Original Article

Outcome of the Surgical Treatment of Gallbladder Cancer: A 10-year Single Center Experience

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Objective: Gallbladder cancer (GBC) is a rare cancer with extremely poor prognosis due to a usual late presentation with an advanced stage. Surgical resection is the only curative treatment. The present study aimed to analyze the outcome after curative resection and to identify the factors affecting prognosis in a single tertiary hospital.

Materials and Methods: A retrospective analysis of GBC patients who underwent surgical resection from 2006 to 2015 at Siriraj Hospital was performed. The clinical characteristics, operative data, and pathological results were reviewed. Survival and prognostic factors were analyzed with the Kaplan–Meier method and Cox proportional hazards model, respectively.

Results: In total, 69 GBC patients underwent surgery during the study period. Among these, 55 cases (80%) underwent resection with curative intent, while unresectable disease was found intraoperatively in 14 patients (20%). Preoperative hyperbilirubinemia was associated with unresectable disease. Among those who underwent curative resection, 37 cases (67%) achieved R0 resection, and 18 cases (33%) presented with a positive margin (R1 resection). The median disease-free survival (DFS) and overall survival (OS) were 18 and 24 months, respectively. The 1-year and 5-year DFS rates were 56% and 27%. The 1-year and 5-year OS rates were 72% and 29% respectively. Factors affecting the outcome according to univariate analysis included the completeness of resection, tumor stage, presence of perineural and lymphovascular invasion on the pathology, and the type of histopathology. Multivariate analysis identified the type of histopathology as an independent prognostic factor for OS (p = 0.008). The completeness of resection margin also showed a trend toward predicting OS, but this did not reach statistical significance (p = 0.079).

Conclusion: The prognosis of GBC is dismal. Adenocarcinoma is associated with a better survival rate than non-adenocarcinoma.

Keywords: Gallbladder cancer, Carcinoma of gallbladder, Radical cholecystectomy, Predictive factor, Survival

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Gallbladder cancer (GBC) is an uncommon biliary tract cancer worldwide; however, its incidence is relatively high in certain geographical areas (Latin America and South Asia)[1, 2]. Although the prevalence of GBC is not high in Thailand, the outcome of treatment is still problematic.

Currently, the prognosis of GBC is unsatisfactory and there is still much room for improvement. The majority of patients have short survival after diagnosis. The disease has no specific symptom and tends to be asymptomatic initially, so most patients present with non-curable disease because of the delayed diagnosis. The probability of it being an unresectable disease at the time of surgery is high, with a rate up to 50%[3,4]. While good survival rates after simple cholecystectomy have been reported for T1 GBC, with a more than 80% 5-year overall survival (OS), patients with T2-T4 GBC have extremely poor 5-year OS[5,6]. At present, there is no guideline to choose the best treatment strategy and operative techniques. Nevertheless, complete surgical resection is, to date, the most recommended treatment providing a long-term survival benefit for localized GBC[6-8]. Given that the anatomical position of the gallbladder is in proximity to the porta hepatis and pancreaticoduodenal complex, challenging operative procedures may be needed to achieve a free resection margin in locally advanced GBC, including liver resection, pancreaticoduodenectomy (PD), or even hepatopancreaticoduodenectomy (HPD).

The present study aimed to evaluate the survival outcome of patients after surgical treatment of GBC in Siriraj Hospital, which is a tertiary university hospital in Bangkok, Thailand. The present study also analyzed the prognostic factors affecting overall survival (OS) after the curative resection.

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Materials and Methods

With institutional review board approval, a retrospective surgical database and chart review were searched from January 2006 to December 2015. In total, 127 patients had been diagnosed with GBC and admitted to the Department of Surgery, Faculty of Medicine Siriraj Hospital, Thailand. Among these, 58 patients were admitted for the palliative treatment of symptoms related to the advanced stage of the disease. Only 69 patients underwent surgery for GBC. Patient characteristics, including the presenting symptoms, biochemical data, operative data, and the pathological data of the patients were reviewed. The objectives of study were to evaluate disease-free survival (DFS) and overall survival (OS) after a curative resection of GBC and to identify prognostic factors for DFS and OS.

Definitions

Incidental GBC was defined as a patient who underwent cholecystectomy from non-cancer related indications but GBC was incidentally found on their pathological report. Asymptomatic GBC involved a patient who underwent abdominal imaging from other indications and a tumor was incidentally found in their gallbladder. From a tumor perspective, early GBC was defined as Tis (carcinoma in situ), T1a, and T1b disease, whereas locally advanced GBC was T2-T4 disease on the surgical pathological report. In terms of operative procedures, simple cholecystectomy (SC), including open cholecystectomy (OC) and laparoscopic cholecystectomy (LC), was defined as cholecystectomy alone without any additional procedure. Whereas radical cholecystectomy (RC) was cholecystectomy with a non-anatomical resection of the gallbladder bed or 4b and 5 segmentectomy with hepatoduodenal lymph node (LN) dissection. Major hepatectomy (MH) was defined as the resection of ≥3 segments in Couinaud's system. Additional visceral resection was defined as an operation that was required to be performed in selected cases in order to achieve a margin-free resection, such as colectomy and a partial duodenal resection.

Management strategies and operative procedures

Common practice in management for GBC in our hospital were stratified by the tumor stage, dividing into incidental and early GBC, and locally advanced GBC.

Incidental GBC and early GBC

The majority of patients with early or incidental GBC were diagnosed based on the pathological report after simple cholecystectomy, LC or OC, in our hospital or referred from other hospitals. The pathological review was performed in every case to assess the tumor stage and margin of resected specimen. A high-quality cross-sectional abdominal scan, computed tomography (CT), or magnetic resonance imaging (MRI) was done for the complete staging and planning for further treatment. Patients with Tis and T1a without evidence of residual disease or metastasis and pathological confirmation of R0 resection were not scheduled for re-resection, and close follow-up was planned for these patients. The management of margin-free T1b GBC varied according to the surgeon preference with either re-resection or close follow-up. Patients with positive-margin T1 GBC were scheduled for radical re-resection and hepatoduodenal lymph node dissection with an aim to achieve an R0 margin, complete staging, and adequate control of the locoregional tumor as long as the condition of the patients was suitable for major surgery.

Locally advanced GBC

Patients with T2-T4 GBC, who were medically suitable to be major operative candidates, were evaluated preoperatively by abdominal CT or MRI in order to assess the resectability of their tumors. Distant metastasis, extensive tumor invasion of the liver or hepatoduodenal ligament, and para-aortocaval lymph node metastasis were contraindicated for radical resection. The surgical decision and planning were made on a case-by-case basis. The potentially resectable patients were scheduled for exploratory laparotomy or diagnostic laparoscopy to assess the operative feasibility. Patients who were found to have advanced disease at the time of exploration or laparoscopy were precluded from radical resection. Otherwise, curative resection including cholecystectomy, resection of segment 4b/5 or the wide non-anatomical resection of gallbladder fossa, and hepatoduodenal lymph node dissection were performed to obtain an R0 margin. Common bile duct (CBD) resection was done selectively in the case of the tumor showing a gross invasion of the bile duct. On the contrary, if the cystic duct area appeared normal, a frozen section was requested to confirm the negative margin of the cystic duct when a pathologist was available. If the frozen section of the cystic duct revealed malignant cells invasion, CBD resection was done to achieve an R0 resection. The indication to perform MH, PD, and additional visceral resection was done to obtain a clear resection margin from the tumor invasion of adjacent organs.

Preoperative preparation

The standard preoperative biochemical tests for GBC in our center mostly included liver function test (LFT), carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), and coagulograms. Preoperative biliary drainage was selectively done on a case-by-case basis by endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic biliary drainage (PTBD) based upon anatomical feasibility. Patients with locally advanced GBC, and who were planned for MH, may need to increase future liver remnant by portal vein embolization (PVE) additionally. Indications for preoperative biliary drainage were cholangitis, required preoperative PVE, and a need to improve the patient's physical condition before surgery.

Postoperative management

The pathology were analyzed by gastrointestinal pathologists and classified according to the TNM system of

the American Joint Committee on Cancer (AJCC) 7th edition. Adjuvant chemoradiotherapy was not routinely offered for those patients with an R0 resection and LN negative disease. Patients were scheduled for postoperative follow-up every 3 to 4 months during first two years and then every six months afterwards. The evaluation included a physical examination, cross-sectional imaging, and blood tests (LFT, CA19-9, CEA).

Statistical analysis

The demographic, clinical, operative, and pathological data were reviewed and evaluated. Continuous variables were compared between groups according to operative resectability by independent sample t-test or Mann-Whitney U-test as appropriate. Categorical variables were compared by the Chi-square test or Fisher's exact test as appropriate. Patients with advanced or unresectable disease were excluded from the survival analysis. The OS and DFS were estimated using the Kaplan-Meier method. The potential prognostic factors were classified in binary fashion, including eight factors: serum total bilirubin (TB) more than or less than 5 mg/dl, negative (R0) or positive (R1) margin, required re-resection after SC, required additional CBD or visceral resection beyond RC, T stage (Tis, T1 vs. T2-4), perineural invasion (PNI), lymphovascular invasion (LVI), and type of histopathology (adenocarcinoma vs. non-adenocarcinoma). The potential prognostic factors for OS were compared univariately by log-rank test. Potential prognostic factors that were statistically significant with a p-value <0.1 were then included in the multivariate analysis. Multivariate analysis of the potential factors from the univariate analyses was performed to identify significant independent prognostic factors for OS by using the Cox proportional hazards model. A p-value of less than 0.05 was considered statistically significant. All the statistical analyses were analyzed by IBM SPSS Statistics version 23.0 (IBM Corp, Somers, NY, USA).

Results

Patient characteristics

In total, 69 GBC patients underwent surgery during 2006 to 2015. Fourteen patients (20%) were found to have non-curative disease (metastatic disease or locally advanced unresectable stage) intraoperatively and the operations were terminated. Fifty-five patients (80%) underwent resection with curative intent successfully. In the resectable group, 46 patients (84%) were female and their median age was 66 years old; whereas, there were 9 females (64%) with a median age of 55 years old in the unresectable group. The clinical presentations were similar between both groups. The most common presentation was abdominal pain (66% in the resectable group vs. 93% in the unresectable group, p = 0.202). Clinical jaundice was higher in the unresectable group (43% in the unresectable group vs. 18% in the resectable group, p = 0.051). Incidental GBC was presented in 47% and 29% of the resectable and unresectable patients, respectively (p = 0.208); while there were 15% asymptomatic patients who were diagnosed with GBC from other indicated abdominal imaging in the resectable group, but there were no asymptomatic patients in the unresectable group (p = 0.129). All the biochemical tests were found to be not different between the two groups, except for the serum TB level. The median TB was 0.65 mg/dl in the resectable patients and 12.4 mg/dl in the unresectable group (p = 0.011). The serum CA19-9 and CEA levels were also not statistically different between the two groups. A summary of the patients' characteristics of both groups is shown in Table 1.

Operative procedures and pathology among resectable patients

Operative procedures

Simple cholecystectomy (SC), open cholecystectomy (OC), or laparoscopic cholecystectomy (LC) were done in 19 cases (35%). Radical cholecystectomy (RC) was performed in 40 cases (73%) in total; in 32 patients, it was

Table 1. Characteristics of patients who underwent abdominal exploration and laparoscopy for gallbladder cancer

Characteristics	Resectable disease (n = 55)	Unresectable disease (n = 14)	p-value
Gender			0.108
Male	9 (16%)	5 (36%)	
Female	46 (84%)	9 (64%)	
Age (years) (IQR)	66 (52 to 75)	55 (30 to 76)	0.031
Presentation			
Asymptomatic/health checkup	8 (15%)	0 (0%)	0.129
Incidental GBC	23 (47%)	4 (29%)	0.208
Abdominal pain	36 (66%)	13 (76.47%)	0.672
Jaundice	10 (18%)	6 (43%)	0.051
Median biochemical test (IQR)			
TB (mg/dl)	0.65 (0.4 to 1.43)	12.40 (0.60 to 22.9)	0.011
CA19-9 (unit/ml)	19.06 (7.2 to 138.4)	126.20 (8.04 to 1647)	0.137
CEA (ng/ml)	2.77 (1.47 to 5.17)	3.04 (1.69 to 5.41)	0.396

CEA = carcinoembryonic antigen, GBC = gallbladder cancer, IQR = interquartile range, TB = total bilirubin

performed as the definitive procedure (58%), while in 8 patients, it was performed as part of a more aggressive operation (15%). The additional visceral resections were done in 16 cases (29%) concurrent with radical cholecystectomy by making the decision based on preoperative imaging and operative finding, with an aim to achieve an R0 resection. CBD resection was done in 15 cases (27%): as the only additional procedure in 7 cases (13%) and as a part of more complex procedures in 8 cases (15%). Major hepatectomy (MH) was done in 4 cases (7%), all combined with CBD resection. Pancreaticoduodenectomy (PD) was performed in 3 patients (5%). Right colectomy and partial resection of the second part of the duodenum were performed in 3 patients (5%) and 1 patient (2%), respectively. Of 55 patients, 3 patients underwent multi-organ combined resections, including one RC with right colectomy with a partial duodenal wall resection, one RC with PD with right colectomy, and one hepatopancreaticoduodenectomy (HPD) with right colectomy.

Pathology

All surgical specimens were examined by gastrointestinal pathologists and were categorized by the AJCC 7th edition as per the TNM system. The most common type of histopathology was adenocarcinoma, which was documented in 48 patients (87%). Non-adenocarcinoma was found in 7 patients (13%). Among the non-adenocarcinoma group, there were 3 adenosquamous carcinomas (5%), 1 squamous cell carcinoma (2%), 2 neuroendocrine tumors (4%), and 1 undifferentiated carcinoma (2%). According to TNM staging, 14 patients (25%) were in early stage GBC, including 5 Tis (9%), 1 T1a (2%), and 8 T1b (15%). Forty-one patients (75%) had locally advanced GBC, which included 20 T2 (36%), 18 T3 (33%), and 3 T4 (5%). Lymph node (LN) metastases were found in 21 patients (38%). The majority of the patients who had synchronous LN metastases in this study were locally advanced GBC, including 36% of T2 patients and 55% of T3 patients. The final staging is described in Table 2. The margin of resection representing the completeness of surgery was carefully analyzed. R0 and R1 resection were achieved in 37 patients (67%) and 18 patients (33%), respectively. Other prognostic indexes, including PNI and LVI, were presented in 23 patients (42%) and 18 patients (33%), respectively.

Survival analysis

Disease-free survival (DFS)

Sixty-two percent of patients had recurrent disease. The commonly recurrent sites were the intraperitoneal cavity, including the liver, LN, and peritoneum. The median DFS was 18 months. The 1-year, 2-year, and 5-year DFS rates were 56%, 45%, and 27%, respectively. The Kaplan-Meier estimation of the DFS is shown in Figure 1A.

Overall survival (OS)

During the study period, one-third of the patients survived longer than 3 years. All of these were in the R0 resection group, except for 2 patients with R1 resection. The median survival was 24 months. The 1-year, 2-year, and 5-year OS rates were 72%, 52%, and 29%, respectively. The Kaplan-Meier estimation of OS is shown in Figure 1B.

Analysis of the prognostic factors

The potential prognostic factors of OS were analyzed using univariate and multivariate analysis (Cox proportional hazards model) (Table 3). According to the univariate analysis, there were 5 prognostic factors that statistically significantly affected OS. The completeness of resection was essential to improve survival. The median OS was 48 months in the R0 group, whereas it was only 12 months in the R1 group. The 2-year OS rates were much better in the R0 group (2-year OS: 71% vs. 17%, $p = 0.001$). The presence of PNI and LVI were also the important predictors of survival. The median OS rates in the PNI negative group were significantly higher than in the PNI positive group (55 months vs. 19 months, $p = 0.003$). No PNI positive patient survived longer than 5 years after surgery. The median OS rates for LVI negative patients were better than for LVI positive patients as well (40 months vs. 12 months, $p = 0.014$). T staging was categorized as early T stage (Tis and T1) vs. locally advanced T stage (T2-T4) because it affected the surgical decision plan. Early T stage had significantly longer survival (median OS: 60 months vs. 30 months, $p = 0.005$). The histopathology of GBC was also an important predictive factor of survival. The median DFS and OS rates were much worse in the non-adenocarcinoma group when compared to the adenocarcinoma group (median OS: 28 months vs. 6 months; $p = 0.001$). The Kaplan-Meier estimations of OS according to each significant factor are shown in Figures 2A to 2E.

Other potential prognostic factors, including additional CBD or visceral resections beyond radical cholecystectomy, serum bilirubin higher than 5 mg/dl, and a required re-resection after simple cholecystectomy to achieve R0, did not have a statistically significant effect on OS in this study.

Multivariate analysis was conducted to identify the independent prognostic factors of OS. The results are shown in Table 3. The only significant independent prognostic factor for OS in this analysis was the type of histopathology of the cancer ($p = 0.008$). In terms of the modifiable factor, the margin of resection showed a trend toward the prediction of OS, but a statistically significant level at $p<0.05$ was not reached ($p = 0.079$).

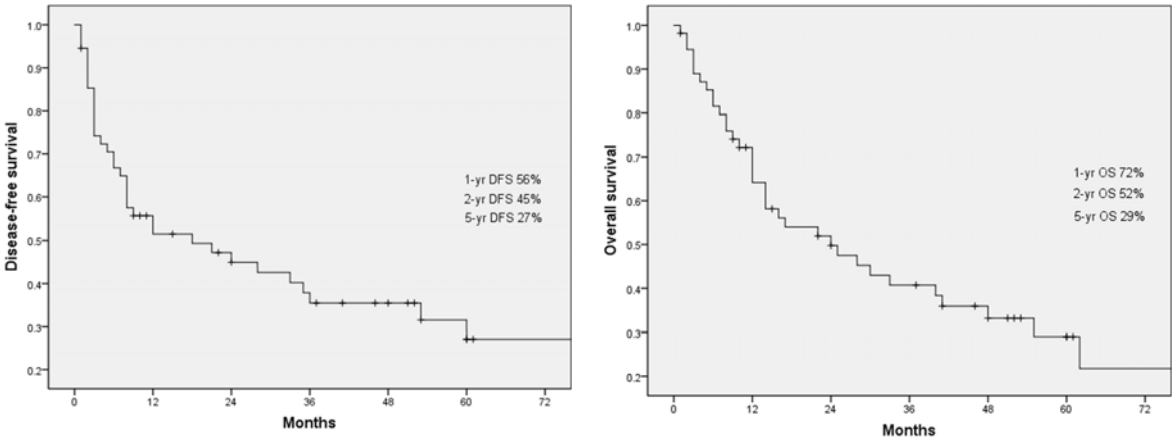
Discussion

GBC is a very aggressive cancer with dismal prognosis. Surgical resection is the mainstay of treatment. The present study presents the outcome after an oncologically surgical approach and an analysis of the factors, which may help in making the decision to select an appropriate surgical candidate. Because GBC usually causes vague and non-specific symptoms, including abdominal pain and jaundice, most patients present with advanced stage cancer that precludes

Table 2. Operative procedures and pathology among patients who underwent curative resection for gallbladder cancer

Operative procedures	n
SC (LC or OC)	19 (35%)
Re-resection after cholecystectomy (due to T≥T1b or margin positive)	4 (7%)
RC	40 (73%)
RC alone	32 (58%)
RC as a part of other procedures	8 (15%)
Additional visceral resection	16 (29%)
CBD resection	15 (27%)
CBD resection alone	7 (13%)
CBD resection as a part of other procedures	8 (15%)
MH	4 (7%)
PD	3 (5%)
HPD	1 (2%)
Right colectomy	3 (5%)
Partial duodenal wall resection	1 (2%)
A: Combined complex operations	
RC + Right colectomy + Partial duodenal wall resection	1 (2%)
HPD + Right colectomy	1 (2%)
RC + PD + Right colectomy	1 (2%)
Pathology according to AJCC 7th edition	
Adenocarcinoma	48 (87%)
Non-adenocarcinoma	7 (13%)
Adenosquamous carcinoma	3 (5%)
Squamous cell carcinoma	1 (2%)
Neuroendocrine carcinoma	2 (4%)
Undifferentiated carcinoma	1 (2%)
TNM staging	
Early T stage	4 (25%)
Tis	15 (9%)
T1a	1 (2%)
T1b	8 (15%)
Locally advanced T stage	41 (75%)
T2	20 (36%)
T3	18 (33%)
T4	3 (5%)
LN positive	21 (38%)
N1	20 (36%)
N2•	1 (2%)
Final staging	
Stage 0	5 (9%)
Stage 1	8 (15%)
Stage 2	12 (22%)
Stage 3A	8 (15%)
Stage 3B	18 (33%)
Stage 4A	3 (5%)
Stage 4B•	1 (2%)
Margin of resection	
R0	37 (67%)
R1	18 (33%)
Presence of PNI	23 (42%)
Presence of LVI	18 (33%)

• = presence of LN metastases in colonic mesentery (N2)
HPD = hepatopancreaticoduodenectomy, LC = laparoscopic cholecystectomy, LVI = lymphovascular invasion, MH = major hepatectomy, OC = open cholecystectomy, PD = pancreaticoduodenectomy, PNI = perineural invasion, RC = radical cholecystectomy, SC = simple cholecystectomy



A) Disease-free survival B) Overall survival

Figure 1. The Kaplan Meier curves demonstrate disease-free survival (DFS; A) and overall survival (OS; B) following surgical resection of gallbladder cancer (GBC) in Siriraj Hospital.

Table 3. Analysis of potential prognostic factors on overall survival

Prognostic factors	Overall Survival (OS)			
	Univariate analysis		Multivariate analysis	
	Median OS (mo)	*p*-value	HR (95% CI)	*p*-value
TB (mg/dl)		0.241	NA	NA
TB <5	28			
TB ≥5	16			
CBD/visceral resection		0.232	NA	NA
No	28			
Yes	14			
Re-resection after SC		0.453	NA	NA
No	24			
Yes	14			
Histopathology		0.001	0.30 (0.12 to 0.73)	0.008
Adenocarcinoma	28			
Others	6			
Resection margin		0.001	2.28 (0.91 to 5.73)	0.079
R0	48			
R1	12			
PNI		0.003	1.51 (0.58 to 3.89)	0.395
No	55			
Yes	19			
LVI		0.014	1.65 (0.78 to 3.52)	0.193
No	40			
Yes	12			
T stage		0.005	0.61 (0.19 to 1.94)	0.398
Tis, T1	60			
T2-T4	30			

CBD = common bile duct, CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, LVI = lymphovascular invasion, mo = months, OS = overall survival, PNI = perineural invasion, SC = simple cholecystectomy, TB = total bilirubin

curative resection. Only a small number of symptomatic GBC patients appear to be operative candidates. Moreover, some of them show evidence of advanced disease at the time of surgery as well. In the current series, 20% of the patients who underwent surgery were found to have locally unresectable disease or distant metastases at the time of

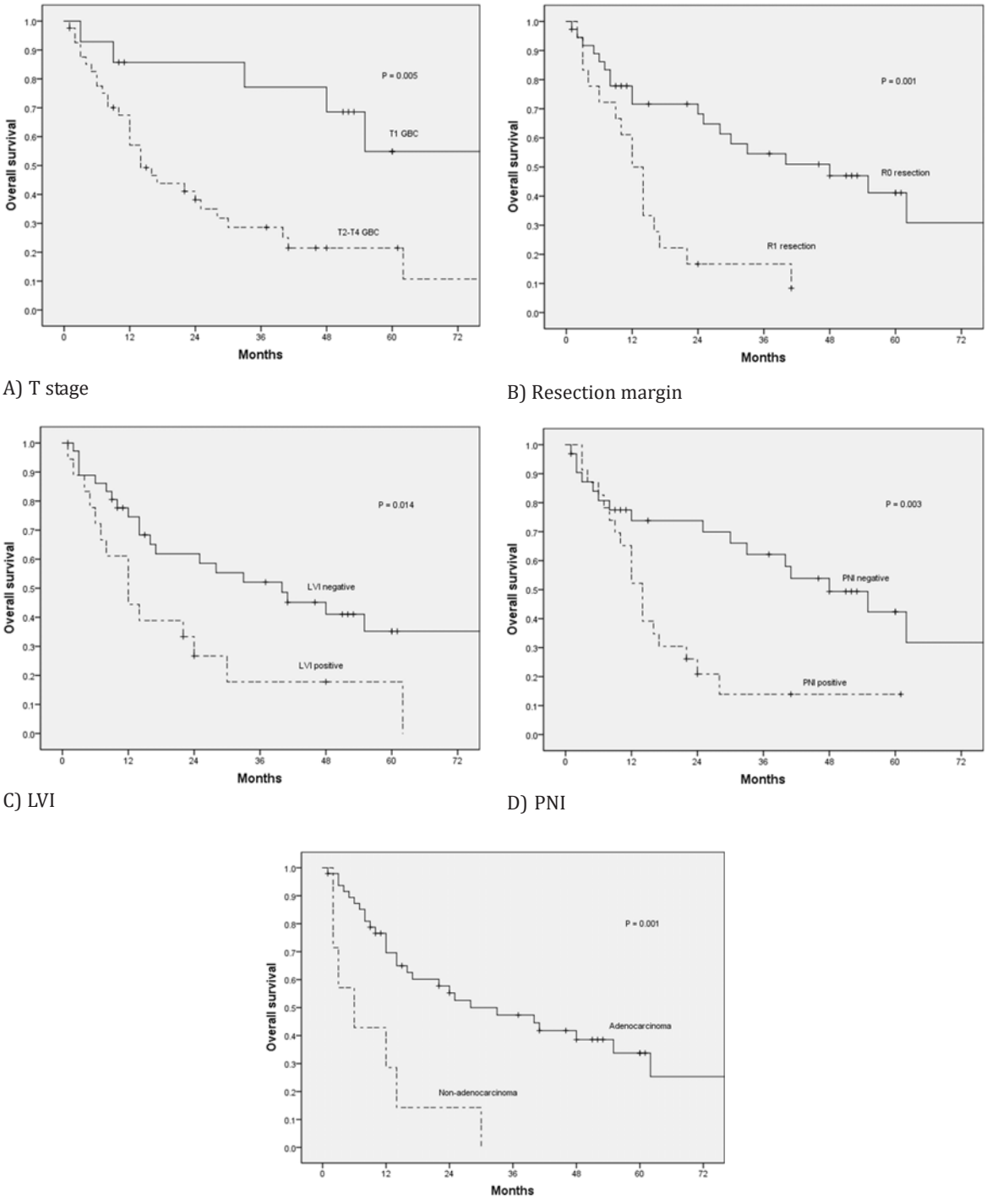


Figure 2. The overall survival (OS) of patients who underwent surgical resection of gallbladder cancer (GBC) by significant prognostic factors in univariate analysis including tumor stage (T stage; A), resection margin status (R0 versus R1; B), presence of lymphovascular invasion (LVI; C), presence of perineural invasion (PNI; D) and histopathology (adenocarcinoma versus non-adenocarcinoma; E).

surgical exploration.

There are two types of presentation that are likely to have a better treatment outcome. First, incidental GBC that is detected from a pathological examination of cholecystectomy specimens from various indications. The incidence here ranges from 0.5 to 2%[9-11]. Patients with incidental GBC have been reported to have relatively higher success rates of curative resection[11-13]. Another type is asymptomatic GBC that is detected with abdominal imaging from other indications and a health check-up. This presentation has been increasingly reported because of the alertness of health screening. Theoretically, both types are defined as early GBC. Thus, the resection rates should be relatively high, as confirmed by the present study (Table 1).

Regarding the influence of jaundice on operative resectability and outcome, several reports have shown relatively low rates of curative resection and poor survival even after curative resection among patients who had jaundice before surgery[14-16]. Some experts even consider jaundice as a relative contraindication for resection[17]. The present study confirmed the negative impact of preoperative jaundice on successful resection rates (median TB 0.65 mg/dL in the resectable group vs. 12.40 mg/dL in the unresectable group, $p = 0.011$). Interestingly, a subgroup analysis of the resectable patients (R0 vs. R1) revealed significantly higher rates of R1 resection if the serum bilirubin of patients was higher than 2 mg/dl ($p = 0.026$). However, some patients could achieve an R0 resection, even with serum bilirubin higher than 5 mg/dl. Based on this data, preoperative jaundice and high serum bilirubin should raise concern of the unresectability, but it should not be considered as an absolute contraindication for surgery.

From a staging perspective, the component that mostly influences the operative strategy is the T-stage. Although survival is excellent after simple cholecystectomy for Tis and T1a GBC that are usually discovered incidentally, T1b and T2 GBC are the most controversial issues. Given a possible unclear surgical margin at hepatic attachment, many studies recommend resection of the liver parenchyma around the gallbladder fossa en-bloc with a gallbladder specimen to make sure of the R0 resection[17-19]. However, there has been no high-quality comparative study performed to confirm this recommendation until now. Recently, there was a study from Korea that studied the relationship between the tumor location and outcome of T2 GBC at the fundus or peritoneal site after R0 resection by simple cholecystectomy with regional LN dissection without liver resection. The authors concluded that a tumor at the peritoneal site might be justified for treatment by this technique with comparable survival[20]. Nonetheless, our center prefers the concept of performing en-bloc liver resection with a gallbladder specimen to clearly obtain the hepatic margin.

T3-T4 GBC is one of the most aggressive cancers in the gastrointestinal tract. The chance to perform curative resection is limited due to the high rate of intraperitoneal metastases or a local invasion of the hilar structures that may preclude R0 resection. The curative resection requires more complex operations, including, but not limited to, CBD resection, major hepatectomy, pancreaticoduodenectomy, or additional resection of the right-sided colon and duodenum. Nevertheless, the 5-year OS rates of T3 and T4 GBC patients were reported to be only 7 to 25% after aggressive surgical resections[5,6,13,21], which were similar to this presenting study (16%). However, the OS rates of patients who did not undergo curative resection were much worse[6,8]. Thus, all T3-T4 GBC patients who have localized disease should be scheduled for surgery whenever margin-free resection is possible and when there are no other comorbidity issues.

Lymph node metastasis is another important prognostic factor in almost all gastrointestinal malignancy, including GBC. According to a previous report, the LN metastatic rate depended on the T-stage[21]. Though a T1b lesion is considered to be early stage GBC, previous studies have shown that T1b GBC had at least 12% of LN metastases[22]; whereas, T2-T4 GBC have much higher rates of LN metastases, ranging from 20% to 60%[22-24]. In present study, at least 36% of T2 and 55% of T3 GBC patients were LN positive. Because LN spreading is common, most centers advocate LN dissection at the time of radical cholecystectomy in order to complete nodal staging and to get more prognostic information. Our center recommends performing hepatoduodenal LN dissection as a part of radical cholecystectomy.

Regarding the operative strategy and prognostic factors, histopathology of non-adenocarcinoma was the only independent prognostic factor on OS in the present study ($p = 0.008$). The present study and previous reports have also confirmed that a clear survival benefit after resection is evidenced only if R0 resection can be achieved[5,6,8,13,17]. Although the completeness of resection margin also has an effect on OS, statistical significance at $p<0.05$ was not reached ($p = 0.079$). An appropriate explanation for this may be related to the small number of patients in our cohort. Other poor prognostic factors that significantly affected survival in univariate analysis were a higher T-stage, and the presence of PNI and LVI on pathology.

Among the non-significant prognostic factors in univariate analysis, CBD resection is the most common concern due to worries about the cystic duct-CBD margin. Recent reports have shown no survival benefit and no significant increase in the number of harvested LNs after routine CBD resection in T2-T4 GBC. In addition, the complications increased significantly[25,26]. Therefore, CBD resection was not routinely performed in the present study. Our strategy is to evaluate the cystic duct margin by frozen section. If the intraoperative pathological results confirm malignant cells in the cystic duct margin, then CBD resection will be subsequently performed.

Other additional resections (MH, PD, HPD, colectomy, or duodenal resection) were indicated only when they could offer a tumor-free resection margin. From this analysis, there were similar survival differences between patients who did undergo additional procedures beyond

radical cholecystectomy and those who did not. Besides, the present study also analyzed the value of the re-resection of incidental GBC after cholecystectomy. There was no significant difference in survival between the re-resection group and the single resection group. Therefore, additional procedures, including re-resection, might benefit survival only when an R0 resection can be obtained and a patient's condition can tolerate such a complex operation.

Several limitations were noted in the present study. The retrospective analysis may suffer from some missed biochemistry and clinical data. Therefore, some potential factors were excluded from the analysis, such as tumor markers and gallstones. Moreover, the number of resectable cases was limited, making the power not strong enough to give some conclusions in the present study. This is because GBC is a rare and aggressive cancer. Most patients come in the later stage, which precludes surgical resection.

In conclusion, the prognosis of GBC patients is extremely poor. Preoperative jaundice may alarm an unresectable disease. The present study reported 1-year and 5-year OS rates at 72% and 29%, respectively. Adenocarcinoma had a significantly better survival after surgery than non-adenocarcinoma. The OS was better in R0 resection patients. Complete surgical resection is the only treatment method offering the long-term survival of non-metastatic GBC patients. To improve survival, radical cholecystectomy, including hepatoduodenal LN dissection, should be performed for T1b-T4 GBC due to the high rates of LN metastases and to maximize the R0 resection probability. Additional complex procedures should be considered in order to obtain an R0 resection whenever the benefit outweighs the risk of operation.

What is already known on this topic?

Gallbladder cancer is an uncommon biliary tract cancer. It has poor prognosis and patients mostly present with an advanced stage, which may preclude curative resection. There is currently no definite guideline to help choosing the best treatment strategy and operative technique.

What this study adds?

Preoperative jaundice raises the concern of unresectable disease; however, it should not be considered as a contraindication to attempt resection. Adenocarcinoma showed significantly better survival after resection than non-adenocarcinoma pathology. Complete surgical resection, including radical cholecystectomy, hepatoduodenal LN dissection, and additional visceral resection as required, is the only treatment that may offer long-term survival for GBC patients.

Potential conflicts of interest

The authors declare no conflict of interest.

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การศึกษาผลการรักษามะเร็งถุงน้ำดีด้วยการผ่าตัด: ประสบการณ์ 10 ปีในโรงพยาบาลตติยภูมิ

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วัตถุประสงค์: มะเร็งถุงน้ำดีเป็นโรคมะเร็งที่พบไม่บ่อยในทางเดินอาหารและมีการพยากรณ์โรคที่ไม่ดี เนื่องจากผู้ป่วยมักมีอาการและอาการแสดงเมื่อโรคลุกลามมากแล้ว การผ่าตัดเป็นการรักษาเพียงวิธีเดียวที่ทำให้หายขาดจากโรคได้ การศึกษานี้มีจุดประสงค์เพื่อวิเคราะห์ผลการรักษาโรคมะเร็งถุงน้ำดีด้วยการผ่าตัด ตลอดจนวิเคราะห์ปัจจัยที่มีผลต่อการรักษาในโรงพยาบาลตติยภูมิ

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาย้อนหลังในผู้ป่วยมะเร็งถุงน้ำดีที่ได้รับการรักษาด้วยการผ่าตัดในโรงพยาบาลศิริราช ตั้งแต่ปี พ.ศ. 2549 ถึง พ.ศ. 2558 โดยศึกษาข้อมูลพื้นฐาน การผ่าตัด และผลพยาธิวิทยาของผู้ป่วย เพื่อวิเคราะห์อัตราการรอดชีวิตด้วยวิธี Kaplan-Meier method และการตรวจหาปัจจัยที่ส่งผลต่ออัตราการรอดชีวิตด้วยวิธี Cox proportional hazards model

ผลการศึกษา: ผู้ป่วยมะเร็งถุงน้ำดี 69 คนเข้ารับการผ่าตัด ในจำนวนนี้ผู้ป่วย 55 คน (ร้อยละ 80) สามารถผ่าตัดมะเร็งออกหมดได้สำเร็จ ในขณะที่ผู้ป่วย 14 คน (ร้อยละ 20) พบมีมะเร็งลุกลามไม่สามารถผ่าตัดออกหมดขณะทำการผ่าตัด ภาวะดังกล่าวสัมพันธ์กับภาวะดีซ่านก่อนผ่าตัด ผู้ป่วยที่ผ่าตัดมะเร็งออกหมดมีอัตราการผ่าตัดมะเร็งออกได้ทั้งหมดจากการตรวจทางพยาธิ (R0 resection) ร้อยละ 67 ขณะที่มีมะเร็งหลงเหลือจากการตรวจทางพยาธิ (R1 resection) ร้อยละ 37 อัตราการอยู่รอดมัธยฐาน disease-free survival (DFS) และ overall survival (OS) เท่ากับ 18 และ 24 เดือนตามลำดับ อัตราการอยู่รอด DFS ที่ 1 ปีและ 5 ปีเท่ากับร้อยละ 56 และร้อยละ 27 ตามลำดับ ขณะที่อัตราการอยู่รอด OS ที่ 1 ปีและ 5 ปีเท่ากับร้อยละ 72 และร้อยละ 29 ตามลำดับ ปัจจัยที่ส่งผลต่ออัตราการอยู่รอด OS อย่างมีนัยสำคัญ จากการวิเคราะห์แบบ univariate ได้แก่ การผ่าตัดมะเร็งออกได้ทั้งหมดจากการตรวจทางพยาธิ, ระยะของโรค, การตรวจพบการลุกลามรอบเส้นประสาทและลุกลามเข้าหลอดเลือดหลอดน้ำเหลือง และชนิดทางพยาธิวิทยาของมะเร็ง ปัจจัยที่ส่งผลต่ออัตราการอยู่รอด OS อย่างมีนัยสำคัญจากการวิเคราะห์แบบ multivariate ได้แก่ชนิดทางพยาธิวิทยาของมะเร็ง (p=0.008) ขณะที่การผ่าตัดมะเร็งออกได้ทั้งหมดจากการตรวจทางพยาธิแสดงถึงแนวโน้มที่ส่งผลต่อ OS เช่นกันแม้จะไม่ถึงระดับที่มีนัยสำคัญทางสถิติ (p=0.079)

สรุป: มะเร็งถุงน้ำดีมีการพยากรณ์โรคไม่ดี มะเร็งชนิด adenocarcinoma มีการพยากรณ์โรคที่ดีกว่าชนิดทางพยาธิวิทยาของมะเร็งแบบอื่น