

Surgical strategy for T2 and T3 gallbladder cancer: is extrahepatic bile duct resection always necessary?

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Received: 2 May 2013 / Accepted: 6 September 2013 / Published online: 21 September 2013
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Abstract

Purpose Resection of the extrahepatic bile duct is not performed uniformly in gallbladder cancer. The study investigated the clinical significance of resection of extrahepatic bile duct (EHBD) in T2 and T3 gallbladder cancer.

Methods Between 2000 and 2010, 71 T2 or T3 gallbladder cancer patients who underwent R0 resection at Korea University Medical Center were included. Clinicopathological data were reviewed retrospectively. Survival analysis and comparison between EHBD resection and non-resection groups were performed.

Results The 32 men and 39 women had 49 T2 tumors and 22 T3 tumors. The overall survival rate was 67.8 % at 3 years and 47.2 % at 5 years. In multivariate analysis for overall survival, lymphovascular invasion and lymph node metastasis were significant independent predictors. Comparing the patients according to EHBD resection, the EHBD resection group demonstrated significantly longer hospital stay, longer operative time, more transfusion requirement, more extensive liver resection, and less treatment of neoadjuvant therapy. Significantly higher proportions of perineural invasion and lymph node metastasis were noted in the EHBD resection group. There were no statistically significant differences in survival between the EHBD resection and non-resection groups.

Conclusions Resection of extrahepatic bile duct was not always necessary in T2 and T3 cancers. However, the patients who undergo resection of extrahepatic bile duct tended to have more aggressive tumor characteristics and undergo more aggressive surgical approach. To enhance overall survival for the

patients with T2 and T3 gallbladder cancers, surgeons should try to perform R0 resection including EHBD resection.

Keywords Extrahepatic bile duct resection · Lymph node metastasis · T2 gallbladder cancer · T3 gallbladder cancer

Introduction

Radical surgery to achieve R0 resection is the treatment of choice for gallbladder cancer [1–4]. In T1 gallbladder cancer, cholecystectomy with/without lymph node dissection is appropriate [5]. For cancers more than T2, various surgical procedures have been adopted. Depth of tumor invasion and the progression of the disease are the key factors determining the extent of surgery. Depth of invasion, presence of lymph node metastasis, perineural invasion, and negative resection margin are significant prognostic factors affecting overall survival in gallbladder cancer [2–4, 6–8]. However, these factors are not easily detectable preoperatively or intraoperatively.

The extent of liver resection and lymph node dissection and whether to perform extrahepatic bile duct (EHBD) resection remains controversial [9–14]. There is no clear indication whether to include EHBD resection or not in gallbladder cancer surgery, except for early gallbladder cancer. Furthermore, the survival benefit of EHBD resection has not been defined precisely.

The aim of this retrospective study was to investigate the significance of EHBD resection in surgery for T2 and T3 gallbladder cancers. We focused on the oncologic benefit of EHBD resection in the resectable cases of gallbladder cancer excluding early gallbladder cancer (T1). The patients were divided into an EHBD resection group and EHBD non-resection group. Clinicopathological characteristics were compared between the two groups. The survival outcome and prognostic predictors affecting

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overall survival in patients with T2 and T3 gallbladder cancers after curative resection were analyzed.

Methods

From January 2000 to December 2010, 194 operations for gallbladder cancers were performed at the Department of Surgery, Korea University Medical Center, Korea University College of Medicine, Seoul, Korea. There were 99 resections for T2 and T3 gallbladder cancers. We excluded patients who underwent R1 resection ($n=24$) and R2 ($n=4$) resections. Seventy-one patients with T2 and T3 gallbladder cancers who underwent R0 resection were included in this study. Of the 71 patients, 49 (69 %) were diagnosed with pT2 tumors and the remaining 22 (31 %) were pT3 tumors. The patients' demographics and clinicopathological information were retrospectively obtained from the medical records and included age, gender, operative procedures, operative time, transfusion requirement, pathological results, postoperative complication, adjuvant therapy, and recurrence.

Lymph nodes were classified according to the TNM classification of the American Joint Committee on Cancer (AJCC) [15]. N1 was defined as metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein. N2 was defined as metastases to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes. N2 disease was not included because R0 resection could not be guaranteed in N2 disease with a possibility of microscopic systemic dissemination.

Pathologically, the gross morphological features were classified into two groups according to the presence of infiltration: infiltrative versus non-infiltrative tumor. Histologic type, differentiation, presence of perineural and lymphovascular invasion, lymph node metastasis, and margin status were investigated. Tumor stage was defined according to the AJCC pathological tumor node metastasis (pTNM) classification [15].

Survival analysis of the 71 R0 resection patients was performed. The survival rates were compared between R0 and R1 patients. Furthermore, the survival time of the R0 resection patients who demonstrated recurrence was compared with that of the R1 patients. The clinicopathological characteristics between the EHBD resection and EHBD non-resection group were compared. Significant prognostic factors affecting overall survival were investigated by univariate and multivariate analyses. Statistical calculations were performed using SPSS version 13.0 for Windows (SPSS, Chicago, IL, USA). Survival was measured from the date of surgery. Disease-free survival was measured from the date of surgery to the diagnosis of recurrence. Follow-up of patients was completed when death occurred or on November 31, 2012. Comparisons between groups were tested using Pearson's chi-square test and independent t test. Overall survival was

calculated using the Kaplan–Meier method. Clinicopathologic prognostic factors were analyzed by the univariate Kaplan–Meier method and compared by the log-rank test to identify the prognostic predictors for survival. Multivariate analysis was performed using Cox proportional hazards model to identify the independent prognostic factors for survival. Variables to be entered into the multivariate analysis were selected on the basis of the results of univariate analysis ($p<0.1$). A p value <0.05 was considered statistically significant.

Results

Clinicopathological characteristics

The patients comprised of 32 men and 39 women, aged 22 to 82 years (mean age 64 years). Gallstones were present in 25 patients (35 %). Fifty-four patients were diagnosed as definite or suspicious for gallbladder malignancy based on preoperative computed tomography scan. However, 17 patients were diagnosed with incidental gallbladder cancers during or after laparoscopic cholecystectomy. Of them, 16 patients received additional liver and/or EHBD resection and lymph node dissection immediately during the laparoscopic cholecystectomy or sometime after cholecystectomy. One patient received only an additional lymph node dissection. The operative procedures were cholecystectomy in 11 patients, cholecystectomy with EHBD resections in 9 patients, cholecystectomy with liver resection in 30 patients, and cholecystectomy with liver and EHBD resections in 21 patients. All patients received lymph node dissection. EHBD resection was performed in 30 patients and liver resection in 51 patients. Most of the liver resections ($n=39$) consisted of a wedge resection of liver around the gallbladder with a margin of approximately 2 cm. More extensive liver resections were performed in 12 patients and involved a right hemihepatectomy in four patients, central bisectionectomy in three patients, and segment 4b and 5 bisegmentectomy in 5 patients. Combined other organ resections were performed in five patients involving the stomach in two patients, colon in three patients, and pancreaticoduodenectomy in the remaining patient. Mean operative time was 256 ± 138 min and mean postoperative hospital stay was 14.6 ± 14.8 days. Postoperative complications occurred in 13 patients (18 %) and comprised with intra-abdominal abscess ($n=4$), surgical site infection ($n=5$), pleural effusion ($n=2$), acute renal failure ($n=1$), and angina ($n=1$). There was no postoperative mortality.

Adjuvant therapy was performed in 38 (54 %) patients and involved chemotherapy in 29 patients, radiation therapy in 2 patients, and concurrent chemoradiation therapy in 7 patients. Adjuvant radiation therapy was performed with external beam radiotherapy, and adjuvant chemotherapy was performed systemically using a 5-fluorouracil, cisplatin, or gemcitabine-based regimen.

Table 1 Clinicopathological characteristics according to depth of invasion (T2 vs T3)

Factor		T2	T3	<i>p</i> value
Liver resection	No resection	16	4	0.014
	Right hepatectomy	0	4	
	Central bisectionectomy	1	2	
	Segmentectomy 4a+5	3	2	
	Wedge resection	29	10	
EHBD resection	No	28	12	0.828
	Yes	21	10	
Laparoscopic	No	37	17	0.872
	Yes	12	5	
Adjuvant therapy	No	22	11	0.690
	Yes	27	11	
Size (cm)		3.1±1.7	5.0±3.2	0.023
Gross	Non-infiltrative	39	14	0.153
	Infiltrative	10	8	
Differentiation	Well	22	7	0.3
	Moderate to poor	27	15	
Lymphatic invasion	Negative	43	12	0.002
	Positive	6	10	
Perineural invasion	Negative	46	11	<0.001
	Positive	3	11	
LN metastasis	Negative	37	8	0.002
	Positive	12	14	

Pathologically, 22 patients were classified into T3 tumors as follows: perforating serosa ($n=4$), invasion to the liver ($n=12$), stomach ($n=1$), colon ($n=1$), omentum ($n=3$), and EHBD ($n=4$). Three patients had tumors invading the liver and other extrahepatic organs simultaneously.

The clinicopathological differences according to depth of invasion (T stage) are shown in Table 1. More extensive liver resections were performed in T3 tumors than in T2 tumors. T3 tumors were significantly greater in size. Significantly higher proportions of lymphovascular invasion, perineural invasion, and lymph node metastasis were detected in T3 tumors. There were no differences in EHBD resection, laparoscopic approach (proportion of incidentally diagnosed gallbladder cancer), adjuvant therapy, proportion of infiltrative tumor, and differentiation.

Overall survival and recurrence

Overall survival rates for the 71 patients who underwent R0 resection for T2 and T3 gallbladder cancers were 67.8 % at 3 years and 47.2 % at 5 years with median survival time of 51.4 months (Fig. 1). Comparing the survival of R0 and R1 ($n=24$) patients, the 3- and 5-year survival rates of R1 patients were 14.3 % and 7.2 %, respectively, with a median survival time of 11.6 months, which was significantly poorer than R0 patients ($p<0.001$). Univariate analysis of the 71 R0 resection

patients revealed that infiltrative tumor ($p=0.002$), lymphovascular invasion ($p<0.001$), lymph node metastasis ($p=0.001$), and advanced AJCC stage were significantly poor predictors for survival (Table 2). There was no survival

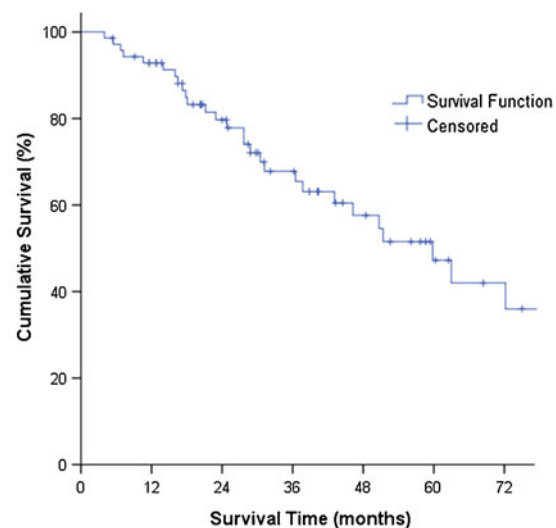


Fig. 1 Overall survival curve of T2 and T3 gallbladder cancer following R0 resection. Overall survival rates for the 71 patients were 67.8 % at 3 years and 47.2 % at 5 years

Table 2 Univariate analysis of prognostic factors for overall survival in T2 and T3 GB cancer

Prognostic factors		Number	3 YSR (%)	5 YSR (%)	<i>p</i> value
Age (years)	<65	36	70.1	36.4	0.531
	≥65	35	65.4	60.4	
Sex	F	39	62.0	34.1	0.150
	M	32	75.1	67.6	
Stone	No	46	66.5	45.1	0.999
	Yes	25	71.5	52.1	
Laparoscopic (incidental)	No	54	64.1	47.4	0.257
	Yes	17	78.8	43.8	
EHBD resection	No	40	76.4	54.2	0.112
	Yes	31	55.6	34.8	
Liver resection	No	20	65.1	51.3	0.728
	Wedge	39	73.5	45.9	
	Others	12	57.0	28.5	
Adjuvant therapy	No	33	69.5	45.6	0.676
	Yes	38	67.1	46.7	
Size	≤3 cm	30	75.6	58.5	0.141
	>3 cm	34	59.6	42.1	
Gross	Non-infiltrative	53	74.7	56.5	0.002
	Infiltrative	18	46.3	0	
Differentiation	Well	29	75.3	49.1	0.254
	Moderate to poor	42	62.3	47.5	
Lymphovascular invasion	Negative	60	75.7	52.8	<0.001
	Positive	11	17.7	17.7	
Perineural invasion	Negative	57	71.4	51.8	0.099
	Positive	14	45.6	0	
LN metastasis	Negative	45	85.6	61.0	0.001
	Positive	26	39.7	25.5	
T stage	T2	49	70.9	49.9	0.304
	T3	22	59.9	38.5	
TNM stage	II	38	82.3	59.9	0.009
	IIIA	8	87.5	58.3	
	IIIB	25	41.4	26.6	

YSR year survival rate

difference between the EHBD resection group and EHBD non-resection group. The extent of liver resection, adjuvant therapy, size, and differentiation did not affect overall survival significantly. Five-year survival rate of T2 and T3 gallbladder cancers after R0 resection was 49.9 % and 38.5 %, respectively, showing no statistically significant difference ($p=0.304$). Perineural invasion was not a significant prognostic factor for overall survival ($p=0.099$). Multivariate analysis using a Cox proportional hazards model demonstrated that lymphovascular invasion ($p=0.001$; hazard ratio (HR), 5.729; confidence interval (CI), 2.096–15.331) and lymph node metastasis ($p=0.012$; HR, 2.826; CI, 1.259–6.345) were significant independent predictors of overall survival.

Recurrence occurred in 30 patients (42.3 %). Of them, four patients had unknown recurrent time and sites. Disease-free survival rates were 77.0 % at 1 year and

58.5 % at 3 years. Comparing the overall survival between the R0 resection patients who demonstrated recurrence ($n=30$) with patients who had R1 resection ($n=24$), median survival time of the former (27.7 months) was superior to those of the latter (11.6 months) ($p=0.031$). The sites and patterns of recurrence were as follows: locoregional recurrence ($n=6$), liver ($n=11$), lung ($n=4$), peritoneum ($n=6$), and distant lymph nodes (paraaortic, aortocaval lymph nodes, $n=13$). Twelve patients demonstrated more than two recurrent sites and/or pattern at the initial diagnosis of the recurrent disease. Only one patient demonstrated solitary local recurrence. The other five patients who demonstrated local recurrence had combined other distant recurrent disease. All recurrent patients except one demonstrated distant metastasis as a recurrent pattern. The liver and distant lymph nodes were common.

Table 3 Comparison of the clinicopathological factors according to the EHBD resection

Prognostic factors		EHBD resection (-) (n=40)	EHBD resection (+) (n=31)	p value
Age (years)		65±9	62±13	0.227
Sex	M	18	14	0.989
	F	22	17	
Preoperative biliary drainage	No	28	26	0.119
	Yes	2	5	
Operative time (min)		186±93	345±136	<0.001
Transfusion	No	31	16	0.022
	Yes	9	15	
Liver resection	No	13	7	0.039
	Right hepatectomy	0	4	
	Central bisectionectomy	1	2	
	Segmentectomy 4a+5	1	4	
	Wedge resection	25	14	
Laparoscopic	No	31	23	0.746
	Yes	9	8	
Postoperative hospital stay (days)		11±5	19±21	0.034
Complication	No	37	21	0.007
	Yes	3	10	
Adjuvant therapy	No	14	19	0.028
	Yes	26	12	
Size (cm)		3.7±2.7	3.5±2.0	0.766
Size	≤3 m	18	12	0.739
	>3 cm	19	15	
Gross	Non-infiltrative	33	20	0.084
	Infiltrative	7	11	
Differentiation	Well	19	10	0.195
	Moderate to poor	21	21	
Lymphovascular invasion	Negative	31	24	0.994
	Positive	9	7	
Perineural invasion	Negative	36	21	0.019
	Positive	4	10	
LN metastasis	Negative	30	15	0.021
	Positive	10	16	
T stage	T2	28	21	0.838
	T3	12	10	
TNM stage	II	25	13	0.035
	IIIA	6	2	
	IIIB	9	16	

Comparison between EHBD resection and EHBD non-resection groups

The EHBD resection group demonstrated significantly longer operative time ($p < 0.001$), more transfusion requirement ($p = 0.022$), more extensive liver resection ($p = 0.039$), and longer postoperative hospital stay ($p = 0.034$) than the EHBD

non-resection group. Significantly, more occurrences of complication ($p = 0.007$) and less treatment of adjuvant chemo- and/or radiation therapy ($p = 0.028$) were evident in the EHBD resection group. Pathologically, significantly higher incidence of perineural invasion ($p = 0.019$), lymph node metastasis ($p = 0.021$), and advanced stage ($p = 0.035$) were present in the EHBD resection group than the EHBD non-resection

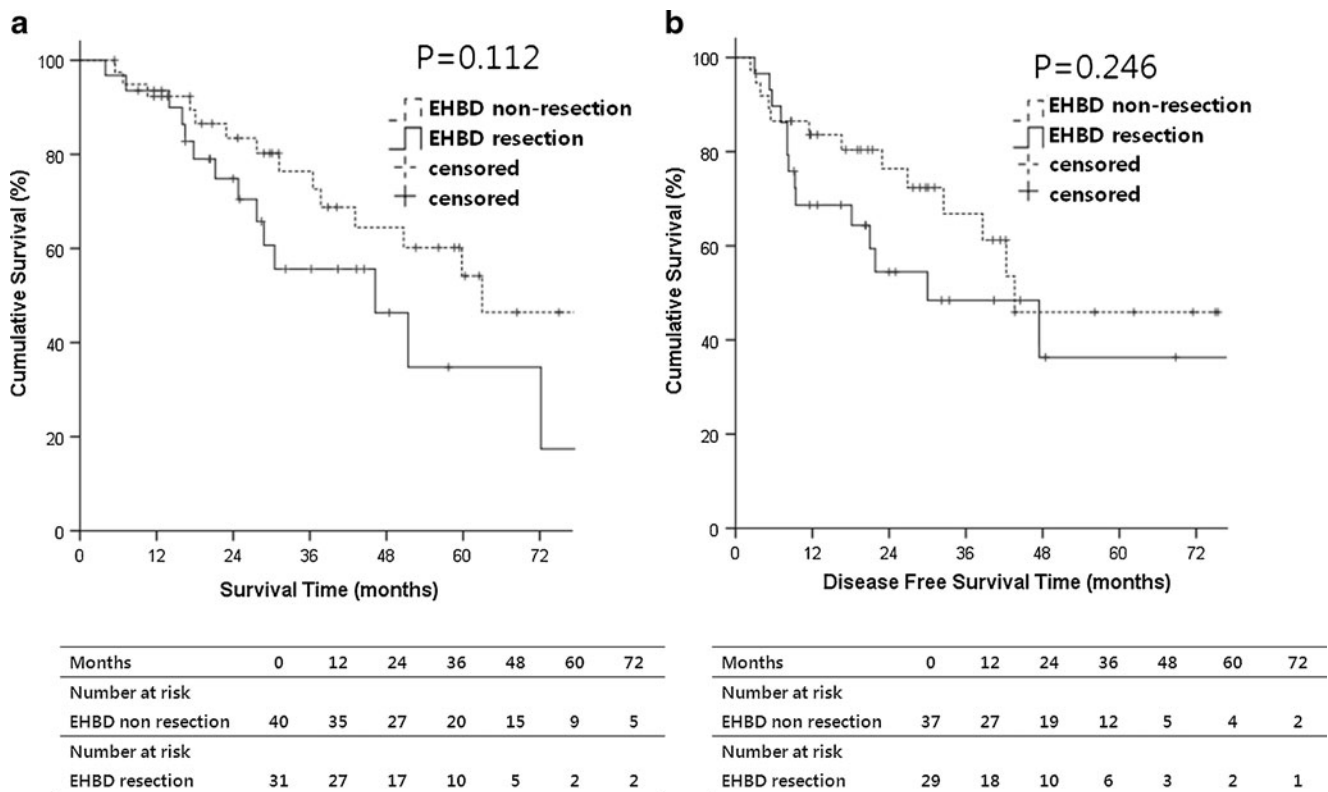


Fig. 2 Overall survival and disease-free survival curves according to EHBD resection. EHBD resection group did not achieve better overall survival (**a**) and disease-free survival (**b**) than the EHBD non-resection group

group. There were no differences in size, proportion of infiltrative tumors, differentiation, presence of lymphovascular invasion, and T stage between the EHBD resection and EHBD non-resection groups (Table 3). According to the survival analysis for EHBD resection, the EHBD resection group did not achieve better survival and disease-free survival than the EHBD non-resection group. The 3- and 5-year survival rates of EHBD resection group were 55.6 % and 34.8 %, respectively, and those of EHBD non-resection group were 76.4 % and 54.2 %, respectively ($p=0.112$). The 3- and 5-year disease-free survival of EHBD resection groups were 48.4 % and 36.3 %, respectively, and those of EHBD non-resection group were 66.8 % and 45.9 %, respectively ($p=0.246$) (Fig. 2).

Discussion

In the current study of T2 and T3 gallbladder cancer following R0 resection, lymphovascular invasion and lymph node metastasis were independent prognostic factors for survival by multivariate analysis, while perineural invasion was not. R0 resection, presence of lymph node metastasis [2, 4, 10, 14, 16], and perineural invasion [6, 10] have been reported to be significant prognostic factors for survival. Several studies have focused on the clinical significance of hepatoduodenal ligament invasion and EHBD resection [6, 11, 17–20].

The surgical extent of T2 and T3 gallbladder cancer remains controversial. Although R0 resection is the treatment of choice, whether or not to perform EHBD resection is still debatable [17–20]. In the current study, patients who underwent EHBD tended to have more aggressive tumor characteristics and to be treated by more extensive liver resection. Significantly higher proportion of perineural invasion and lymph node metastasis were detected in the EHBD resection group than the EHBD non-resection group. However, there was no survival difference between the groups, perhaps reflecting a selection bias in which more aggressive tumors tended to be addressed using a more aggressive surgical approach including EHBD resection. Therefore, it seems reasonable to conclude that EHBD resection might offer some survival benefit.

Several studies have verified the efficacy of EHBD resection or the indication of EHBD resection in gallbladder cancer. Sakamoto et al. reported no survival benefit of EHBD resection in patients with T2 or higher grader gallbladder cancer, with or without lymph node metastasis [6]. However, in gallbladder cancers with the presence of perineural invasion, patients with EHBD resection showed significantly better survival than those without EHBD resection, prompting the conclusion that EHBD resection might offer a prognostic advantage when perineural invasion exists. However, the precise assessment of lymph node metastasis and perineural invasion was limited preoperatively, leading the authors to

suggest routine EHBD resection in all patients with gallbladder cancer higher than T2 [6]. In another study [18], modes of hepatoduodenal ligament invasion were classified into four groups: direct invasion of bile duct, continuous intramural interstitial spread, distant spread separated from the primary tumor, and metastatic lymph node. The survival of the patients with direct invasion of bile duct was poorer than the other three types. The authors also suggested that strong consideration should be given to resection of EHBD in patients with gallbladder cancer higher than T2.

On the contrary, the recent Japanese Society of Biliary Surgery survey reported that there was no difference in overall survival between the EHBD resection and EHBD non-resection groups in patients with lymph node metastasis at each T2, T3, and T4 stage gallbladder cancer [19]. Therefore, EHBD resection might be unnecessary in advanced gallbladder cancer without a direct infiltration of the hepatoduodenal ligament and the cystic duct [17, 19]. EHBD resection has a potential adverse effect of bilioenteric anastomosis [17] and is associated with a significantly higher occurrence of postoperative complications [19] similar to our result. Moreover, presently, the EHBD resection group demonstrated significantly longer operation time and postoperative hospital stay, and more transfusion requirement; these factors are associated with a higher occurrence of complications. However, these factors will be overcome by efforts to improve the surgical technique, anesthesia, and postoperative care.

Tumor cells spread into the interstitial tissues of the hepatoduodenal ligament, which are abundant in lymphatic and nerve tissues [11, 18]. The interstitial tissue invasion progresses not only to the hepatoduodenal ligament, head of the pancreas, and the paraaortic fat but also to Glisson's sheath in the liver, followed by invasion of the interstitial tissue around the hilar bile duct [11]. As shown presently, most of the recurrent pattern was distant metastasis not local recurrence. Liver and the paraaortic and aortocaval lymph node were common sites for recurrence. Therefore, EHBD resection requires complete clearance of the interstitial tissues and lymph nodes of the hepatoduodenal ligament as systemic control, as well as regional control to minimize lymphatic and interstitial spread.

In this retrospective study, to decide whether or not to perform EHBD resection was dependent on the surgeons' policy or the patients' general condition including age and comorbidity. Although the indications of EHBD resection were not always clear-cut in the retrospective basis of this study, EHBD resection was performed in patients with suspected direct invasion of cancer cells in the bile duct by intraoperative finding although the final pathology are not always positive of cancer cell, or positive cystic duct margin, or performed for complete clearance of the hepatoduodenal ligament.

The efficiency of adjuvant therapy was controversial in a review of literature [21–23]. There was no influence of

adjuvant therapy on survival when R0 resection was performed, and adjuvant therapy was less administered in EHBD resection group than EHBD non-resection group in the current study. From a meta-analysis of the adjuvant therapy in the treatment of biliary tract cancer including gallbladder cancer [23], there was not a significant survival benefit in adjuvant therapy group comparing with surgery alone group. However, in patients who had lymph node-positive disease or advanced gallbladder cancer and R1 disease, adjuvant therapy was beneficial [22, 23]. Although there was no efficacy of adjuvant therapy after R0 resection from this study, however, in patients with advanced gallbladder cancer with lymph node metastasis, adjuvant therapy could be considered.

In conclusion, lymphovascular invasion and lymph node metastasis were significant independent prognostic factor for overall survival in T2 and T3 gallbladder cancer following R0 resection. EHBD resection groups tended to have more aggressive tumor characteristic than the EHBD non-resection group. Furthermore, there was no survival difference between the two groups. Therefore, EHBD resection was not always necessary in T2 and T3 cancers. However, to enhance the overall survival for patients with T2 and T3 gallbladder cancer, especially demonstrating aggressive tumor characteristics, surgeons should try to perform R0 resection including EHBD resection.

Acknowledgments The research was supported by a grant from Korea University.

Conflicts of interest None.

References

1. Chan SY, Poon RT, Lo CM et al (2008) Management of carcinoma of the gallbladder: a single-institution experience in 16 years. *J Surg Oncol* 97:156–164
2. Kai M, Chijiwa K, Ohuchida J et al (2007) A curative resection improves the postoperative survival rate even in patients with advanced gallbladder carcinoma. *J Gastrointest Surg* 11:1025–1032
3. Yagi H, Shimazu M, Kawachi S et al (2006) Retrospective analysis of outcome in 63 gallbladder carcinoma patients after radical resection. *J Hepatobiliary Pancreat Surg* 13:530–536
4. Behari A, Sikora SS, Waghlikar GD et al (2003) Longterm survival after extended resections in patients with gallbladder cancer. *J Am Coll Surg* 196:82–88
5. You DD, Lee HG, Paik KY et al (2008) What is an adequate extent of resection for T1 gallbladder cancers? *Ann Surg* 247:835–838
6. Sakamoto Y, Kosuge T, Shimada K et al (2006) Clinical significance of extrahepatic bile duct resection for advanced gallbladder cancer. *J Surg Oncol* 94:298–306
7. Shimada H, Endo I, Togo S et al (1997) The role of lymph node dissection in the treatment of gallbladder carcinoma. *Cancer* 79:892–899
8. Sasaki R, Uesugi N, Itabashi H et al (2005) Clinicopathological study of depth of subserosal invasion in patients with pT2 gallbladder carcinoma. *J Surg Oncol* 92:83–88

9. Shimada H, Endo I, Fujii Y et al (2000) Appraisal of surgical resection of gallbladder cancer with special reference to lymph node dissection. *Langenbecks Arch Surg* 385:509–514
10. Chijiwa K, Nakano K, Ueda J et al (2001) Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. *J Am Coll Surg* 192:600–607
11. Endo I, Shimada H, Fujii Y et al (2001) Indications for curative resection of advanced gallbladder cancer with hepatoduodenal ligament invasion. *J Hepatobiliary Pancreat Surg* 8:505–510
12. Araida T, Higuchi R, Hamano M et al (2009) Hepatic resection in 485 R0 pT2 and pT3 cases of advanced carcinoma of the gallbladder: results of a Japanese Society of Biliary Surgery survey—a multicenter study. *J Hepatobiliary Pancreat Surg* 16:204–215
13. Kondo S, Nimura Y, Hayakawa N et al (2000) Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. *Br J Surg* 87:418–422
14. Kohya N, Miyazaki K (2008) Hepatectomy of segment 4a and 5 combined with extra-hepatic bile duct resection for T2 and T3 gallbladder carcinoma. *J Surg Oncol* 97:498–502
15. Edge SB, Byrd DR, Compton CC et al (eds) (2009) *AJCC Cancer staging manual*, 7th edn. Springer, New York
16. Shimizu H, Kimura F, Yoshidome H et al (2007) Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification. *J Hepatobiliary Pancreat Surg* 14:358–365
17. Kosuge T, Sano K, Shimada K et al (1999) Should the bile duct be preserved or removed in radical surgery for gallbladder cancer? *Hepatogastroenterology* 46:2133–2137
18. Shimizu Y, Ohtsuka M, Ito H et al (2004) Should the extrahepatic bile duct be resected for locally advanced gallbladder cancer? *Surgery* 136:1012–1017, discussion 1018
19. Araida T, Higuchi R, Hamano M et al (2009) Should the extrahepatic bile duct be resected or preserved in R0 radical surgery for advanced gallbladder carcinoma? Results of a Japanese Society of Biliary Surgery Survey: a multicenter study. *Surg Today* 39:770–779
20. Kaneoka Y, Yamaguchi A, Isogai M et al (2003) Hepatoduodenal ligament invasion by gallbladder carcinoma: histologic patterns and surgical recommendation. *World J Surg* 27:260–265
21. Park HS, Lim JY, Yoon DS et al (2010) Outcome of adjuvant therapy for gallbladder cancer. *Oncology* 79:168–173
22. Mojica P, Smith D, Ellenhorn J (2007) Adjuvant radiation therapy is associated with improved survival for gallbladder carcinoma with regional metastatic disease. *J Surg Oncol* 96:8–13
23. Horgan AM, Amir E, Walter T et al (2012) Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 30:1934–1940