

Surgical outcomes and prognostic factors influencing long-term survival in patients with gallbladder cancer

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Backgrounds/Aims: The aim of this study is to analyze surgical outcomes and prognostic factors affecting survival after surgical resection in patients with gallbladder cancer. **Methods:** We retrospectively reviewed 86 patients treated surgically for gallbladder cancer from January 2000 to December 2009 at Chonbuk National University Hospital. Clinicopathologic factors, surgical treatment and outcome data were analyzed. **Results:** Among the 86 patients (44 male, 42 female) with gallbladder cancer, the mean age was 62.9 years (range: 32-80) and the median survival was 42.4±3.5 month. The overall cumulative survival rates of 86 patients were for 1 year, 83.7%; 3 year, 67.4%; 5 year survival, 61.7%. Univariate analysis revealed that preoperative serum alanine aminotransferase, alkaline phosphatase, total bilirubin, carcinoembryonic antigen (CEA), T staging, N staging were statistically significantly associated with survival. CEA ($p=0.004$) and T staging ($p=0.005$) were associated with survival in multivariate analysis. Two-year survival rates were analyzed according to the methods of surgical resection, with simple cholecystectomy showing 100%, whereas extended cholecystectomy showed about 83% in T1b. We could not find out any adverse effect of the simple cholecystectomy for survival. **Conclusions:** CEA and T stage are independent significant prognostic factor associated with patient survival in our study. Simple cholecystectomy can be regarded as curative resection in stage T1b. Longer observation periods and more cases will be needed to confirm these conclusions. ([Korean J Hepatobiliary Pancreat Surg 2012;16:59-64](#))

Key Words: Gallbladder cancer; Prognostic factors; Survival rate

INTRODUCTION

Gallbladder cancer is the most common cancer of the biliary tract. According to the Korea Central Cancer Registry report in 2008, gallbladder cancer is the fifth most frequent cancer in the gastrointestinal tract.¹ Early detection of gallbladder cancer is difficult due to asymptomatic growth. Many patients have infiltration of surrounding structures such as the portal vein and hepatic artery at time of diagnosis. Therefore gallbladder cancer has the shortest median survival duration in biliary cancers.^{2,3}

Five-year survival rate has been reported as 17.3%.¹ However, recent studies show improved survival rates, attributable to early detection through the development of pre-operative radiologic diagnostic tools, increased awareness of personal health and spread of routine health checkups, as well as improved surgical methods and post operative care.

The aim of this study is to analyze surgical outcomes and prognostic factors affecting survival after surgical resection in patients with gallbladder cancer at our institution.

METHODS

We retrospectively reviewed age, gender, clinical factors, stage distribution, and surgical method of 133 patients operated with primary gallbladder cancer at Chonbuk National University Hospital from January 2000 to December 2009. This study design was approved by the institutional review board of our institution. Of these 133 patients, 86 patients were followed for post-operative survival. Survival status and cause of death were confirmed through phone calling and reviewing medical records. Age, gender, pre-operative clinical factors within one month, T stage, N stage and surgical method were

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analyzed. Stages of the cancer were classified according to the American Joint Committee on Cancer (AJCC) 7th edition. Curative resection defined as simple cholecystectomy with no remnant cancer on permanent pathologic report in Tis and T1a, and radical cholecystectomy combined hepatectomy or not with no remnant cancer on permanent pathologic report in T1b, T2 and T3.

Univariate analysis was performed using the Kaplan-Meier method and compared with the log-rank test. Multivariate analysis was performed using the Cox regression hazards model to identify independent prognostic factors. All statistical analyses used SPSS 18.0 for Windows (SPSS Inc. Chicago, III). A *p*-value less than 0.05 was considered statistically significant.

Table 1. Survival according to clinical factors of patients

| Variable | No. of patient (%) | 5-year survival (%) | <i>p</i> |
|---------------|--------------------|---------------------|----------|
| Gender | | | 0.287 |
| Male | 44 (51.2) | 59.9 | |
| Female | 42 (48.8) | 64.5 | |
| AST (IU/L) | | | 0.133 |
| >40 | 9 (10.5) | 37 | |
| ≤40 | 77 (89.5) | 61.5 | |
| ALT (IU/L) | | | 0.05 |
| >40 | 15 (17.4) | 36.7 | |
| ≤40 | 71 (82.6) | 68.2 | |
| T-bil (mg/dl) | | | 0.021 |
| >1.2 | 5 (5.8) | 0 | |
| ≤1.2 | 81 (94.2) | 64.7 | |
| D-bil (mg/dl) | | | 0.834 |
| >0.4 | 7 (8.1) | 57.1 | |
| ≤0.4 | 59 (68.6) | 61.1 | |
| ALP (IU/L) | | | 0.011 |
| >300 | 15 (17.4) | 35.6 | |
| ≤300 | 68 (79.1) | 65.4 | |
| GGT (IU/L) | | | 0.061 |
| >75 | 14 (16.3) | 40 | |
| ≤75 | 52 (60.5) | 69.5 | |
| CEA (ng/ml) | | | 0.007 |
| >10 | 7 (8.1) | 28.6 | |
| ≤10 | 64 (74.4) | 60.3 | |
| CA19-9 (U/ml) | | | 0.157 |
| >40 | 23 (26.7) | 45.8 | |
| ≤40 | 51 (59.3) | 64.7 | |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-bil, total bilirubin; D-bil, direct bilirubin; ALP, alkaline phosphatase; GGT, Gamma-glutamyl transferase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9

RESULTS

Age and gender distribution

Of the 86 patients, gender distribution is similar, 44 male and 42 female. Mean age was about 62.9 years, with a range of 32 to 80. Highest prevalence was seen in the 5th decade, 29 cases (33.7%).

Survival rates according to clinical factors

Preoperative serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-bil), direct bilirubin (D-bil), alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) were analyzed, and among these factors, ALT, ALP, T-bil, and CEA showed a statistically significant association with 5-year survival in univariate analysis (Table 1).

Survival rates according to T stage and N stage

T stage and N stage were classified by the 7th AJCC classification system, with 6 cases of Tis (7.0%), 5 cases of T1a (5.8%), 13 cases of T1b (15.1%), 32 cases of T2 (37.2%), 26 cases of T3 (30.2%) and 4 cases of T4 (4.7%). According to T stage, the 5-year survival rate decreased as stages increased. Tis and T1a showed 100% 5-year survival rate, and T1b showed 84.6%, T2 61.4%, T3 40.9%, T4 0% survival rate. All 11 patients of the Tis and T1a stages showed more than 10 year survival (*p*=0.000) (Fig. 1).

Excluding 30 patients (34.9%) who did not undergo

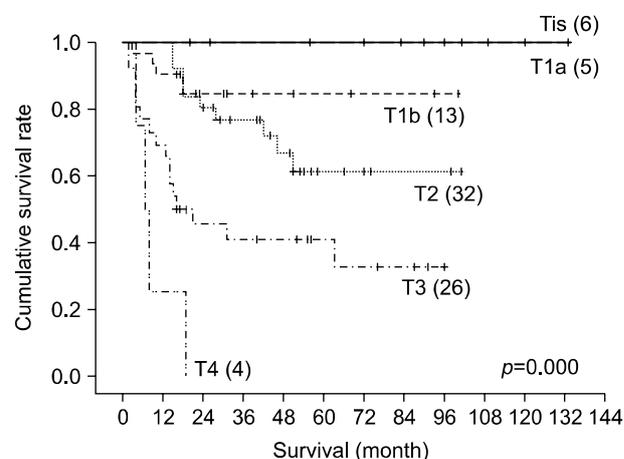


Fig. 1. Cumulative survival rates related to T stage (AJCC 7th edition).

lymph node dissection, 56 patients were classified according to the N stage of the 7th AJCC classification. Results were 32 cases (37.2%) of N0, 17 cases (19.8%) of N1, and 7 cases (8.1%) of N2 stages. The 5-year survival rates according to N stage were 80.6% in N0, 27.6% in N1, and 19.0% in N2 ($p=0.003$) (Fig. 2).

Prognostic factors

ALT, ALP, T-bil and CEA, T and N stage were significant factors on univariate analysis.

Of these factors, CEA and T stage were statistically significant independent prognostic factors on multivariate analysis (Table 2).

Survival rates according to surgical method in T stage

Of the 86 cases, 60 cases underwent curative resection, while 26 cases were operated palliatively. In the curative resection groups, the survival rates were 1-year (90.0%),

3-year (77.0%), and 5-year (72.1%). Survival in the palliative resection group was 1-year 69.2%; 3-year 42.3%; and 5-year 33.8%. These suggested a higher survival rate in curative resection ($p=0.000$) (Fig. 3).

Comparison between curative and palliative resection was carried out in the T1b, T2, and T3 groups. Tis and T1a groups, in which only curative resection were performed, were not comparable and therefore excluded, along with the T4 groups, in which no case was treated with curative resection at all.

Survival in patients with T1b tumor: In group T1b, excluding one case where second-look operation was rejected despite a positive margin of cancer on the cystic duct, 6 cases of simple cholecystectomy and 6 cases of extended cholecystectomy were compared. Median survival was 54.7 ± 33.8 months in the simple cholecystectomy subgroup, and 32.0 ± 19.7 months in the extended cholecystectomy subgroup, with no statistically significant difference. During the observation period, one patient expired due to liver metastases 15 months after extended cholecystectomy. 2-year survival rates were compared according to surgical method. All of the simple cholecystectomy subgroup survived, while in the extended cholecystectomy subgroup 83.3% survived.

Survival in patients with T2 tumor: Twenty-four cases of curative resection and 8 cases of palliative resection were performed in the T2 group (3 cases in which second-look operations were not performed; 3 cases in which lymph node dissection was not performed; and 2 cases in which only simple cholecystectomy was per-

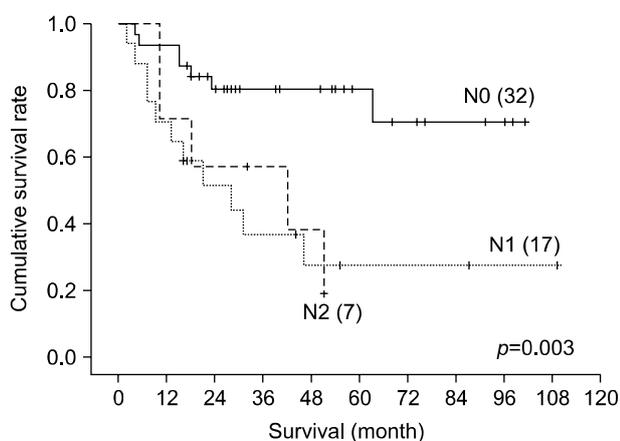


Fig. 2. Cumulative survival rates related to N stage (AJCC 7th edition).

Table 2. Multivariate analysis of variables as prognostic factors for survival rate

| Variables | Univariate p-value | Multivariate p-value |
|---------------|--------------------|----------------------|
| ALT (IU/L) | 0.05 | 0.889 |
| T-bil (mg/dl) | 0.021 | 0.986 |
| ALP (IU/L) | 0.011 | 0.469 |
| CEA (ng/ml) | 0.007 | 0.004 |
| T stage | 0.000 | 0.005 |
| N stage | 0.003 | 0.055 |

ALT, alanine aminotransferase; T-bil, total bilirubin; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen

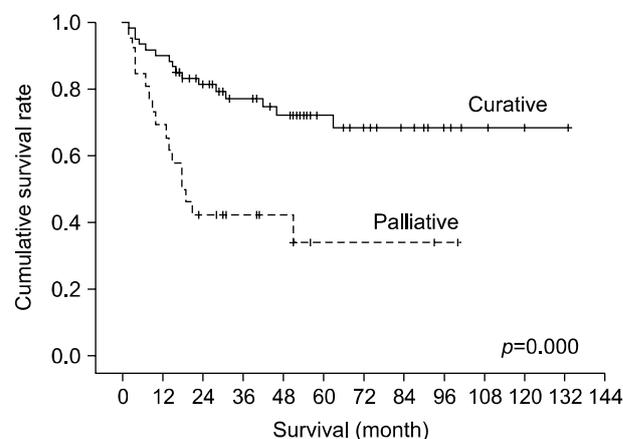


Fig. 3. Cumulative survival rates related to types of surgical resection.

formed due to diagnosis of distant metastasis during operation). Cases treated with curative resection showed 74% 5-year survival rates, whereas cases operated palliatively resulted in 0% 5-year survival rates, a statistically significant difference ($p=0.003$).

Survival in patients with T3 tumor: Nineteen cases of curative resection and 7 cases of palliative resection were performed in the T3 group. The 5-year survival rates were 51.5% when treated with curative and 0% for palliative resection not a significant difference ($p=0.103$).

Overall survival rates and survival rates according to stage

Medial survival of the 86 cases was 42.4 ± 32.5 months, with the shortest of 2 months and the longest of 133 months. Overall survival rates were 83.7% at 1 year, 67.4% at 3 years, and 61.7% at 5 years.

Except for the 24 cases in which lymph node dissection was not performed, final pathologic stages of the remaining 62 cases were as followed: 4 cases of stage 0 (4.7%), 10 cases of stage I (11.6%), 15 cases of stage II (17.4%), 9 cases of stage IIIa (10.5%), 16 cases of stage IIIb (18.6%), 1 case of stage IVa (1.2%), and 7 cases of stage IVb (8.1%).

Five-year survival rates according to pathologic stage were stage 0 (100%), in stage I (90%), II (85.7%), IIIa (66.7%), IIIb (29.3%), IVa (0%), IVb (0%), showing decreased survival as stage increased ($p=0.000$) (Fig. 4).

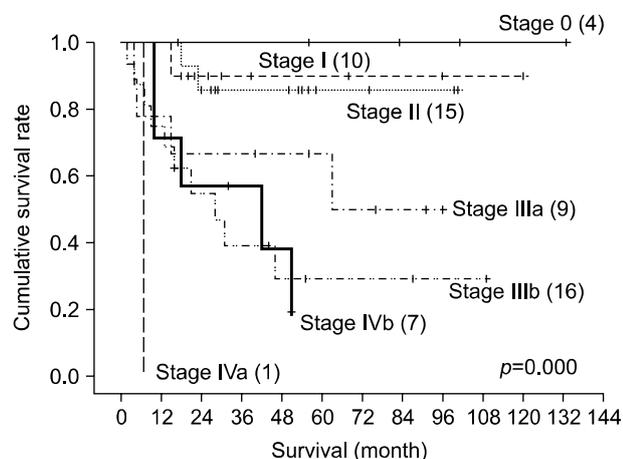


Fig. 4. Cumulative survival rates related to stage system (AJCC 7th edition).

DISCUSSION

Despite increased early detection through the development of preoperative diagnostic tools, greater acceptance of routine health checkups, and increased survival rate through advanced operative procedures and post-operative care, gallbladder cancer still has a poor prognosis, especially since many patients are inoperable at diagnosis.^{3,4}

In a study of 724 cases carried out by the French Surgical Association in 1994, the median survival period was 3 months, and 5 year survival rates were 5%.⁵ Konstantinidis et al.⁶ reported a 40-year follow-up study which showed medial survival of 3.5 months between 1962 and 1979, 6.5 months between 1980 and 1997, and 12 months between 1998 and 2008. Liang et al.⁷ reported a 25 year follow-up study which showed medial survival of 12.3 months and survival rates at 1 year (50.5%), 3 years (29.5%), and 5 years (26.2%). In our study, comparable survival rates are 1 year (83.7%), 3 years (67.4%), and 5 years (61.7%).

Various clinical prognostic factors in gallbladder cancer have been reported. Generally, incidence is 2 to 6 times higher in women, which is probably due to the fact that cholelithiasis is more frequent in women. Despite the lower incidence rate, male gender is a poor prognostic factor, showing shorter medial survival periods.^{2,8} There was no survival difference according to gender in our study.

There are no characteristic symptoms in early gallbladder cancer, but as disease progresses various symptoms arise, generally showing poorer prognosis with acute/chronic cholecystitis or focal biliary complications.⁹ In our study, poorer prognosis was observed when there were abnormal results in the liver function tests, such as ALT, bilirubin, and ALP, in univariate analysis.

CEA is a typical tumor marker elevated not only in gallbladder cancer but also in colon cancer and other types of cancer. Chakravarty et al.¹⁰ reported that serum CEA levels were independent prognostic factors that affect long-term survival regardless of T stage. Likewise, CEA was an independent prognostic factor in our study. CA19-9 is a tumor marker frequently elevated in gallbladder cancer, especially associated with intra-epithelial dysplasia and adenocarcinoma. It has been reported to show significant association with other important prognostic factors such as a history of jaundice and lymph

node metastasis.¹¹ Study to distinguish CA19-9 as a prognostic factor in gallbladder cancer has been insufficient, and in our study there was no association in univariate analysis.

The major principle in treatment of gallbladder cancer is surgical resection, with radiation therapy, chemotherapy, immunotherapy as optional choices, although effectiveness is meager. Recently, there has been a tendency towards determining surgical methods in gallbladder cancer according to T stage.^{2,12}

Tis and T1a have shown complete remission with simple cholecystectomy alone.¹³ In our study, all cases of Tis and T1a cancers were treated with simple cholecystectomy, and although comparison with radical cholecystectomy was unavailable, both groups showed 100% survival rates at 5 and 10 years. In the case of stage T1b, the extent of resection is controversial. Lee et al.¹⁴ reported that radical cholecystectomy had no benefit over simple cholecystectomy, whereas studies by Pilgrim et al.¹⁵ and Abramson et al.¹³ showed increased survival with radical resection, due to extraction of lymph node metastases and recurrence. There was no statistically significant difference according to surgical method in this study. There was no disadvantage to simple cholecystectomy, when compared with extended cholecystectomy according to median survival and 2-year survival rates in this study. As there were no deaths in the simple cholecystectomy subgroup, simple cholecystectomy in stage T1b could be regarded as curative resection.

There have also been disagreements on the extent of resection in stage T2. Abramson et al.¹³ calculated mean 5-year cancer - specific survival of 61.3% in simple cholecystectomy alone group, but 87.5% in radical cholecystectomy group. Pilgrim et al.¹⁵ reported much higher 5 year survival rates in radical cholecystectomy (61% to 100%) when compared with simple cholecystectomy (19% to 50%). Zhu et al.² and Kang et al.¹² supported radical resection over simple resection, which showed higher 5-year survival rates in the T2 groups. On the contrary, Konstantinidis et al.⁶ reported that there was no significant difference between radical and simple cholecystectomy. In addition, Kohya et al.¹⁶ subdivided stage T2 patients into whether or not there was hepatic, biliary, lymphatic, venous, peri-neural or lymph node invasion, and proposed that radical resection was unnecessary in negative sub-

groups, whereas liver and/or biliary resection was needed when positive findings were present. Five year survival rates were confirmed to be higher in stage T2 radical resection subgroups in his study.

Stages T3 and T4 lead to poor prognosis, even after radical cholecystectomy. According to the French Surgical Association survey, 90% of patients with completed radical cholecystectomy expired within 12 months.³ Likewise, this study also had no significant difference in surgical method in the T3 subgroups, with 5 year survival rates at 40.9% in the T3 and 0% in the T4 subgroups. On the other hand, Kondo et al.¹⁷ reported T3, T4 with N1 patients were improved survival rate by lymph node dissection and with no detectable difference in 5-year survival rates between N0 (66%) and N1 (53%) patients.

In conclusion, CEA and T stage were independent prognostic factors significantly associated with patient survival in multivariate analysis. Although observation periods were short and number of cases was small, both simple and extended cholecystectomy showed similar survival rates in the T1b subgroups. Longer observation periods and more cases will be needed to confirm these conclusions.

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