

Relationship between Prognosis and Time Interval from Cholecystectomy to Reoperation in Postoperative Incidental Gallbladder Carcinoma

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To the Editor: Gallbladder cancer (GBC), a rare entity with poor prognosis, is often discovered incidentally during or after cholecystectomy.^[1] It tends to disseminate early through lymphatic, peritoneal, endobiliary, and hematogenous pathways. Patients usually present with metastatic diseases. If GBC is suspected during cholecystectomy, conversion to open surgery to perform radical resection after confirmation of cancer by intraoperative frozen biopsy is considered. When GBC is diagnosed after cholecystectomy, reoperation for radical resection according to depth of invasion of cancer (T stage) is inevitable.^[1] However, reoperation with radical surgery is not performed in all patients for several reasons including refusal to undergo radical surgery, poor medical condition, or cancer progression suggesting unresectability.

At present, few studies have defined an ideal time interval for reoperation since the impact of delay on survival is unknown. If reoperation is performed too late, some patients could lose the chance of radical surgery because of rapid tumor progression. In practice, the best interval is difficult to determine. In this study, we assessed the optimized timing of referral for re-resection in PI-GBC.

A prospectively maintained hepatobiliary surgery database at the Eastern Hepatobiliary Hospital (Shanghai, China) was reviewed for all patients with a diagnosis of GBC who underwent surgical resection with curative intent between January 2004 and December 2014. Permission from the Second Military Medical University's Institutional Review Board was obtained before data review.

Resection completeness was classified by: R0 without residuals on hepatic margins, R1 microscopically positive margin, and R2 macroscopic residuals on hepatic margins. R0 or R1 resections were considered to be surgical resection with curative intent. All patients that had undergone either palliative or exploratory surgery were excluded from analysis. In our experience, extensive invasion to the hepatoduodenal ligament, excessive presence of liver or peritoneal metastases beyond areas near the gallbladder, or bulky lymph node metastases have been considered a contraindication to surgery.

Surgical procedures used to treat patients are summarized as follows. All patients underwent *en bloc* dissection of regional lymph nodes (lymph nodes along the hepatoduodenal ligament and common hepatic artery and behind pancreatic head). Hepatectomies were carried out in all 276 patients. Resection of laparoscopic port sites was routinely performed in all patients receiving laparoscopic cholecystectomy. Combined resection of adjacent organs was performed as long as R0 resection could be expected. Data were analyzed with SPSS version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA) and the significance level was set at $P < 0.05$.

Of the 276 patients managed with curative intent for GBC during this 10-year inclusion period, 196 (71.0%) had preoperative suspicion (PS) of malignancy (PS-GBC), and 80 (29.0%) were discovered incidentally (postoperative incidentally discovered GBC [PI-GBC]). There was no significant difference between PI-GBC and PS-GBC in mortality and morbidity. The two cohorts were similar in age, gender, histological differentiation, extent of liver resection, and combined resections of adjacent organs but some tumor characteristics differed significantly. A higher proportion of associated gallstones was associated with PI-GBC ($P = 0.013$), suggesting that the presence of incidentally discovered GBC might be covered by the symptoms of gallstones. Rates of hepatic invasion ($P < 0.001$) and nodal metastases ($P < 0.001$) were also significantly higher in PS-GBC. A more advanced T category was associated with PS-GBC, suggesting more seriously local tumor invasion in PS-GBC patients. More intraoperative bleeding and operative time were found in PS-GBC group ($P < 0.001$).

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and $P = 0.001$), suggesting a wider range of lesion resection performed in PS-GBC patients. However, R0 resection rate was similar between PS-GBC and PI-GBC ($P = 0.518$). There was no significant difference in mortality between PS-GBC and PI-GBC ($P = 0.577$). Morbidity was significantly lower in PI-GBC patients than in PS-GBC patients (5.0% vs. 17.9%, $P = 0.004$). Average postoperative hospital stay in PS-GBC patients was 13.2 days (range: 4–85 days), longer than PI-GBC patients ($P = 0.001$).

Median survival for PI-GBC was 39.9 versus 14.3 months for PS-GBC ($P < 0.001$). Cumulative 1-, 3-, and 5-year survival rates in PI-GBC group (88.8%, 52.2%, and 33.0%, respectively) were significantly better than those in the PS-GBC group (57.5%, 25.7%, and 16.6%, $P < 0.001$).

To identify factors influencing long-term survival in 80 PI-GBC patients, univariate and multivariate analyses were performed [Supplementary Table 1]. In univariate analysis, depth of invasion of cancer (T stage), age, hepatic invasion, tumor location, extent of liver resection, and time from cholecystectomy to referral for re-resection were identified as significant prognostic factors. In multivariate analysis, only T stage, hepatic invasion, and time from cholecystectomy to referral for reoperation were independent prognostic factors [Supplementary Table 2].

According to the time interval from cholecystectomy to referral for reoperation, 80 PI-GBC patients were divided into three groups including group within 2 weeks, group with 2 weeks to 1 month, and group with more than 1 month. Differences in survival and clinical characteristics among the three groups were analyzed. We found no significant difference in age, sex, T stage, liver invasion, and lymph node metastasis among the three groups [Supplementary Table 3]. Median survival for the three groups according to the time interval of within 2 weeks, 2 weeks to 1 month, and more than 1 month was, respectively, 86.1, 26.0, and 27.4 months. Cumulative 1-, 3-, and 5-year survival rates in the group with time interval within 2 weeks were 94.6%, 69.6%, and 41.4%, respectively, significantly better than the other two groups [$P = 0.003$, $P = 0.001$, Figure 1]. There was no statistically significant difference in survival between groups with time interval of 2 weeks to 1 month and more than 1 month ($P = 0.850$).

As the number of cholecystectomy operations increases, it is likely that the number of incidentally discovered GBC will also increase.^[2]

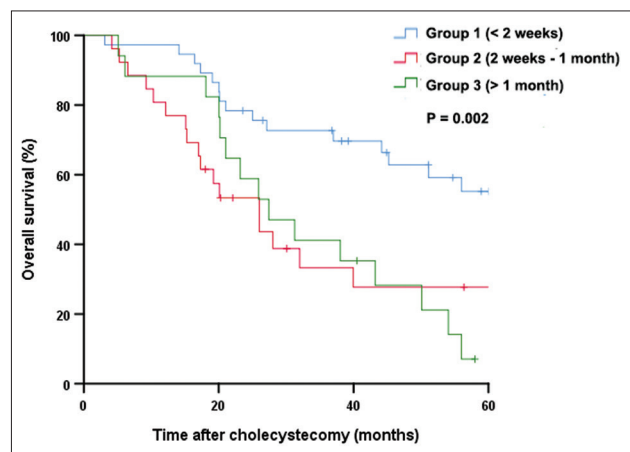


Figure 1: Actuarial survival curve of 80 patients with postoperative incidentally discovered gallbladder cancer according to the time interval from cholecystectomy to reoperation.

An incidentally discovered GBC forces a rapid decision by the surgeon during the initial operation and presents an unexpected challenge to patients, postoperatively. To effectively manage the disease and counsel patients regarding diagnosis, it is necessary to understand the prognosis of incidental GBC.

Rational decisions regarding therapeutic strategies play an important role in the treatment of incidental GBC, and intraoperative diagnosis is closely associated with timely treatment and prognosis of the disease. Meanwhile, histopathological study of the gallbladder together with suspected lymph nodes is suggested to facilitate a decision on further surgical strategies. Accidental opening of gallbladder and tumors should be avoided to prevent seeding and dissemination of cancer cells. Once GBC is confirmed intraoperatively, an open surgical procedure and rapid frozen section are recommended. However, many non-hepatobiliary specialist doctors lack experience in this area, resulting in relative high presence of incidental GBC. The majority of patients with postoperative incidentally discovered GBC in our study had received cholecystectomy in other non-hepatobiliary hospitals. However, only two such cases in our center were identified.

The most important clinical problem related to incidentally found GBC is the decision of whether to proceed with corrective surgery for radical cholecystectomy. If GBC is found during the operation, conversion to radical surgery is relatively easy. However, if GBCs are found after the operation, reoperation for corrective surgery is both necessary and critical. Although R0 resection is the treatment of choice, some patients with incidental GBCs diagnosed following cholecystectomy have refused reoperation for corrective surgery. As most publications are based on retrospective review of medical records, an exact proportion of patients that have refused corrective surgery has not been determined. Several publications have reported the number of patients that refused corrective surgery even though it was indicated due to advanced tumor stage.^[2] As described before, because R0 resection is the most important factor determining prognosis, reoperation for corrective surgery should be strongly recommended. In this study, we had a better prognosis in patients with postoperative incidentally discovered GBC mainly due to aggressive and urgent referral to radical reoperation.

The prognostic impact of incidentally diagnosed GBC on survival compared with preoperatively suspected GBC has not been widely studied. It is not clear whether incidental GBC has the same prognosis, or poorer prognosis, compared with the same stage of non-incidental GBC. For incidental GBCs, it is likely that the combined presence of cholecystitis complicates the diagnosis of GBC. Incomplete *en bloc* resection during cholecystectomy that causes spillage of cancer cells might affect the prognosis of GBC considering the relatively high pooled proportion of patients with residual cancerous lesions after corrective surgery. In our study, we also found that overall prognosis of incidentally discovered GBC was better than preoperative suspected GBC. Thus, we strongly recommend reoperation in patients with postoperative incidentally discovered GBC.

When comparing the survival impact of laparoscopic versus open procedures for treatment of GBC, several studies have reported no significant prognostic difference between the two procedures, suggesting that laparoscopic cholecystectomy does not decrease survival.^[3] However, another study showed that laparoscopic cholecystectomy had an increased risk of disseminating tumor cells, suggesting that open surgery is warranted in cases of known or suspected GBC.^[4] However, more recently, several authors have reported that early lesions of GBC can be managed successfully

using laparoscopic cholecystectomy, achieving a satisfactory survival result and low rate of port site recurrence.^[5] In this study, there was no statistically significant difference in survival between laparoscopic cholecystectomy and open cholecystectomy. Surgical procedure was not a significant prognosis factor. However, in the difficult cholecystectomy, we recommend open cholecystectomy as the risk of gallbladder rupture and intraoperative biliary injury is lower. In addition, gallbladder rupture during cholecystectomy is highly associated with tumor spread.

We recommended reoperation in patients with postoperative incidentally discovered GBC. It is very important to determine when and which reoperation is most suitable for postoperative incidentally discovered GBC.

Taking those facts into account, it is our practice to shorten the interval restaging of incidentally discovered GBC. In our experience, early postoperative imaging was multidetector computed tomography of the abdomen within 2 weeks from index cholecystectomy. The presence of liver metastases, main portal vein and hepatic artery involvement, and nonregional lymphadenopathy and peritoneal nodularity are criteria of unresectability. The choice of a 2-week time frame was essentially based on an estimation of time that a tumor would require to appear on a follow-up scan. This time frame is what radiologists usually recommend for following up undetermined nodules or discovering tumor recurrence.^[6]

A previous report has shown that the approach of delayed interval restaging eliminated exploratory laparotomies and significantly improved survival in a group of patients that underwent radical re-resection.^[7] In this study, the overall prognosis of postoperative incidentally discovered GBC patients, that were suitable for radical resection after assessment, was expected to be better. Based on the findings above, we summarized a suggested management algorithm for both incidental GBCs and indeterminate gallbladder lesions. It is recommended that all patients with suspicious or histologically proven GBC should be referred to a tertiary hepatobiliary center for further management, within 2 weeks. In line with current national guidelines which require a referral to be made within 2 weeks for any suspected malignancy, the 2-week rule was applied in the management algorithm presented here. In this study, we found that patients receiving reoperation within 2 weeks had better overall prognosis and were expected to achieve better prognostic outcomes. There was no significant difference in the prognosis of patients between 2 weeks and 1 month and more than 1 month. Due to the high degree of malignancy of GBC, delayed treatment may cause tumor spread, losing the chance of radical resection. Therefore, we recommend early (within 2 weeks) reoperation. Most patients have returned to a normal condition after 2 weeks and will withstand surgical treatment. In multivariate analysis, we found that T stage and liver invasion time interval is an independent prognostic factor. Therefore, we recommend that patients expecting to undergo radical resection after initial assessment should be treated as soon as possible. Our proposal is within 2 weeks.

In conclusion, postoperative incidental GBC has significantly better survival than preoperatively suspected GBC. Urgent referral within 2 weeks in patients with postoperative incidental GBC is a useful

strategy in selecting patients that will benefit from resection and avoid further tumor invasion.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Univariate analysis of clinicopathologic variables related to survival in PI-GBC patients who underwent surgical resection with curative intent (*n* = 80)

Variables	Cutoff levels	<i>n</i>	Survival rates (%)			<i>P</i>
			1 year	3 year	5 year	
Age (years)	<60	33	84.8	34.8	15.9	0.002
	≥60	47	89.4	62.1	45.3	
Gender	Male	27	81.5	38.4	13.2	0.065
	Female	53	90.6	71.5	29.8	
Associated gallstone	Present	51	96.4	67.1	43.4	0.058
	Absent	29	82.4	41.5	27.7	
pT (TNM)	pT1 and 2	61	96.7	68.0	43.1	0.000
	pT3 and 4	19	57.9	23.7	20.0	
Lymph node metastasis	Negative	62	90.3	54.8	35.4	0.168
	Positive	18	77.8	35.9	23.9	
Histologic differentiation	Well/moderate	66	90.9	52.6	32.5	0.827
	Poor	14	71.4	37.5	0.0	
Hepatic invasion	Present	16	68.8	14.1	0.0	0.000
	Absent	64	92.2	59.6	39.5	
Combined resection of adjacent organs	Present	3	66.7	33.3	0.0	0.605
	Absent	77	88.3	51.6	26.9	
Intraoperative blood loss	<500	73	87.7	48.8	31.8	0.227
	≥500	7	85.7	71.4	0.0	
Pathology	Adenocarcinoma	68	88.2	48.2	29.0	0.199
	Not adenocarcinoma	12	83.3	64.3	0.0	
Tumor location	Neck	13	75.0	33.3	0.0	0.048
	Body + tail	67	89.7	53.8	36.3	
Extrahepatic bile duct resection	Present	72	90.3	53.7	35.7	0.028
	Absent	8	62.5	25.0	0.0	
Extent of liver resection	Gallbladder bed	23	78.3	35.9	0.0	0.000
	Anatomical segments IV–V	35	97.1	63.6	27.9	
	Major hepatectomy (>3 segments)	22	77.3	39.0	14.6	
Cholecystectomy approach	Open	14	92.9	63.5	0.0	0.091
	Laparoscopic	66	86.4	63.5	27.2	
Time interval from cholecystectomy to reoperation	<2 weeks	37	94.6	69.6	41.4	0.002
	2 weeks–1 months	26	76.9	27.7	20.8	
	>1 months	17	82.4	35.3	0	

PI-GBC: Postoperative incidentally discovered gallbladder cancer; TNM: Tumor-node-metastasis.

Supplementary Table 2: Results of multivariate analysis

Variables	Regression coefficient	SE	<i>P</i>	Relative risk	95% <i>CI</i>
Age	0.060	0.350	0.864	1.062	0.535–2.108
pT	1.328	0.489	0.007	3.775	1.448–9.841
Hepatic invasion	1.459	0.666	0.028	4.301	1.167–15.861
Time since cholecystectomy	0.577	0.199	0.004	1.781	1.206–2.630
Tumor location	−0.497	0.487	0.307	0.608	0.234–1.579
Extrahepatic bile duct resection	−0.607	0.572	0.288	0.545	0.178–1.672
Extent of liver resection	−0.490	0.260	0.059	0.613	0.368–1.020

SE: Standard error; *CI*: Confidence interval.

Supplementary Table 3: Clinicopathologic features of PI-GBC patients by time interval group

Variables	n (%)			P
	Group 1 (<2 weeks)	Group 2 (2 weeks–1 month)	Group 3 (>1 month)	
Total	37	26	17	
Age, mean (SD), year	57.7 (9.3)	57.2 (10.9)	58.1 (9.2)	0.958
Time to reoperation, median (rang), week	1.2 (0.3–1.5)	2.8 (2.2–3.8)	4.9 (4.5–6.2)	0.000
Gender				
Male	11 (29.7)	13 (50.0)	3 (17.6)	0.077
Female	26 (70.3)	13 (50.0)	14 (82.4)	
Associated gallstone				
Present	23 (62.2)	18 (69.2)	10 (58.8)	0.757
Absent	14 (37.8)	8 (30.8)	7 (41.2)	
pT (TNM)				
pT1 and 2	31 (83.8)	17 (65.4)	13 (76.5)	0.240
pT3 and 4	6 (16.2)	9 (4.6)	4 (23.5)	
Extent of liver resection				
Gallbladder bed	12 (32.4)	5 (19.2)	10 (58.8)	0.066
Anatomical segments IV–V	17 (45.9)	11 (42.3)	3 (17.6)	
Major hepatectomy (>3 segments)	8 (21.6)	10 (38.5)	4 (23.5)	
Lymph node metastasis				
Negative	30 (81.8)	19 (73.1)	13 (76.5)	0.782
Positive	7 (18.9)	7 (26.9)	4 (23.5)	
Histologic differentiation				
Well/moderate	31 (83.8)	22 (84.6)	13 (76.5)	0.801
Poor	6 (16.2)	4 (15.4)	4 (23.5)	
Hepatic invasion				
Present	6 (16.2)	8 (30.8)	1 (5.9)	0.107
Absent	31 (83.8)	18 (69.2)	16 (94.1)	
Combined resection of adjacent organs				
Present	0 (0)	2 (7.7)	1 (5.9)	0.211
Absent	37 (100)	24 (92.3)	16 (94.1)	
Pathology				
Adenocarcinoma	29 (78.4)	23 (88.5)	16 (94.1)	0.333
Not adenocarcinoma	8 (21.6)	3 (11.5)	1 (5.9)	
Tumor location				
Neck	4 (10.8)	7 (26.9)	1 (5.9)	0.176
Body + tail	33 (89.2)	19 (73.1)	16 (94.1)	
Extrahepatic bile duct resection				
Present	3 (8.1)	4 (15.4)	1 (5.9)	0.621
Absent	34 (91.9)	22 (84.6)	16 (94.1)	
Intraoperative blood loss (ml)				
<500	34 (91.9)	25 (96.2)	14 (84.2)	0.262
≥500	3 (8.1)	1 (3.8)	3 (15.8)	
Cholecystectomy approach				
Open	10 (27.0)	3 (11.5)	1 (5.9)	0.154
Laparoscopic	27 (73.0)	23 (88.5)	16 (94.1)	

PI-GBC: Postoperative incidentally discovered gallbladder cancer; TNM: Tumor-node-metastasis; SD: Standard deviation.