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Incidental Gallbladder Cancer on Cholecystectomy: Strategy for Re-resection of Presumed Benign Diseases from a Retrospective Multicenter Study by the Yokohama Clinical Oncology Group

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Abstract. *Background/Aim: Current expert consensus recommends re-resection for incidental gallbladder cancer (IGBC) of pT1b-3. This study examined whether this consensus was reasonably applicable to patients with IGBC in one Japanese region. Patients and Methods: This was a multicenter, retrospective analysis of cholecystectomies for presumed benign diseases between January 2000 and December 2009. Results: IGBC was diagnosed in 70 (1.0%) out of 6,775 patients undergoing cholecystectomy. Five-year disease-specific cumulative survival was 100% in 19 patients with pT1a, 80.0% in five with pT1b, 49.5% in 33 with pT2, and 23.1% in 13 with pT3. Re-resection was not performed for the 24 patients with pT1a/1b disease, whereas 24 out of 46 patients with pT2/3 underwent re-resection. Regardless of re-resection, independent factors associated with a poor prognosis on multivariate analysis were grade 2 or poorer disease and bile spillage at prior cholecystectomy. In the 24 patients with pT2/3 re-resection, 11 patients without either of these two factors had significantly better 5-year disease-specific cumulative survival than the 13 patients with one or two independent factors associated with a poor prognosis (72.7% vs. 30.8%, p=0.009). Conclusion: This Japanese regional study suggests that indication of re-resection for IGBC should not be determined by pT-factor alone and that much more attention should be paid to pathological and intraoperative findings at prior cholecystectomy.*

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Gallbladder cancer (GBC) is the most common biliary malignancy and the sixth most common gastrointestinal malignancy worldwide (1). Complete surgical removal is the only modality that can provide a chance of cure. However, the overall prognosis of patients with GBC has been dismal because the majority of cases have been judged to have unresectable disease at presentation (2) because it is very

difficult to diagnose GBC preoperatively. As such, even today, GBC is often discovered incidentally on pathological examination following cholecystectomy for presumed benign diseases, despite recent advancements in diagnostic modalities (3-5). Furthermore, the number of patients undergoing cholecystectomy has been increasing since the advent of laparoscopic procedures, and, thus, cases of incidentally diagnosed GBC (IGBC) is considered to have further increased in number. Therefore, the clinical significance of IGBC should attract much more attention (3-8).

Current expert consensus (9) recommends re-resection for patients with IGBC with pT1b-3 disease because re-resection has been considered to provide a better chance of cure (5-9). However, a recent study demonstrated that the median survival time of patients with pT2/3 IGBC after extended cholecystectomy with adjuvant therapy was 16.1 months, while that after simple cholecystectomy with adjuvant therapy was 16.4 months (10). Although direct comparison of survival between these two procedures for pT2/3 IGBC was not performed in that study, these results suggested that adjuvant therapy without re-resection may be able to provide a treatment outcome comparable to that of re-resection for pT2/3 IGBC (10). In addition, a recent multicenter study comparing outcomes of surgery for pT1b GBC between simple cholecystectomy and extended resection found there to be no difference of treatment outcomes between these two procedures (11). As such, results of these studies may suggest that re-resection is unnecessary for most patients with IGBC (10, 11). In other words, the above-stated expert consensus may still include much room for debate.

This retrospective, multicenter study, which was conducted by the Yokohama Clinical Oncology Group (YCOG), examined whether the current expert consensus can be reasonably applied to patients with IGBC found in one Japanese region.

Patients and Methods

YCOG is a research group for investigating various concerns regarding surgery and oncology, and comprises the Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, and regional medical centers. The YCOG-1003 study group was organized to produce a retrospective registry of IGBC. Twelve centers of YCOG participants agreed on the contents of YCOG-1003 and were asked to identify all patients with IGBC to complete a multi-item questionnaire. Among patients who underwent cholecystectomy for preoperative diagnoses other than GBC between January 2000 and December 2009, cases of IGBC were extracted and retrospectively reviewed. A questionnaire sheet included the preoperative diagnosis for prior cholecystectomy, intraoperative findings of prior cholecystectomy, histopathological findings of prior cholecystectomy specimens, re-resection, use and details of additional treatment for patients in whom re-resection was not undertaken, interval between prior cholecystectomy and re-resection, procedure of re-resection, histopathological findings of re-resection specimens, the American Joint Committee on Cancer (AJCC) TNM classification staging (seventh edition) (12), short-term clinical course, and long-term outcomes. Furthermore, total number of cholecystectomies for preoperative diagnosis other than GBC performed during the study period in each institution was investigated and accumulated. This study was approved by the Ethical Committee Review Board of Yokohama City University School of Medicine (B100513018).

Table I. *Patient demographic and tumor characteristics.*

Variable		Value
Age, years	Median (range)	69 (37-90)
Gender, n (%)	Male	36 (51.4%)
	Female	34 (48.6%)
Initial diagnosis, n (%)	Cholecystolithiasis	58 (82.9%)
	GB polyps	10 (14.3%)
	Chronic cholecystitis	5 (7.1%)
	Adenomyomatosis	1 (1.4%)
	PBMJ	1 (1.4%)
Prior surgical procedure, n (%)	Open cholecystectomy	30 (42.9%)
	Laparoscopic cholecystectomy	40 (57.1%)
T-Stage, n (%)a	1a	19 (27.1%)
	1b	5 (7.1%)
	2	33 (47.1%)
	3	13 (18.5%)
Tumor differentiation, n (%)[a]	G1	44 (62.9%)
	G2	16 (22.9%)
	G3	9 (12.9%)
	G4	1 (1.4%)
Re-resection, n (%)	Absent	46 (65.8%)
	Present	24 (34.2%)

GB: Gallbladder, PBMJ: pancreaticobiliary maljunction. [a]American Joint Committee on Cancer seventh edition (12).

Statistical analysis. Continuous variables are presented as medians (range), and categorical variables are presented as frequencies. Categorical data were analyzed using the chi-squared test or Fisher's exact test. The Mann-Whitney *U*-test was used to compare continuous variables. Disease-free survival (DFS) was defined as the duration from the day of cholecystectomy to the day of diagnosis of relapsed disease or no evidence of relapsed disease. Disease-specific survival (DSS) was defined as the duration from the day of cholecystectomy to disease-specific death of the patient or latest follow-up. Cumulative survival rates were calculated by the Kaplan-Meier method and compared using the Peto-Prentice-Wilcoxon test. Factors found to be significant on univariate analysis or considered important for logical or biomedical grounds were subjected to multivariate analysis using a Cox proportional hazards model. A two-tailed *p*-value of less than 0.05 was considered significant. All statistical tests were performed using Microsoft Excel software (Microsoft, Redmond, WA, USA) and SPSS software ver. 22 for Windows (IBM Corporation, Armonk, NY, USA).

Results

Patient demographics and tumor characteristics. Between January 2000 and December 2009, 6,775 patients underwent cholecystectomy for presumed benign diseases at the 12 YCOG

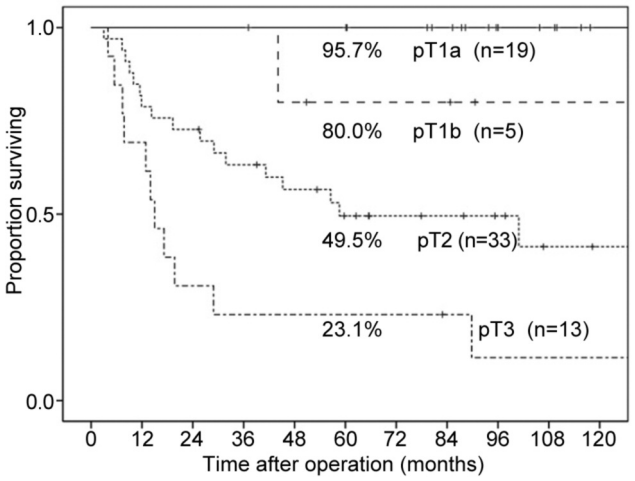

Figure 1. *Kaplan-Meier survival curves of the entire study cohort stratified by the American Joint Committee on Cancer pT classification. These curves were clearly stratified by the American Joint Committee on Cancer pT classification.*

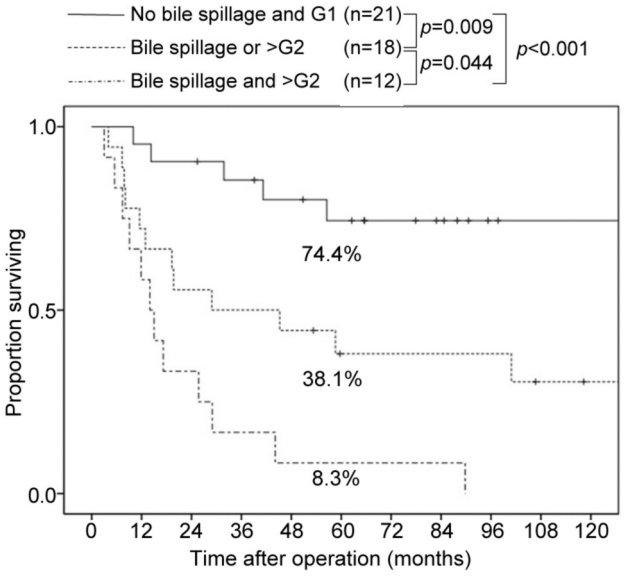

Figure 2. *Survival outcomes of patients with pT1b, pT2 or pT3 incidental gallbladder cancer stratified by number of accompanying independent factors associated with a poor prognosis identified in the present study. Regardless of re-resection, survival outcomes of patients with pT2/3 disease are clearly stratified by the number of the following 2 independent factors associated with a poor prognosis: Grade (G) 2 or poorer disease and bile spillage at prior cholecystectomy. These rates decrease significantly according to the number of accompanying factors.*

institutions. Of these 6,775 patients, IGBC was diagnosed in 70 (1.03%). Patient demographics and tumor characteristics are summarized in Table I. According to the AJCC staging system, cholecystectomy specimens showed pT1a tumor in 19 patients (27.1%), pT1b in five (7.1%), pT2 in 33 (47.1%), and pT3 in 13 (18.6%). None of the 24 patients with pT1a/1b underwent re-resection. Among the 51 patients with pT1b, pT2 or pT3 disease, for whom current expert consensus recommends re-resection (9), 24 (47.1%) underwent re-resection. No patients received treatments other than re-resection surgery for IGBC.

Prognostic significance of the AJCC pT classification. The observation period after prior cholecystectomy ranged from 4.0 to 194.4 months, with a median of 62.5 months. Regardless of whether re-resection was performed, survival outcomes after cholecystectomy were clearly stratified by the AJCC pT classification. The 5-year cumulative DSS was 100% in pT1a (n=19), 80.0% in pT1b (n=5), 49.5% in pT2 (n=33), and 23.1% in pT3 (n=13) cases (Figure 1). As stated above, no patients with pT1a/1b disease underwent re-resection. One patient with pT1b disease who died of peritoneal recurrence 45 months after cholecystectomy showed bile spillage at cholecystectomy and grade 2 tumor differentiation on pathological examination. The remaining 23 patients with pT1a/1b disease showed no bile spillage at cholecystectomy and none of the 23 patients died during the study period.

Prognostic analyses for patients with pT1b/T2/T3 disease. Cholecystectomy alone achieved a 5-year DSS of 100% in the 19 patients with pT1a disease. As the current expert consensus regards re-resection unnecessary for pT1a disease, a prognostic analysis was considered unnecessary for these patients. Thus, the 19 patients with pT1a disease were excluded from the subsequent prognostic analyses.

Considering only the 51 patients with pT1b, pT2 or pT3 disease, the prognostic significance of the following four variables was examined: Re-resection; AJCC pT classification; tumor differentiation; and occurrence of bile spillage at prior cholecystectomy. These four variables were evaluable at the time when the need for re-resection was decided. As shown in Table II, pT3 disease, poorer tumor differentiation (grade 2 or poorer), and bile spillage at prior cholecystectomy were significant factors associated with a poor prognosis on univariate analyses. Multivariate analysis using these four variables showed that poorer tumor differentiation (hazard ratio=3.405; 95% confidence interval=1.466-7.909, and p=0.004) and bile spillage at prior cholecystectomy (hazard ratio=2.768; 95% confidence intervaI=1.288-5.951; and p=0.009) were independent prognostic factors for survival of the 51 patients with pT1b-3 disease. The 51 patients with pT1b-3 disease were divided into three groups by the number of these independent factors they had: 21 Patients who had grade 1 disease and no bile spillage at prior cholecystectomy (no risk factor); 18 patients with either grade 2/poorer disease or bile spillage (one risk factor); and 12 patients with both grade 2/poorer disease and bile spillage (two risk factors). The

Table II. *Prognostic factors of 51 patients with pT1b, pT2 or pT3 incidental gallbladder cancer.*

Variable		Univariate analysis				Multivariate analysis		
		n	5-Year survival (%)	Median survival (Months)	*p*-Value	Hazard ratio	95% Confidence interval	*p*-Value
Re-resection	No	27	42.6	44.1	0.334			
	Yes	24	49.7	56.5				
T-Stagea	1b and 2	38	53.3	100.9		1 (Ref)		
	3	13	23.1	15.0	0.004	1.732	0.751-3.993	0.198
Tumor differentiationa	Grade 1	26	67.9	N.R.		1 (Ref)		
	>Grade 2	25	23.3	19.3	<0.001	3.405	1.466-7.909	0.004
Bile spillage	No	34	59.9	100.9		1 (Ref)		
	Yes	17	17.6	15.0	<0.001	2.768	1.288-5.951	0.009

[a]American Joint Committee on Cancer seventh edition (12).

survival curves of these groups were clearly stratified by the number of independent factors (Figure 2). The corresponding 5-year cumulative patient survival rates were 74.4%, 38.1%, and 8.3%, respectively. These rates were significantly better in those with one risk factor than in the other two groups (p=0.009 and p<0.001, respectively) and significantly better in those with one risk factor than in those with two (p=0.044).

Effects of re-resection. Because none of the five patients with pT1b disease underwent re-resection, these patients were excluded from the following analyses. Among the 46 patients with pT2/pT3 disease, the comparison of clinicopathological variables between the patients who underwent re-resection and those who did not is shown in Table III. Other than patient age, patient and tumor characteristics were similar between the two groups.

A comparison of cumulative survival between patients who underwent re-resection and those who did not showed that the 5-year cumulative survival rate was not significantly different (49.7% in the former and 34.6% in the latter, p=0.155) (Figure 3A). Considering the two independent factors associated with a poor prognosis, that is grade 2/poorer disease and bile spillage at prior cholecystectomy, however, the 5-year cumulative survival rate was significantly better in the 11 patients without either of the two independent factors associated with a poor prognosis who underwent re-resection than in the remaining 35 patients (72.7% *vs*. 32.6%, p=0.007) (Figure 3B). Furthermore, a comparison of the 11 patients without independent factors and the 13 with one or two independent factors, who all underwent re-resection, showed that the 5-year cumulative survival rate was significantly better in the first group than those in the latter (72.7% *vs*. 30.8%, p=0.007) (Figure 3C).

Unlike a recent report in which the interval between initial cholecystectomy and re-resection was significantly associated with outcomes of re-resection, there was no correlation between outcomes of re-resection and the interval (data not shown) (13). Furthermore, a recently introduced pathology-based preoperative risk score for re-resection of IGBC did not successfully stratify the survival outcomes of re-resection in the present study cohort (data not shown) (14).

Implications of grade 2/poorer disease and bile spillage at prior cholecystectomy. Based on the above analyses, grade 2/poorer disease and bile spillage at prior cholecystectomy were noted to have significant negative impacts on survival outcomes of patients with pT2/3 IGBC, regardless of whether re-resection was performed. To clarify the effects of these two factors on postoperative survival outcomes after re-resection, DFS and recurrence patterns were compared in the 24 patients who underwent re-resection between those with grade 1 disease and those with grade 2/poorer disease, and between patients with and without bile spillage at prior cholecystectomy.

With regard to tumor differentiation, the 5-year DFS rate and the median DFS were significantly lower in patients with grade 2/poorer disease (n=10) than in those with grade 1 disease (n=14) (13.1% *vs*. 57.1%; and 12.0 months in those with grade 2/poorer group *vs*. not reached, p=0.031). However, the site of recurrence did not differ among the groups (Table IV).

Regarding bile spillage at prior cholecystectomy, the 5-year DFS rate and median DFS were significantly lower in patients with bile spillage (n=7) than in those without (n=17) (5-year DFS rate: 14.3% *vs*. 52.3%; median DFS: 11.5 months *vs*. not reached, p=0.048) (Table IV). Unlike tumor differentiation, the recurrence pattern was significantly different between patients with and without bile spillage at prior cholecystectomy. Peritoneal recurrence was significantly more common in patients with bile spillage (6/6, 100%) than in those without (2/8, 25%) (p=0.023) (Table IV).

Discussion

The present study demonstrated that IGBC was observed in 1% of patients undergoing cholecystectomy for preoperative

Table III. *Comparison of clinicopathological variables of 46 patients with pT2/pT3 incidental gallbladder cancer between patients who underwent re-resection and those who did not.*

Variable		Re-resection (n=24)	No re-resection (n=22)	*p*-Value
Age, years	Mean±SD	66.3±6.7	74.7±8.7	<0.001
Gender, n (%)	Male	13 (54.2)	12 (54.5)	0.800
	Female	11 (45.8)	10 (45.5)	
Initial diagnosis, n (%)[a]	Cholecystolithiasis	22 (50.0)	20 (90.9)	0.649
	GB polyps	2 (8.3)	1 (4.5)	
	Chronic cholecystitis	4 (16.7)	1 (4.5)	
	Adenomyomatosis	0 (0.0)	1 (4.5)	
	PBMJ	0 (0.0)	0 (0.0)	
Prior cholecystectomy, n (%)	Open	11 (45.8)	12 (54.5)	0.800
	Laparoscopic	13 (54.2)	10 (45.5)	
pT stage, n (%)[b]	2	15 (62.5)	18 (81.8)	0.196
	3	9 (37.5)	4 (18.2)	
Tumor differentiation, n (%)[b]	Grade 1	14 (58.3)	10 (45.5)	0.825
	Grade 2	5 (20.8)	9 (40.9)	
	Grade 3	5 (20.8)	2 (9.1)	
	Grade 4	0 (0.0)	1 (4.5)	
Bile spillage in prior operation, n (%)	No	17 (70.8)	13 (59.1)	0.403
	Yes	7 (29.2)	9 (40.9)	
Time to re-resection	Median (range)	30 (14 -84)		
Surgical re-resection, n (%)	Gall bladder bed	14 (58.3)		
	Segment 4b/5	10 (41.6)		
Bile duct resection, n (%)	Yes	11 (45.8)		
	No	13 (54.1)		
Cancer remnant in re-resected specimen, n (%)	No	21 (87.5%)		
	Yes	3 (12.5%)		
Lymph node metastasis, n (%)	No	17 (70.8%)		
	Yes	7 (29.1%)		

PBMJ: Pancreatico biliary maljunction. [a]Data overlap. [b]American Joint Committee on Cancer seventh edition (12).

diagnoses other than GBC, that almost all patients with AJCC pT1 disease survived more than 5 years without re-resection, and that the effect of re-resection was limited in patients with pT2/3 disease who did not have the two independent factors associated with a poor prognosis: grade 2 or poorer disease and bile spillage at prior cholecystectomy.

Geographic variation in the incidence of GBC is well known. The 1% incidence of IGBC which was confirmed by the present study was considered reasonable compared to previous studies (15-18).

In the basic concept, re-resection is considered to have the following two purposes: Elimination of residual disease, and accurate understanding of the extent of disease. For the former, resection of adjunct organs such as liver parenchyma or common bile duct, in which the disease is likely to remain, is considered necessary. Lymphadenectomy, which is usually included in the re-resection procedure, may be effective for both purposes. However, the prognosis of lymph node metastasis-positive GBC is reportedly dismal even when R0 resection is achieved (2, 19, 20). Furthermore, it has been reported that the number of metastatic lymph nodes or the number of dissected lymph nodes, regardless of whether metastatic disease is proven in dissected lymph nodes, is significantly correlated with survival outcomes of surgery for GBC (20, 21). Thus, lymphadenectomy should be considered necessary for accurate staging of the disease rather than for the elimination of residual disease.

Current expert consensus and the National Comprehensive Cancer Network (https://www.nccn.org/professionals/physician_gls/default.aspx) recommended that patients with non-metastatic pT1b, pT2, or pT3 stage disease undergo extended/radical cholecystectomy with en bloc liver resection (9, 21-26). If this recommendation had been followed, 51 out of 70 patients with IGBC in the present study who had pT1b, pT2, or pT3 disease would have had to have undergone re-resection, although only 24 out of the 51 patients actually underwent re-resection. With regard to pT1b GBC, the present study included only five patients with pT1b, none of whom underwent re-resection. Thus, it was not possible to obtain conclusive findings regarding re-resection for pT1b IGBC from the results of the present study. However, all of the four patients with pT1b disease who did not exhibit bile spillage at cholecystectomy survived throughout the study period without re-resection. Furthermore,

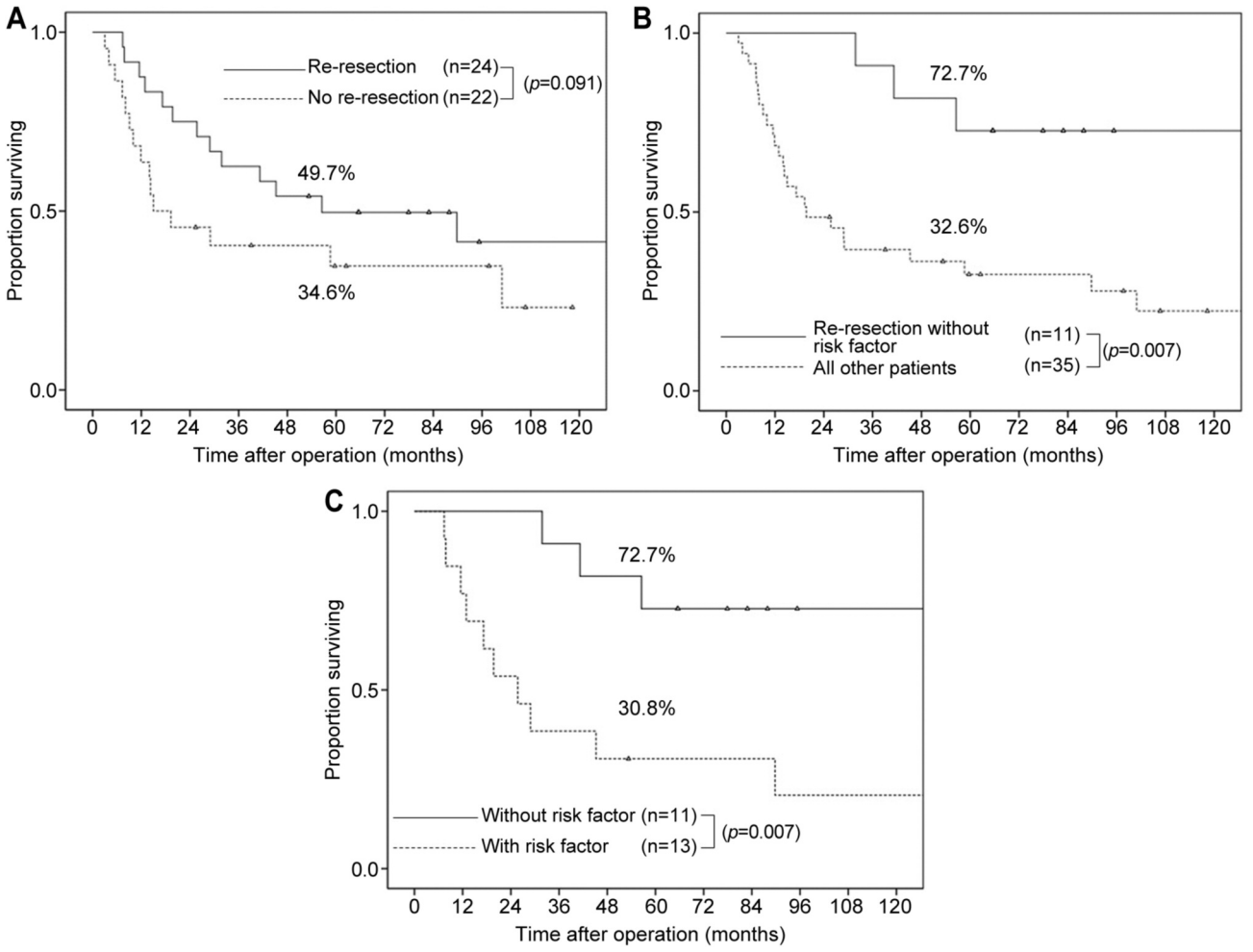

Figure 3. *Effect of re-resection for pT2/3 incidental gallbladder cancer on survival outcomes. A: Comparison between those who underwent re-resection and those who did not. The 5-year disease-specific survival rates were not significantly different (p=0.155). B: Comparison according to the presence of independent factors associated with a poor prognosis, namely grade 2 (G2) or poorer disease, or bile spillage at prior cholecystectomy. Survival of patients without any risk factor was significantly better (p=0.007). C: Comparison of patients who underwent re-resection between those without any risk factor associated with a poor prognosis and those with one or two factors. The 5-year disease-specific survival rate was significantly better in those who had neither of the two independent factors associated with a poor prognosis (p=0.007).*

several Japanese institutions reported that survival outcomes of patients with pT1b GBC after cholecystectomy were satisfactory, with 5-year DSS of more than 90% regardless of re-resection (22-24). In addition, a very recent international multicenter study by Kim *et al*. comparing outcomes of surgery for pT1b GBC between simple cholecystectomy and extended resection showed that 5-year DSS of more than 90% was similar for these two procedures (11), suggesting that pT1b IGBC does not necessitate re-resection. In contrast, some reports from Western countries showed that the prognosis of pT1b was disappointing, with 5-year DSS of 50-60% (5, 25, 26) and upheld the necessity of re-resection. Although it cannot be denied that the GBC that develops in Western populations may have a more biologically aggressive nature than that which develops in Asian patients, the report of Kim *et al*. included a considerable US population (11). Therefore, these discrepant surgical outcomes of pT1b GBC among reports appear to have resulted from interobserver variability in sampling methods of gallbladder specimen for presumed benign diseases rather than a difference in biological aggressiveness (27, 28). Hence, based on the above-stated Japanese reports (20-22) and the international multicenter study suggesting no need for re-resection for pT1b IGBC, we consider that re-resection is unnecessary for pT1b disease, at least in Japan.

Regarding pT2/3 disease, the results of the present study may sound a warning against the current expert consensus (9) because the survival benefit of re-resection was not proven. In other words, regardless of re-resection, survival outcomes of patients with pT2/3 were clearly stratified by the number of

Table IV. *Comparisons of disease-free survival and the site of recurrence after re-resection between patients according to the prognostic factors tumor grade and bile spillage at prior cholecystectomy.*

		Grade			Bile spillage		
		>2 (n=10)	1 (n=14)	*p*-Value	Yes (n=7)	No (n=17)	*p*-Value
Disease-free survival, %	5-Year	13.1	57.1	0.031	14.3	52.3	0.048
Time to relapse, months	Median (range)	12.0 (4.8-18.1)	N.R.	-	11.5 (0.4-22.5)	N.R.	-
Recurrence, n (%)	Yes	8 (80.0%)	6 (42.8%)	0.161	6 (85.7%)	8 (47.0%)	0.196
Recurrence site, n (%)	Local	2 (25.0%)	0 (0%)	0.581	1 (16.6%)	1 (12.5%)	0.581
	Lymph node	5 (62.5%)	2 (33.3%)	0.589	2 (33.3%)	5 (62.5%)	0.589
	Lung	0 (0%)	2 (33.3%)	0.321	0 (0%)	2 (25.0%)	0.581
	Liver	0 (0%)	1 (16.6%)	0.880	0 (0%)	1 (12.5%)	0.880
	Peritoneum	4 (50.0%)	3 (50.0%)	0.589	6 (100%)	2 (25.0%)	0.023

accompanying independent prognostic factors identified in the present study, namely tumor histological differentiation and bile spillage at prior cholecystectomy. Even with re-resection, eight out of 10 patients who underwent re-resection for grade 2 or poorer pT2/3 disease developed recurrence, and the median DFS for these 10 patients was only 12 months. Similarly, six out of seven patients with a history of bile spillage at prior cholecystectomy who underwent re-resection for pT2/3 IGBC developed peritoneal recurrence, and the median DFS of these seven patients was less than 12 months. Grade 2 or poorer disease was not significantly associated with any site of recurrence, whereas bile spillage was significantly associated with peritoneal recurrence after re-resection. Therefore grade 2 or poorer disease is likely to disseminate systemically due to its aggressive biological nature, and cancer cells may be scattered into the peritoneal cavity through bile spillage. As a result, micro-residual disease, which cannot be eliminated by re-resection, was considered to have arisen. In the present study, an obvious survival benefit of re-resection was obtained only in patients without these two independent risk factors. Both these factors can be evaluated at the time the decision of whether to proceed with re-resection is made. Recently, the significance of adjuvant therapy for GBC was reported (10); simple cholecystectomy with adjuvant therapy was shown to provide significantly better survival outcomes than extended resection alone, and a benefit of re-resection for pT2/3 IGBC was not shown (10). Therefore, systemic treatment, rather than re-resection, may have a greater impact for patients with factors associated with a poor prognosis. Hence, adjuvant therapy without re-resection for pT2/3 IGBC may be a choice of treatment in selected patients with either of the independent risk factors. Regarding bile spillage at cholecystectomy, Clemente *et al*. reported that treatment outcomes of IGBC after laparoscopic cholecystectomy for patients with acute cholecystitis were significantly worse than patients without cholecystitis (29), probably because of bile spillage related to intraoperative gallbladder emptying. As suggested in the current Japanese treatment guideline for acute cholecystitis (30), when bile spillage seems likely to occur, more detailed preoperative diagnostic imaging modalities may be necessary to detect GBC. Furthermore, careful selection of the operative procedure (open or laparoscopic) and meticulous intraoperative procedures are required for preventing intraoperative bile spillage. Although this may be an exaggeration, it may be stated that IGBC should always be kept in mind at cholecystectomy even if the preoperative diagnosis does not indicate it.

There were several drawbacks in the present study. Firstly, the sample size was very small despite it being a multi-institutional study. At the same time, probable variations in management strategy existed due to the multicenter design. Despite these drawbacks, however, the results of the present study were quite convincing and worth taking into consideration when deciding treatment strategies for future patients because the survival outcomes of patients with IGBC in the present study were clearly stratified.

In conclusion, IGBC was observed in 70 out of 6,775 patients undergoing cholecystectomy for preoperative diagnoses other than GBC. Patients with pT1a had 5-year DSS of 100% without re-resection. Furthermore, an obvious survival benefit of re-resection was not found in patients with pT1b, pT2, or pT3 disease in univariate and multivariate analyses. The survival benefit of re-resection was obtained only in patients without either of two independent factors associated with a poor prognosis identified in the present study: Grade 2/poorer disease and bile spillage at prior cholecystectomy. These results suggest that indication for re-resection should not be determined by pT-factor alone in Japanese patients with IGBC and that much more attention should be paid to pathological findings as well as intraoperative findings at prior cholecystectomy.

Conflicts of Interest

The Authors declare no conflicts of interest for this article.

Authors' Contributions

Conception and design of work: RM, IE. Acquisition of data: RM, KM, RM, MS, NY, TK, KK, YM, RT, TK, GM, NK. Data analysis and interpretation: All Authors have participated in critical revision of the manuscript for important intellectual content. Wrote the initial draft of the manuscript: RM. All Authors finally approved of the version to be published and agreed to be 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. All Authors have read and approved the manuscript.

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