

Role of Cholecystectomy and Lymph Node Dissection in Patients with T2 Gallbladder Cancer

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Abstract

Background Incidental findings of gallbladder cancer (GBCA) have dramatically increased as an initial presentation of the disease because of the expansion of laparoscopic cholecystectomy. However, the optimal management of T2 GBCA remains at issue.

Methods We compared our 10-year experience with the consensus surgical strategy for T2 GBCA. Between January 2000 and December 2009, 70 patients at Severance Hospital, Yonsei University Health System, Seoul, Korea, underwent surgical treatment for GBCA stage T2. The medical records of 70 patients with T2 GBCA were retrospectively reviewed.

Results Radical cholecystectomy was performed on only 32 (45.8 %) patients. In patients with T2 GBCA and positive lymph nodes (LN), the overall survival rate between cholecystectomy with LN dissection and radical cholecystectomy did not show a significant difference. Twenty patients experienced recurrence during the follow-up period. Among the 11 patients who underwent cholecystectomy with liver resection, only 2 (18.2 %) patients had an intrahepatic recurrence. Of the 9 patients who underwent cholecystectomy without liver resection, 3 (33.3 %) patients had an intrahepatic recurrence. However, recurrences at the gallbladder bed occurred only in one and

two patients, respectively, and were not significantly different between the two groups.

Conclusions There was a large gap between clinical practice and treatment guidelines. Though relatively few patients enrolled in this study experienced recurrence, cholecystectomy and LN dissection without liver resection showed similar survival and recurrence patterns compared with those of radical cholecystectomy. To improve consistency between clinical practice and consensus guidelines, the role of limited resection for T2 lesions needs further evaluation.

Introduction

Gallbladder cancer (GBCA) is a relatively rare disease with different epidemiology by geographic region, ranging from low incidence in Northern Europe and the United States to high incidence in Chile, India, Korea, and Japan [1]. The typical presenting symptoms of GBCA are nonspecific, and historically most patients have been diagnosed when the disease is already at an advanced stage. As a result, GBCA has a highly lethal malignancy [2], with a 5-year overall survival (OS) rate that ranges from 5 % [3] to 41 % [4].

In recent years, however, the incidental finding of GBCA has dramatically increased as the initial presentation of the disease because of the expansion of laparoscopic cholecystectomy [5, 6]. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend radical reoperation in patients with stages T1b to T3 GBCA [7]. The seventh American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging guidelines also recommended radical reoperation in patients with stages T2 to T3 GBCA [8]. This radical operation includes en bloc hepatic resection and lymphadenectomy with/without bile

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duct excision. However, some studies have reported that a less extensive procedure consisting of cholecystectomy with lymphadenectomy is a feasible and effective surgical strategy in patients with T2 GBCA [9, 10]. Additionally, the rate of hepatic resection and lymphadenectomy is very low, and clinical practice is performed in accord with NCCN and AJCC recommendations [11–14]. Thus, the optimal management of incidental T2 GBCA remains an issue for debate. In this article, we compare our 10-year clinical experience with the consensus-based guidelines for the surgical treatment strategy for GBCA.

Methods

Patients

Between January 2000 and December 2009, 70 patients at Severance Hospital, Yonsei University Health System, Seoul, Korea underwent surgical treatment of GBCA with stage T2. The medical records of those patients were retrospectively reviewed.

Preoperative studies

Abdominal ultrasonography and computed tomography were generally performed at the baseline. Position emission tomography was conducted to evaluate for distant metastasis. However, position emission tomography was performed after laparoscopic cholecystectomy in patients with incidentally diagnosed GBCA. Laboratory tests, including some on liver function, were also performed. Carbohydrate antigen (CA) 19-9 was evaluated as a tumor marker.

Definition of surgical strategies

The extent of resection was classified as R0, R1, or R2. R0 was defined as complete resection without microscopic residual disease. R1 was assigned when microscopic residual disease was present after resection. R2 was defined as having grossly residual disease after surgery.

Lymph node (LN) dissection was classified as Dx, D1, or D2 dissection. Dx indicated that no LN dissection was performed. D1 was defined as dissection around the hepatoduodenal ligament (LN removal around the cystic duct, bile duct, portal vein, and hepatic artery) with or without dissection of LN around the gastrohepatic ligament. D2 was defined as D1 dissection plus para-aortic LN dissection.

Simple cholecystectomy was defined as only cholecystectomy without liver resection and LN dissection.

Determination of surgical strategy

Fourteen patients underwent cholecystectomy and were diagnosed with GBCA. They underwent a second operation. Surgeons decided the extent of resection in consideration of the patient's age and any comorbidity. If patients showed more than Eastern Cooperative Oncology Group performance status 2 and were more than 75 years old or had severe coronary or pulmonary diseases limiting normal physical activity, limited resection was performed.

Outcomes

The OS by surgical strategy was analyzed. We also evaluated associations between clinical manifestations, laboratory test results, histopathological characteristics, and the OS. The concordance rate between our experiences and the NCCN and AJCC recommendations was calculated.

Statistical analysis

Statistical analysis was performed with SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Results for all continuous data are presented as the median (range). Results for all categorical data are presented as the number (percentage). The OS and disease-free survival (DFS) were calculated with the Kaplan–Meier method. The univariate and multivariate analyses of OS to identify prognostic factors were conducted with Cox's proportional hazard model. Statistical significance was defined by a *p* value <0.05.

Results

Baseline characteristics

Our patients were predominantly female ($n = 44$, 62.9 %) and the median age was 63 years (range 49–79 years). The median levels of carcinoembryonic antigen (CEA) and CA 19-9 were 9.3 ng/mL (0–2270.5) and 1.7 U/mL (0–72.54), respectively.

Surgical strategies

Fourteen patients (20 %) underwent a second operation after cholecystectomy. The rate of R0 resection was 90 % ($n = 63$) (Table 1). Cholecystectomy with/without LN dissection was performed with a laparoscopic approach in 21 patients (30 % of all patients). Cholecystectomy, LN dissection, and liver resection as suggested by the NCCN and AJCC recommendations were performed in only 32 (45.8 %) patients. Thirty-five patients underwent D2 LN

dissection, and ten patients did not undergo any LN dissection (Table 1).

Survival

There was no operative mortality. There was a loss of three patients during the median 46 months follow-up period

Table 1 Surgical strategies for T2 stage GBCA

Second operation	
No	56 (80 %)
Yes	14 (20 %)
Extent of resection	
R0	63 (90 %)
R1	3 (4.3 %)
R2	4 (5.7 %)
Cholecystectomy only	
LN dissection ^a	26 (37.1 %)
D1 dissection	16
D2 dissection	10
Laparoscopic approach	12
Open approach	14
LN dissection + BD resection	2 (2.8 %)
D1 dissection	1
D2 dissection	1
Liver resection ^b	
LN dissection + liver resection	17 (24.3 %)
D1 dissection	6
D2 dissection	11
LN dissection + BD resection + liver resection	15 (21.5 %)
D1 dissection	2
D2 dissection	13

LN lymph node, BD bile duct

^a D1 dissection includes lymph node dissection around the hepatoduodenal and gastrohepatic ligaments; D2 dissection includes D1 plus para-aortic lymph node dissection

^b Liver resection was performed because of intrahepatic duct stones

(range 4–127 months). The 5-year DFS and OS rates were 65 and 73 %, respectively (Fig. 1).

LN negative group

The 5-year OS rate did not differ significantly by operation type ($p = 0.517$) (cholecystectomy only = 75 %, cholecystectomy with LN dissection = 84 %, and radical cholecystectomy = 69 %) (Fig. 2a).

LN positive group

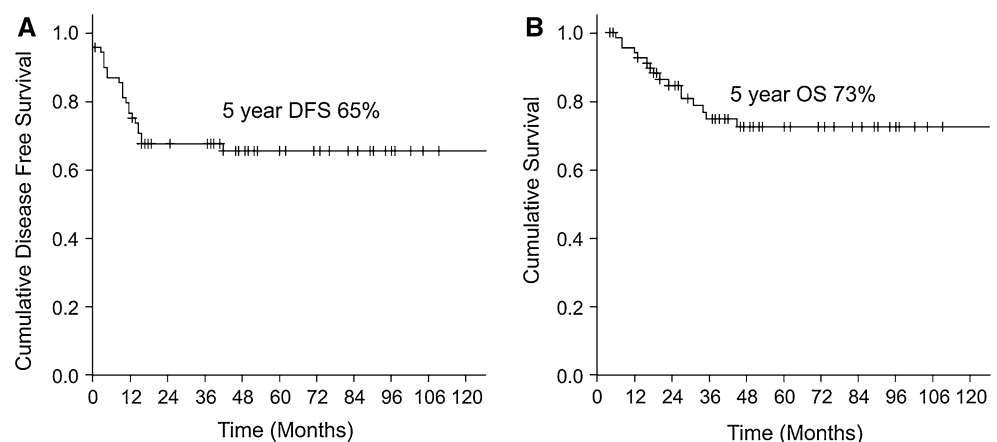
The 5-year OS rate in patients who underwent cholecystectomy only (0 %) was poorer than that of patients who underwent cholecystectomy with LN dissection (68 %) or radical cholecystectomy (78 %) (Fig. 2b). However, the 5-year OS rate in patients who underwent cholecystectomy with LN dissection or radical cholecystectomy did not reveal a statistically significant difference ($p = 0.464$) (Fig. 2b).

The median number of LN retrieved during a procedure was 5.5 (range 1–20) in patients undergoing D1 dissection and 19 (range 6–60) in patients undergoing D2 dissection. Patients who underwent only LN biopsy showed a poorer 5-year survival rate (0 %) than patients who underwent either D1 (72.9 %; $p = 0.01$) or D2 dissection (73.8 %; $p < 0.001$) (Fig. 2c). The 5-year OS rate was not significantly different between patients who underwent D1 and D2 dissection ($p = 0.713$) (Fig. 2c).

Univariate and multivariate analysis for prognostic factors of OS

In univariate analysis, levels of CEA and CA 19-9, the extent of resection, and the N stage were significantly associated with OS. However, only the CA 19-9 level [CA 19-9 >37 U/mL; hazard ratio (HR), 5.626; $p = 0.045$] and the extent of resection (R2 vs R0; HR, 22.26; $p = 0.025$)

Fig. 1 DFS and OS. **a** 5-year DFS for T2 GBCA was 65 %. **b** Five-year OS for T2 GBCA was 73 %



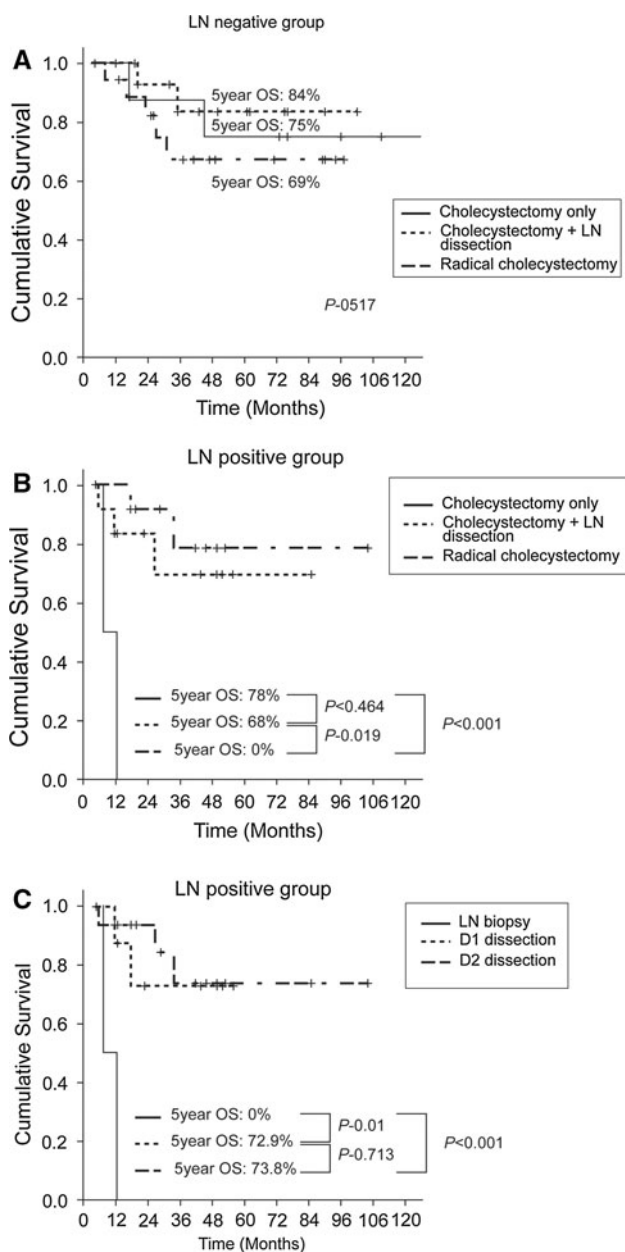


Fig. 2 In T2 GBCA, OS by operation type and the extent of lymph node dissection in the LN negative and positive groups. **a** In the LN negative group, 5-year OS is not significantly different by operation type. **b, c** In the LN positive group, 5-year OS in patients who underwent cholecystectomy only or LN biopsy is significantly lower. However, 5-year OS in the cholecystectomy plus LN dissection and the radical cholecystectomy groups are not significantly different. The 5-year OS for D1 and D2 dissection are also not significantly different

were found to be independent prognostic factors in multivariate analysis (Table 2). The patients with LN metastasis or some patients who did not undergo liver resection received chemotherapy or radiotherapy. However, adjuvant therapy did not show a significant correlation with OS.

Recurrence

Patients were regularly followed at three-month intervals with CT scans and measurement of tumor markers. During the median 40-month follow-up period, 20 (28.69 %) patients had a recurrence. Fourteen (70 %) patients had extrahepatic recurrences and only five (25 %) patients had intrahepatic recurrences. Recurrences in the gallbladder bed or on the surgical margins of the livers were observed in only three patients. Recurrence patterns and types did not show significant differences between patients who had cholecystectomy with liver resection and those who did not have a liver resection ($p = 0.438$) (Table 3).

Discussion

Laparoscopic surgery has been established as the mainstream treatment for benign gallstone disease. As a result of this treatment transition, the rate of incidental GBCA has increased substantially [5, 6]. The majority of incidental GBCAs are T2 lesions (67 %) [15]. The NCCN and AJCC Guidelines, seventh Edition, have consistently recommended reoperation for incidental T2 GBCA. This recommendation for reoperation includes en bloc hepatic resection and lymphadenectomy with or without bile duct excision. Pawlik et al. [15] reported a 10 % rate of residual disease in the liver at the time of reoperation, and other studies have recommended radical resection because of the high rates of LN metastasis, as well as a documented survival benefit in incidental T2 GBCA [2, 16–18]. However, recent population-based analysis using the surveillance, epidemiology and end results (SEER) data revealed a 13.4 % rate of radical cholecystectomy in clinical practice for T2 GBCA [13]. This suggests that the rate of hepatic resection and lymphadenectomy is very low, and out of accordance with the NCCN and AJCC recommendations for this stage of disease [11–14].

In our study, 9 (12.9 %) of 70 patients underwent only cholecystectomy, and 32 (45.8 %) patients underwent radical cholecystectomy. Our data showed a higher rate of radical cholecystectomy compared with that of SEER data, but the surgeons at our institution did not adhere to the guidelines of the NCCN and AJCC in many cases.

Some studies have reported a high survival rate following cholecystectomy only, contrary to previous reports [10, 19]. Consistent with this, in our study the 5-year OS rate of patients without LN metastasis who underwent cholecystectomy only was 75 % and was not significantly different when compared with the 84 and 69 % 5-year OS rates in other treatment groups. Kohya et al. [19] have suggested that these results may reflect the short follow-up time for many patients or a difference in tumor invasion

Table 2 Univariate and multivariate analysis of prognostic factors for OS in T2 GBCA

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95 %CI	<i>p</i> value	Hazard ratio	95 %CI	<i>p</i> value
Age (years)						
>65 versus ≤65	0.809	0.281–2.329	0.694			
CEA (ng/mL)						
>5 versus ≤5	4.142	1.167–14.701	0.028	0.467	0.045–4.827	0.523
CA 19-9 (U/mL)						
>37 versus ≤37	4.429	1.533–12.799	0.006	5.626	1.042–30.392	0.045
2nd operation						
Yes versus no	0.836	0.188–3.718	0.814			
Extent of resection						
R1 versus R0	0	0	0.985	0	0	0.992
R2 versus R0	17.02	5.003–57.893	<0.001	22.68	1.47–349.858	0.025
BDR						
No versus yes	4.718	0.623–35.723	0.133			
Hepatectomy						
No versus yes	1.112	0.414–2.988	0.833			
Lymph node dissection						
Dx or D0 versus D2	1.871	0.593–5.898	0.285			
D1 versus D2	2.467	0.66–9.225	0.18			
Differentiation						
MD versus WD	2.556	0.813–8.037	0.108			
PD versus WD	0.696	0.078–6.2229	0.746			
Lymphovascular invasion						
Yes versus no	2.458	0.771–7.843	0.129			
Perineural invasion						
Yes versus no	1.759	0.395–7.824	0.459			
N stage						
N1 versus Nx or N0	0.953	0.293–3.097	0.936	0.405	0.047–3.499	0.411
N2 versus Nx or N0	16.134	3.713–70.103	<0.001	1.686	0.028–99.808	0.802
Adjuvant treatment						
No versus yes	0.469	0.174–1.262	0.134			

D1 dissection included lymph node dissection around the hepatoduodenal and gastrohepatic ligaments

D2 dissection included D1 plus para-aortic lymph node dissection

CI confidence interval, CEA carcinoembryonic antigen, CA carbohydrate antigen, BDR bile duct resection, WD well-differentiated, MD moderately differentiated, PD poorly differentiated, N stage lymph node stage

depth. However, in the LN positive group, patients who underwent only cholecystectomy showed definitively poorer survival.

Interestingly, the 5-year OS rate of patients undergoing cholecystectomy with LN dissection has been reported to be similar to that of patients undergoing radical cholecystectomy [9], and our results showed a similar finding. The OS rates between cholecystectomy with LN dissection and radical cholecystectomy were comparable. Patients who underwent laparoscopic cholecystectomy and LN dissection did not have a survival advantage over patients who underwent open cholecystectomy with LN dissection or

radical cholecystectomy. Additionally, the recurrence rate was similar between cholecystectomy with LN dissection and radical cholecystectomy. Operation type and reoperation did not affect OS rates in the multivariate analysis. T2 GBCA was diagnosed by frozen pathologic examination or permanent pathologic examination. Frozen pathologic diagnosis was not accurate enough in terms of the invasion depth. Therefore, the effectiveness of limited resection must be evaluated further.

In conclusion, although the treatment guidelines for GBCA, as well as many investigators, recommend radical cholecystectomy as the optimal surgical strategy for T2

Table 3 Recurrence pattern according to liver resection status

Site of recurrence	With liver resection	Without liver resection	<i>p</i> value
Intrahepatic recurrence	2 (18.2 %)	3 (33.3 %)	0.438
Sg 4/5	1	2	
Others	1	1 ^a	
Extrahepatic recurrence	9 (81.8 %)	5 (55.6 %)	
Lymph node	5	2	
Peritoneal seeding	3	1	
Others	1 ^b	2 ^c	
Combined	0 (0 %)	1 (11.1 %)	

Sg liver segment

^a Multiple liver metastasis in both lobes

^b One patient had lung metastasis

^c One patient had lung metastasis and the other had muscle and lung metastasis

GBCA, our report of our clinical experience was not consistent with those recommendations. Though our findings showed discordance, they do suggest that cholecystectomy with LN dissection excluding liver resection may be an effective strategy for the surgical treatment of T2 GBCA. Limited resection, as with a laparoscopic cholecystectomy with LN dissection in T2 GBCA, may be a feasible and effective surgical strategy in some cases, particularly when the surgeon is able to perform an R0 resection. However, extent of LN dissection or number of essential retrieved LN must be further investigated. To improve consistency between guidelines and clinical practice, the role of limited resection in T2 GBCA requires further evaluation.

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