ORIGINAL RESEARCH

A Comparison Between the Prognosis of Simultaneous and Salvage Radical Resection in Incidental Gallbladder Cancer

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Purpose: Incidental gallbladder cancer (IGBC) is defined as gallbladder cancer (GBC) that is accidentally discovered during cholecystectomy to treat benign lesions. We aimed to compare the prognosis of IGBC patients who underwent simultaneous radical resection (SIR) vs salvage radical resection (SAR).

Patients and Methods: We retrospectively reviewed data for IGBC patients admitted to Sir Run Run Shaw Hospital from January 2000 to May 2016. Survival analysis was performed using Kaplan–Meier (univariate) and COX regression (multivariate) analyses.

Results: Eighty-four patients with IGBC underwent radical resection; 43/84 underwent SIR, and 41/84 underwent SAR. Compared with SIR, the SAR group was more likely to receive comprehensive preoperative radiographic evaluation, port-site excision, and have more lymph nodes excised (all $P < 0.05$). Kaplan–Meier analysis indicated that the prognosis in the SAR group was better than that in SIR (overall survival: $P = 0.050$, recurrence-free survival: $P = 0.028$). Regression analysis indicated that the type of radical resection (SIR/SAR) was not an independent prognostic factor (overall survival: $P = 0.737$, recurrence-free survival: $P = 0.957$).

Conclusion: Patients undergoing SAR had non-inferior survival compared with SIR. It is possible that patients in SAR underwent preoperative radiographical evaluations more comprehensively and the surgical operations were more well performed.

Keywords: incidental gallbladder carcinoma, simultaneous surgery, salvage surgery, prognosis

Introduction

Gallbladder cancer (GBC) is a type of rare cancer worldwide, and the incidence varies geographically, with higher rates of occurrence in parts of South America and Central and Eastern Asia. The incidence is also high in Hispanic and certain indigenous populations in the americas.[1] Due to insidious symptoms, most GBC cases are diagnosed at an advanced stage, with an estimated 5-year survival rate of 5–14%.[2–4] Currently, surgical resection is the only option to achieve long-term survival in GBC, and adjuvant therapy helps prolong patient survival.[5,6]

Incidental gallbladder cancer (IGBC) is defined as GBC that is unexpectedly discovered in patients undergoing cholecystectomy for benign gallbladder diseases. IGBC was first reported in 1961 by Marcial-Rojas et al[7]. With the extensive use of laparoscopic cholecystectomy, the incidence of IGBC has been increasing.[8] For IGBC staged ≥ T1b, simple cholecystectomy results in residual cancerous lesions,

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and causes disease progression and early recurrence.[9–11] In patients with this stage of IGBC, standardized radical resection should be performed, namely, partial liver parenchymal resection (wedge resection of the gallbladder bed or IVb-V segmental hepatectomy), and lymphatic dissection in the porta hepatis. In cases of IGBC involving extrahepatic bile ducts, resecting the common bile duct and bilioenteric anastomosis may be performed.[12] However, routine resection of extrahepatic ducts in GBC is not supported by current evidence.[13,14]

When diagnosed by frozen section intraoperatively, radical resection for IGBC should be performed simultaneously. However, when IGBC is discovered in the postoperative pathological examination, a secondary operation, salvage radical resection (SAR) should be considered. This study aims to compare the prognosis of IGBC patients who underwent simultaneous radical resection (SIR) with those who underwent SAR. We hypothesized that survival after SAR is worse than that after SIR. The major reason for this hypothesis was that SAR involves a delay between the cholecystectomy and radical resection, and there is a risk of cancerous dissemination during this delay.

Patients and Methods

We retrospectively evaluated the medical records of all GBC patients in Sir Run Run Shaw Hospital (SRRSH) between January 2000 and May 2016. Study approval was obtained from the Ethical Committees for Human Subjects at SRRSH, which is affiliated with Zhejiang University, China. Two criteria were used to identify IGBC cases. First, patients were preoperatively diagnosed with benign gallbladder diseases (stone, polyp, adenomyosis) with no sign of malignancy in preoperative radiographic examinations (ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI)). Second, the diagnosis of GBC was confirmed by intraoperative frozen section or postoperative pathological examination. We excluded patients who did not undergo radical resection or who were failed to follow-up within three months.

Clinical and pathological characteristics were collected from the patients' medical records. Pathological staging was based on the American Joint Committee on Cancer (AJCC) 7th edition classification. Although the AJCC classification was updated to the 8th edition, it was difficult to subdivide stage T2 cases into the T2h and T2p subgroups according to the 8th edition based on the medical or pathological records in our center; therefore, the 7th edition classification was applied in our study.

Patients' survival data were obtained from the medical records and regular follow-up. The latest date for follow-up was June 15th, 2019. We used Pearson's χ^2 test or Fisher's exact test for the categorical data to compare the distributions of the clinicopathological variables, and the Mann–Whitney U-test for continuous variables. Univariate survival analysis was performed using the Kaplan–Meier method (Log-rank test). Variables with $P < 0.10$ were entered into the multivariate Cox regression model. All analyses were performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). A $P < 0.05$ was considered statistically significant.

Results
Selection Process

From January 2000 to May 2016, 728 patients were diagnosed with GBC in SRRSH, and 169 cases were identified as IGBC. The detail of the selection process is summarized in Figure 1.

Sixty-nine IGBC cases were diagnosed intraoperatively by frozen sections. Amongst the 69 patients, one was diagnosed as Tis and two was diagnosed as T1a by frozen section, which required no further resection. There were six patients refused to undergo further resection intraoperatively, and 15 patients were unsuitable for the curative resection due to the disseminated metastases or unresectable lesions, namely, four patients with hepatic metastases, five patients with peritoneal metastases, two patients with extensive lymphatic metastases, one patient with invasion to the portal vein, one patient with invasion to both the liver and common bile duct, one patient with invasion to the duodenum, and one patient with colonic invasion. Consequently, 45 patients underwent further resection with curative intent, including one patient undergoing R2 resection (unresectable invasion into the pancreas was identified during the resection), and one withdrawal within three months. Finally, 43 patients underwent concurrent radical resection and constituted the SIR group, including two patients with R1 resection (pathological examination suggested positive cystic duct margins) (Figure 1).

One hundred IGBC cases were diagnosed postoperatively. Among the 100 patients, nine were diagnosed as Tis, and two were diagnosed as T1a by pathological examinations, and cholecystectomy alone was considered sufficient. Forty-five patients were considered to have disseminated metastases, unresectable lesions, or the patient declined to undergo reoperation. Therefore, 44
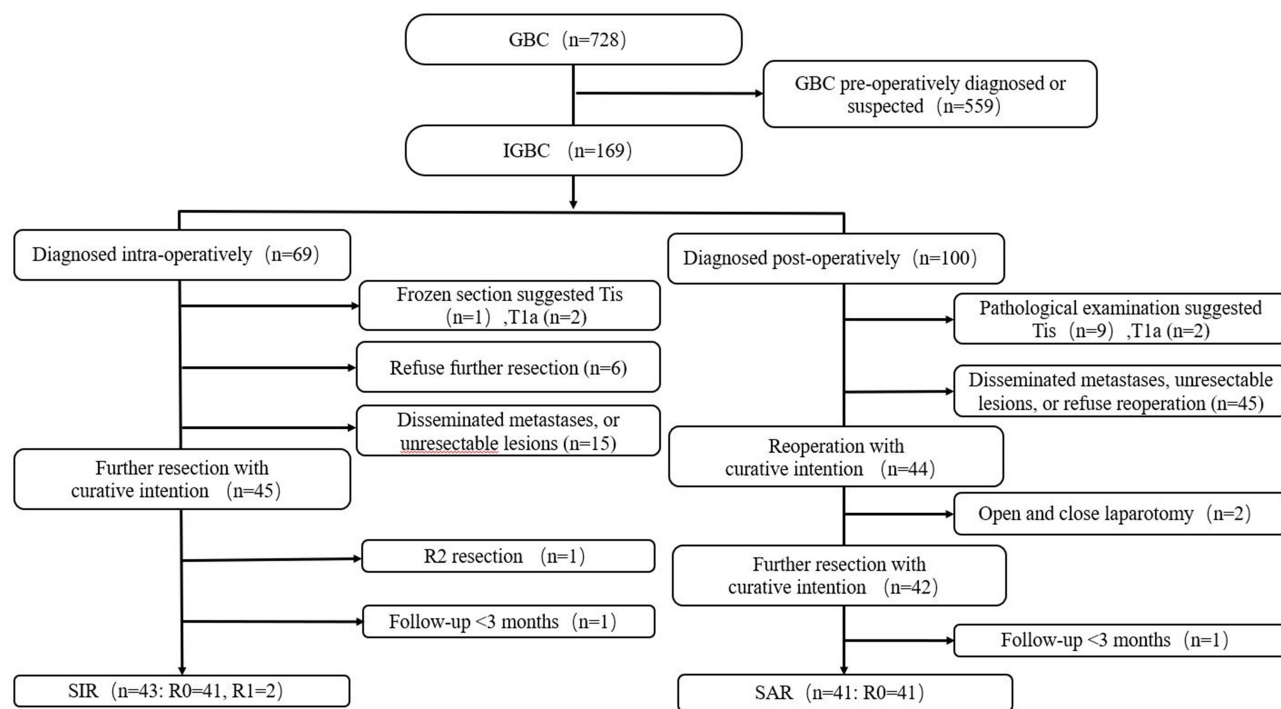
Figure 1 Selection process for incidental gallbladder cancer patients.

patients underwent reoperation with curative intent, among which two of the 44 patients had peritoneal metastases identified during abdominal exploration, and their surgeons aborted the plan for further resection (open-and-close laparotomy). Forty-two patients went through the radical resection (R0), and one patient withdrew at three months. Consequently, 41 patients were constituted the SAR group (Figure 1).

Patients' Clinicopathological Characteristics

The median age of all 84 patients (SIR + SAR groups) was 60 years (range: 38–84 years). Sixty-eight patients (81.0%) were women. Based on ultrasonographic examination, 66 patients (78.6%) had gallstones, 11 patients (13.1%) had polyps, five patients (6.0%) had both gallstones and polyps, and two patients (2.4%) had adenomyosis. All patients underwent laparoscopic cholecystectomy first. Eighty-two radical resections were performed via laparotomy (97.6%), while two patients (2.4%), one in the SIR group and one in the SAR group, underwent total laparoscopic radical resection. Pathological examination reported six patients (7.1%) as stage T1b, 62 patients (73.8%) as stage T2, and the remaining 16 patients (19.0%) as stage T3. Seventeen patients (20.2%) had lymphatic metastases, nine patients

(10.7%) had nerve invasion, and six patients (7.1%) had microvascular invasion.

The patients' clinicopathological variables are shown in Table 1. The preoperative nutritional status of the two groups, as indicated by albumin, did not differ significantly (P = 0.607). The SAR group was more likely to have received comprehensive preoperative radiographic evaluation (enhanced abdominal CT/MRI), port-site excision and more lymph nodes dissected intraoperatively (all $P < 0.05$). Additionally, the SAR group (21/41, 51.2%) was more likely to have had more than six harvested lymph nodes vs the SIR group (10/43, 23.3%) (P = 0.015). It should be noted that there was no significant difference in T stage and lymph node metastasis between the two groups. Therefore, we believe that the two R1 cases in the SIR group were accidental, rather than caused by more advanced tumors.

Survival Analysis

The 1-year, 3-year, and 5-year overall survival (OS) rates in the SIR group were 74.4%, 50.4%, and 41.4%, respectively, compared with 90.2%, 70.6%, and 62.4% in the SAR group. Kaplan–Meier analysis indicated that the OS in the SAR group was better than SIR group (P = 0.050; Table 2 and Figure 2).

Table I Comparison of the Clinicopathological Variables Between Patients Undergoing SIR vs SAR

Variables	SIR Group	SAR Group	P-value
Age (Median, range)	58 (38–84)	59 (39–76)	0.497
Sex			0.314
Male	10	6	
Female	33	35	
Albumin (Median, range)	40.2(31.5–51.3)	40.1(26.0–49.1)	0.607
Enhanced CT/MR examination			<0.001
Yes	9	41	
No	34	0	
Surgical procedures			0.321
Hepatic wedge resection + lymphadenectomy of porta hepatis	42	37	

Hepatic wedge resection
     +resection of common bile duct
     +choledochojejunostomy
     +lymphadenectomy of porta hepatis
	1	3	

Hepatic segmental resection (V, VI, VII) +lymphadenectomy of porta hepatis	0	1	
Port-site resection			0.001
Yes	0	10	
No	43	31	
Dissected lymph node (Median, range)	5 (1–14)	6 (1–23)	0.009
Dissected lymph nodes (cut-off level as 6)			0.015
>6	10	20	
≤6	33	21	
T stage			0.253
T1b	5	1	
T2	29	33	
T3	9	7	
Lymphatic metastasis			0.138
Present	12	6	
Absent	31	35	
Grade of differentiation			0.899
G1	21	22	
G2	5	4	
G3&G4	17	15	
Nerve invasion			0.125
Present	8	3	
Absent	35	38	
Microvascular invasion			0.266
Present	6	2	
Absent	37	39	
Adjuvant therapy			0.884
Yes	13	13	
No	30	28	

Abbreviations: SIR, simultaneous radical resection; SAR, salvage radical resection; CT, computed tomography; MR, magnetic resonance.

Table 2 Univariate Analysis for Prognostic Variables in IGBC

Variables	Comparison	OS		RFS	
		χ^2	P-value	χ^2	P-value
Age	≤65 vs >65	0.020	0.967	0.122	0.727
Sex	Male vs Female	1.416	0.234	0.258	0.611
Enhanced CT/MR examination	Yes vs No	4.278	0.038*	4.714	0.030*
Type of radical resection	SIR vs SAR	3.853	0.050*	4.822	0.028*
Port-site resection	Yes vs No	1.938	0.164	2.089	0.148
T stage	T1b vs T2 vs T3	23.927	<0.001*	19.786	<0.001*
Lymphatic metastases	Present vs Absent	14.924	<0.001*	12.568	<0.001*
Dissected lymph nodes	≤6 vs >6	2.608	0.106	3.351	0.067*
Grade of differentiation	G1 vs G2 vs G3&G4	13.909	0.001*	13.240	0.001*
Nerve invasion	Present vs Absent	1.004	0.316	2.863	0.091*
Microvascular invasion	Present vs Absent	13.416	<0.001*	12.829	<0.001*
Adjuvant therapy	Yes vs No	0.543	0.474	0.830	0.362

Note: *Variables with P-value <0.10, and further analyzed with COX model.
Abbreviations: OS, overall survival; RFS, recurrence-free survival; vs, versus; SIR, simultaneous radical resection; SAR, salvage radical resection; CT, computed tomography; MR, magnetic resonance.

The 1-year, 3-year, and 5-year recurrence-free survival (RFS) rates in the SIR group were 60.5%, 40.8%, and 35%, respectively, compared with 82.9%, 62.7%, and 62.7% in the SAR group. Kaplan–Meier analysis indicated that the RFS in the SAR group was better than SIR group (P = 0.028; Table 2 and Figure 3).

In the regression analysis, T stage, lymphatic metastasis, and grade of differentiation were independent prognostic factors (all P < 0.05), while the type of radical resection (SIR/SAR) was not (OS: P = 0.737, RFS: P = 0.957; Table 3).

Time Interval Analysis

In the SAR group, the time interval from the date of initial cholecystectomy to the date of salvage operation differed by subgroup. We divided the SAR group into three groups: intA group, with an interval of < two weeks (11 patients); intB group, with an interval between two and four weeks (19 patients); and intC group, with an interval > four weeks (11 patients). Survival analysis showed that the prognosis of the intB group was statistically superior to that of the SIR group (P < 0.05). However, there were no statistical differences between the SIR and intA groups (P = 0.797). We also found no statistical difference between the SIR and intC groups (P = 0.192; Figure 4).

Discussion

It is estimated that 50–70% of GBCs are diagnosed accidentally by the pathological examination during or after surgery,[10,15,16] and these cancers are termed IGBC. The incidence of IGBC after cholecystectomy is 0.25%-3%.[17,18] Performing frozen section histopathology is the most effective way to detect IGBC intraoperatively and minimize the likelihood of secondary surgery. However, reckoning that cholecystectomy is a mature technique and globally performed as routine procedure, the increased medical costs and prolonged operative time caused by the use of frozen section histopathology is considerably high.[19,20] Some researchers held the opinion that IGBC occurred rarely in macroscopically normal cholecystectomy specimens, and a "selective strategy" was adopted based on the macroscopic abnormalities of the gross specimens.[21–25] In SRRSH, we used frozen section histopathology selectively in laparoscopic cholecystectomies. Every gross gallbladder specimen was examined by the chief surgeons, and intraoperative frozen section histopathology was performed when a cancerous lesion was suspected, for instance, when the gallbladder wall was thickened or there was a mass invading the gallbladder mucosa. However, it was concerned that tumor size in patients undergoing SIR may be larger than that of SAR. Therefore, we compared patients' clinicopathological characteristics between the SIR and SAR groups (Table 1) and found no significant differences in T stage, lymphatic metastasis, grade of differentiation, and microvascular and nerve invasion (all P > 0.05). Furthermore, we used a COX regression model to adjust for the effect of potential confounding covariates.

To our knowledge, it is the first time that the outcome of patients undergoing SAR were directly compared with SIR.
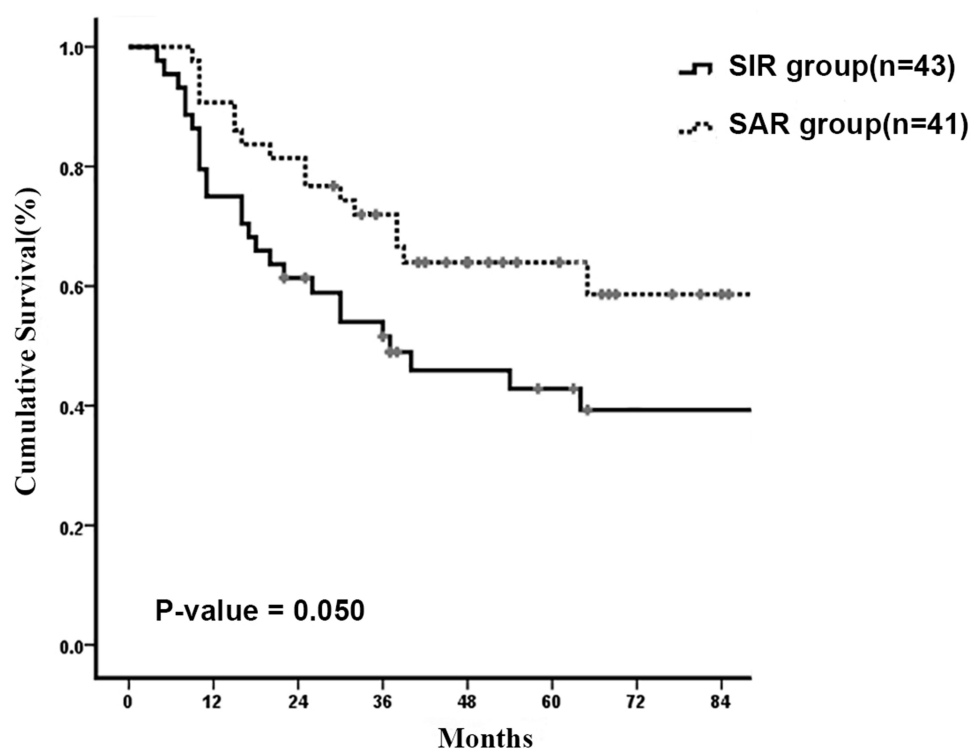
Figure 2 Kaplan–Meier survival curve for overall survival in incidental gallbladder cancer.
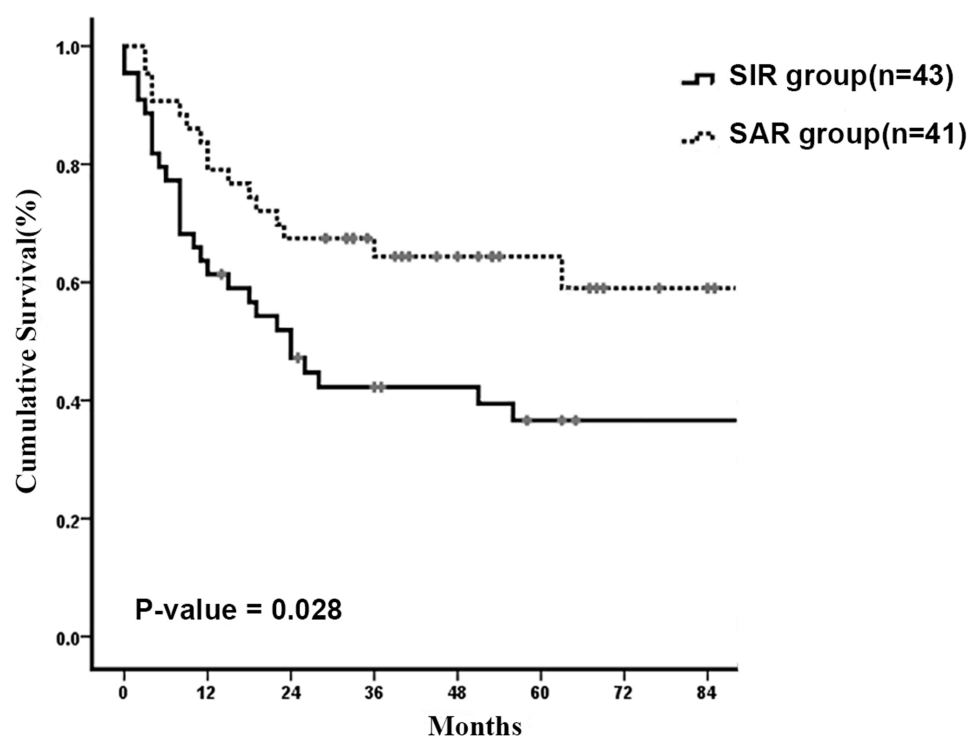**Abbreviations:** SIR, simultaneous radical resection; SAR, salvage radical resection.

Figure 3 Kaplan–Meier survival curve for recurrence-free survival in incidental gallbladder cancer.
Abbreviations: SIR, simultaneous radical resection; SAR, salvage radical resection.

Table 3 Multivariate Analysis of Prognostic Risk Factors for Survival After Incidental Gallbladder Cancer Surgery Using Cox Regression Model

Variables	Group	OS		RFS	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Type of radical resection			0.737		0.957
	SIR	Ref.		Ref.	
	SAR	0.824 (0.266~2.548)		0.971(0.336~2.806)	
T stage			0.004*		0.003*
	T3	Ref.		Ref.	
	T2	0.179 (0.021~1.551)	0.119	0.223(0.025~1.979)	0.178
	T1b	0.287 (0.135~0.610)	0.001*	0.278(0.131~0.587)	0.001*
Lymphatic metastases			0.027*		0.164
	Absent	Ref.		Ref.	
	Present	2.308 (1.098~4.852)		1.779(0.790~4.005)	
Grade of differentiation			0.016*		0.009*
	G1	Ref.		Ref.	
	G2	3.725 (1.319~10.519)	0.013*	4.330(1.48~12.663)	0.007*
	G3&G4	2.415 (1.160~5.028)	0.018*	3.059(1.324~7.065)	0.009*
Microvascular invasion			0.185		0.376
	Absent	Ref.		Ref.	
	Present	1.871 (0.742~4.720)		1.535(0.594~3.968)	
Enhanced CT/MR examination			0.661		0.576
	No	Ref.		Ref.	
	Yes	0.776(0.250~2.408)		0.744(0.264~2.098)	
Nerve invasion			-	-	0.76
	Absent	-	-	Ref.	
	Present	-	-	2.650(0.902~7.784)	
Dissected lymph nodes			-	-	0.167
	≤6	-	-	Ref.	
	>6	-	-	0.582(0.270~1.253)	

Note: *Variables with P-value <0.05.
Abbreviations: OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; Ref, reference; SIR, simultaneous radical resection; SAR, salvage radical resection; CT, computed tomography; MR, magnetic resonance.

The major finding in this study was that in IGBC, patients undergoing SAR had non-inferior survival compared with patients undergoing SIR (OS: P = 0.737, RFS: P = 0.957). Our study suggested that high-quality SAR might also achieve optimal long-term prognosis in IGBC. It provided evidence that SAR surgery may also be helpful for IGBC patients detected postoperatively. Still, it should be noted that detailed imaging evaluation and sufficient excised nodes are necessary. We speculate that there are two reasons for this difference from previous hypothesis. First, preoperative radiographic evaluation in the SAR group was more comprehensive; almost all patients in the SAR group underwent abdominal enhanced CT/MRI preoperatively, compared with 20.9% of patients in the SIR group. High-quality CT and MRI certainly helps to detect lymph node metastasis, peripheral organ invasion, and distant metastasis, thereby aiding better development of surgical procedures.[26–28] Second, radical resection in the SAR group was of higher quality, especially including the lymphatic and port-site resection. A sufficient number of excised nodes help with accurate lymphatic staging and can potentially improve long-term prognosis.[29–31] We analyzed the number of patients who received adequate lymphadenectomy in each cohort. The cut-off value for lymph node dissection number was set at six according to the 8th AJCC staging manual.[32] Our results showed that the SAR group (21/41, 51.2%) was more likely to have had more than six excised lymph nodes vs the SIR group (10/43, 23.3%) (P = 0.015).
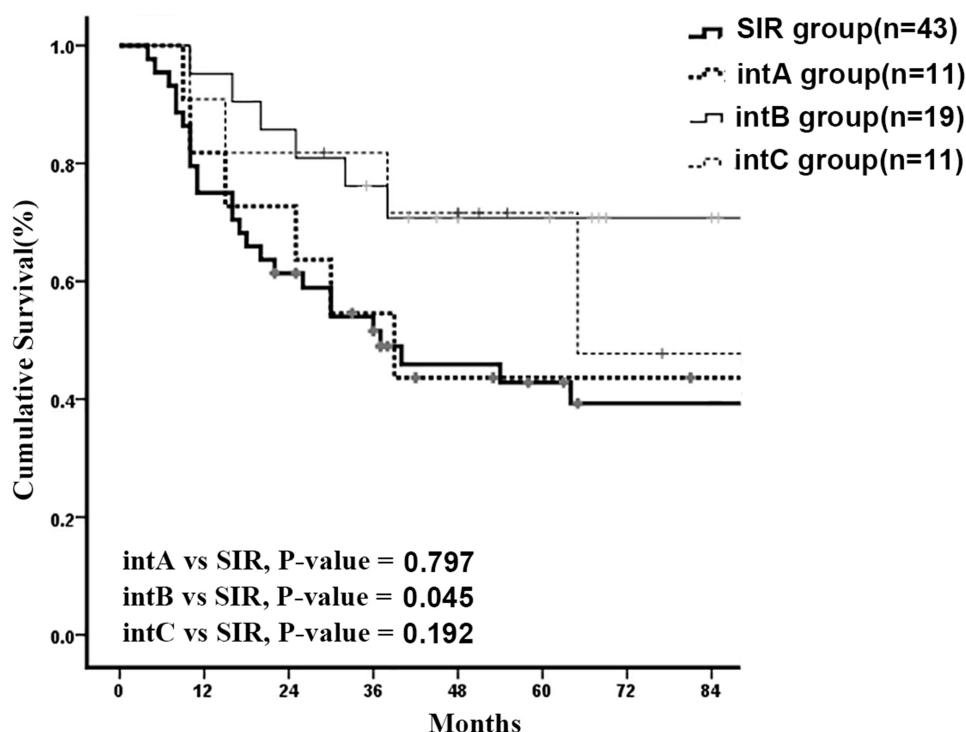
Figure 4 Time interval analysis for incidental gallbladder cancer patients undergoing previous cholecystectomy and delayed resection.
Abbreviations: SIR, simultaneous radical resection; intA, interval <2 weeks; intB, interval between 2 and 4 weeks; intC, interval >4 weeks.

Several studies suggested that port-site resection does not improve long-term survival in GBC patients, such as the multi-institutional analysis of Ethun et al[33] in 2017 and the systematic review performed by Soreide et al[34]. However, the port-site resections in the 10 patients in our study were performed before 2014 when the therapeutic value of this procedure was controversial and inconclusive. In the SAR group, 10 patients underwent port-site resection, while none of the patients in the SIR group underwent this procedure.

For IGBC diagnosed postoperatively, the optimum time interval from original cholecystectomy to SAR is controversial. Ethun et al[35] retrospectively analyzed 449 patients from 10 institutions in the USA and suggested that the optimal time interval was 4–8 weeks. The authors believed that secondary resection too soon after the first surgery may not allow sufficient time for subclinical disease to present, while if too late, disease dissemination could occur. In our study, patients in the subgroup with an interval of 2–4 weeks (intB subgroup) had the best prognosis within the SAR group. However, it should be noted that there may be significant bias in this analysis of interoperative time interval because the number of patients in both the intA and intC groups was small (n = 11, each).

More researches are required to be done in the future concerning the right timing for secondary resection.

There are several limitations to be mentioned in our study. First, we evaluated data from a single tertiary center. Considering the low incidence of IGBC in routine cholecystectomy, data from multicenter studies would provide more concrete evidence. Second, some clinical information, such as bile spillage, was not recorded and thus could not be collected for analysis in this study.[36] Intraoperative bile spillage could cause cancer cells to spread out of the gallbladder, causing the original disease to progress and upgrade.[37] Third, laparoscopic exploration[38] (one patient in the SAR group) and radical resection[39] (one patient in the SIR group and one patient in the SAR group) were used rarely in this study. The effects of these procedures on long-term prognosis were not analyzed because of the small numbers of patients undergoing these procedures. Additionally, because of insufficient patient volume, our data were unable to investigate the effect of SIR/SAR on margin status. Finally but importantly, the majority of patients in this study were T2 stage, and therefore, the long-term prognosis in this study was optimistic considering the extreme malignancy of GBC (5-year OS, 41.4% for the SIR group and 62.4% for the SAR group). In IGBC

with extensive invasion or severe residual disease,[11] whether large-scale resections such as major hepatectomy or pancreatoduodenectomy[40] prolong survival is currently unknown.

Conclusions

In this study, patients undergoing SAR had non-inferior survival compared with SIR, possibly benefited from more comprehensive preoperative radiographic evaluations and higher-quality of surgical operations.

Ethics Approval

This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University (Approval no. 20,200,225-36). The need for informed patient consent was waived because of the retrospective nature of the study. As a retrospective study, waiver of informed consent was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University. This study protected patient data confidentiality and was in compliance with the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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