preoperative imaging examination and intraoperative observation. This explains the high rate of early stage tumors in IGBC after LC. In the present study, T1a disease accounted for 38.5% (10/26) of all cases. Consequently, the expected survival period and cumulative overall survival rate of patients diagnosed with IGBC after LC are much better than those of GBC in general.

A major feature of this study is that the majority of patients (23/26, 88.5%) did not undergo reoperation. Therefore, the prognosis of patients in the present study can basically reflect the natural course of IGBC. Of the 23 patients who did not undergo reoperation, 9 of 10 (90.0%) patients with T1a survived without recurrence, one of three (33.3%) for T1b, zero of three (0.0%) for T2, and one of seven (14.3%) for T3. This result also proves that simple cholecystectomy is feasible only in T1a lesion.

There are some limitations to this study. First, the number of patients, registration information, and variables assessed are limited by its retrospective design. Second, due to the limited patient volume, IGBC with different T-stages cannot be discussed and compared separately. Third, the small number of patients who underwent reoperation did not allow for an evaluation of the prognostic impact of this factor. Multicenter, prospective, and controlled clinical trials are needed to confirm our findings.

In conclusion, IGBC after LC has an incidence of 0.2%, and this accounts for 5.4% of all GBC cases. IGBC was more common in older and female. The 1-, 3-, and 5-year cumulative overall survival rates

of IGBC after LC were 79.8, 49.0, and 40.8%, respectively. The mean survival period was 50.5 months. IGBC patients with T1a stage had significantly longer survival than those with T1b or more advanced stages (96.1 vs 32.6 months, $P = .006$). Simple cholecystectomy is probably feasible only in T1a lesion.

CONFLICT OF INTERESTS

All authors declare no conflict of interests.

ETHICAL APPROVAL

The present study was approved by the Peking Union Medical College Hospital Institutional Review Board. The requirement of informed consent for publication of data was waived owing to the retrospective nature of the study.

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