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# Validation of Revised American Joint Committee on Cancer Staging for Gallbladder Cancer Based on a Single Institution Experience

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## Abstract

Gallbladder cancer is a rare malignancy, which often goes undiagnosed until advanced stages of disease and is associated with poor prognosis. The only potentially curative treatment is surgical resection. This retrospective study aims to investigate the validity of the revised 7th edition American Joint Committee on Cancer staging criteria and determine prognostic factors. Forty-two patients with confirmed gallbladder cancer who underwent attempted curative resection from 1999 to 2012 at the University of California, Irvine Medical Center were reviewed. Survival probability was determined using the Kaplan-Meier method. Ten patients underwent laparoscopy, were deemed unresectable, and no further surgical intervention was performed. R0 surgical resection, which included radical portal lymphadenectomy, liver segment IVb/Vresection, with or without bile duct resection, was performed in the remaining 32 patients. N2 nodes were resected if positive on frozen section. Overall survival probability for Stage I to II patients was 100 per cent. Overall survival probability for Stage III patients was 80 per cent (95% confidence interval [CI], 61 to 99%) and 39.3 per cent (95% CI, 28 to 78%) for Stage IV patients. This study demonstrates that 7th edition clinical stage, T stage, and liver involvement are statistically significant predictors of prognosis. These data also demonstrate a benefit to extended resection in patients even with Stage III and IV disease.

The Surveillance, Epidemiology, and End Results program demonstrated that gallbladder cancer is a relatively rare malignancy with an incidence of 2.5 per 100,000 persons in the United States. It often goes undiagnosed until advanced stages of disease and is associated with poor prognosis. Some of the factors that contribute to poor prognosis include nonspecific symptoms, late presentation, early hematogenous and lymphatic spread, and lack of standardized adjuvant therapy.[1] Gallbladder cancer is more prevalent in females and

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in certain regions of the world including Chile, Japan, and northern Inida.[2] The only potentially curative treatment is surgical resection, the extent of which depends on staging. There are limited studies investigating surgical management based on the revised 7th edition American Joint Committee on Cancer (AJCC) staging. This study aims to investigate the validity of the revised 7th edition AJCC staging criteria and determine factors that contribute to survival outcome.

## Methods

A retrospective analysis of patients with histologically confirmed diagnosis of gallbladder cancer was performed. Patients were identified using electronic case logs at the University of California, Irvine Medical Center. Patients who underwent surgical management for proposed curative resection from January 1999 to September 2012 were included in the study. A total of 42 patients were identified. Data extracted from electronic medical records included demographics, date of diagnosis, mode of diagnosis, extent of surgical resection or reresection, pathology, adjuvant therapy, time to recurrence, and time to death. Institutional Review Board approval was given before initiation of chart review.

Patients with Stage IVb disease (distant metastasis) on computed tomography (CT) or magnetic resonance imaging (MRI) were excluded from this study. Diagnostic laparoscopy was performed on every patient undergoing attempted curative resection. Ten patients were deemed unresectable and were referred for chemotherapy. Thirty-two patients underwent R0 surgical resection, which included radical portal lymphadenectomy, liver segment IVb/V resection, with or without bile duct resection, and reconstruction. N2 nodes were resected if positive on frozen section. N1 nodes were defined as metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein. N2 nodes were defined as metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes.

The Kaplan-Meier method was applied to estimate 5-year overall survival rates. The log-rank test was applied to test for the equality of survival curves between strata at a significance level of 0.05. The association between survival and time between laparoscopic cholecystectomy and curative operation in days was assessed by the score test. Univariate and multivariate Cox proportional hazard regression models were formed with predictors including patient characteristics, tumor factors, and treatment factors. The estimated hazard ratios were calculated and 95 per cent confidence intervals for the hazard ratios were obtained. The backward elimination model selection procedure with a significant level of 0.1 for removing a covariate from a model was performed to select statistically significant covariates with respect to the survival outcome, adjusted for age, gender, and race/ethnicity. The software package SAS Version 9.2 (Cary, NC) was used for statistical analysis.

## Results

This study included 33 females (78.6%) and nine males (21.4%). The median age of diagnosis was 65.3 years. Twenty-eight patients (66.7%) were incidentally found to have gallbladder cancer after routine laparoscopic cholecystectomy, 27 of which were performed

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at an outside facility and referred for reresection. Average time from diagnosis to attempted curative resection was 106 days. Two patients (4.8%) presented with Stage I disease. These two patients underwent surgical reresection as a result of equivocal margins from their cholecystectomy. Seven patients (16.7%) presented with Stage II, 17 patients (40.5%) presented with Stage IIIa/IIIb, and 16 patients (38.1%) presented with Stage IVa/IVb. A total of 16 patients (38.1%) received adjuvant therapy (chemotherapy and/or radiation therapy).

Median overall survival for all patients has not yet been reached. Median follow-up for all patients was 20.1 months. Thirty-two patients are still alive: 26 with no known recurrent disease and five alive with recurrent disease. Ten patients (23.8%) are actual 5-year survivors. Three Stage II patients, four Stage III patients, and three Stage IV patients are actual 5-year survivors. The Kaplan-Meier method was used to extrapolate 5-year survival probability using all 42 patients. Five-year probability for Stage I to II, Stage III, and Stage IV patients was 100, 80 (95% confidence interval [CI], 61 to 99%), and 39.3 per cent (95% CI, 28 to 78%), respectively (Fig. 1A). For comparison, 6th edition AJCC staging is shown in Figure 1B. Seventh edition AJCC staging was a statistically significant predictor of prognosis ($P = 0.0075$).

Results of univariate analyses are presented in Table 1. Five-year survival probabilities for T1, T2, T3, and T4 tumor stage were 100, 94 (95% CI, 63 to 99%), 63 (95% CI, 23 to 86%), and 42 per cent (95% CI, 17 to 66%), respectively. Tumor stage was a statistically significant predictor of prognosis ($P = 0.02$). Five-year survival probability for patients with liver involvement was 36.4 per cent (95% CI, 11 to 63%) compared with 83.1 per cent (95% CI, 63 to 92%) in patients without liver involvement. Liver involvement is a statistically significant predictor of prognosis ($P = 0.01$). Five-year survival probability for patients who had positive lymph node status was 57.8 per cent (95% CI, 31 to 77%) compared with 78 per cent (95% CI, 53 to 90%) in patients with negative lymph node status. Lymph node status was not a statistically significant predictor of prognosis. Five-year survival probability for patients receiving adjuvant therapy was 61 per cent (95% CI, 26 to 83%) compared with 70 per cent (95% CI, 49 to 84%) in patients who did not receive adjuvant therapy. Adjuvant therapy was not shown to be a statistically significant predictor of prognosis.

In multivariate modeling, AJCC 7th edition staging, T stage, and liver involvement were shown to be statistically significant predictors of prognosis, adjusted for age, gender, and race. The multivariate modeling strategy using backward elimination showed that AJCC 7th edition staging was the strongest predictor of prognosis.

## Discussion

To our knowledge, this study is the first from the United States to use the revised 7th edition AJCC staging criteria to investigate surgical outcomes for gallbladder cancer. In general, compared with the previous 6th edition, staging of Stage IB to III gallbladder cancer upstages patients when using the 7th edition AJCC staging criteria.[3] With the 6th edition staging criteria, there was no discrimination between Stage III and Stage IV in terms of 5-year survival; therefore, the 7th edition staging was developed to provide better prognostic

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discrimination based on outcome.[4] Using the 6th edition system, our Stage IV patients were actually shown to have better survival outcome than Stage III patients (Fig. 1B). Based on the 7th edition system, it is clear that there is a stepwise correlation between increasing stage and worse prognosis (Fig. 1A). This shows that the 6th edition staging system was not an accurate indicator of prognosis.

These data show survival for Stage III and IV patients of 80 and 39 per cent, respectively, which is higher than expected compared with other previous single-center studies conducted in the United States. The explanation for these results is multifactorial. First, patients with Stage IVb disease confirmed by CT or MRI were excluded from analysis, therefore leading to improved 5-year survival shown in this study. Detailed data pertaining to these patients were not attainable as a result of limitations of the Institutional Review Board application. Second, there were two patients included in this study with Stage IVb disease who had adjuvant chemotherapy with complete response and are both alive today. Additionally, the extent of lymphadenectomy conducted at most institutions is radical portal lymphadenectomy, which includes excision of N1 lymph nodes. It is our practice to obtain frozen sections of both N1 and N2 lymph nodes at the time of surgery. Positive N2 lymph nodes then precipitated N2 nodal dissection. Based on the 6th edition AJCC staging criteria, there was no distinction between N1 and N2 lymph nodes. However, in the revised 7th edition system, N2 nodes are automatically categorized as Stage IVb disease. Other studies have shown that lymph node involvement is a statistically significant predictor of prognosis, although not found to be significant in this study.[5] Given the improved survival in Stage IV patients in this study, further analysis is needed to determine if N2 and M1 disease should be distinguished because both are currently categorized as Stage IVb disease. Clearly, this study confirms that radical resection is appropriate for patients with even Stage IV gallbladder cancer as long as disease is localized and R0 resection is possible.

These results may also be explained by a trend in the extent of surgical resection for treatment of gallbladder cancer, which has shifted toward a more aggressive approach in recent years.[6, 7] A study from Massachusetts General Hospital showed that overall median survival has improved in the last four decades with more aggressive surgical management including liver resection and common bile duct resection.[8] This may contribute to the optimistic findings of this study compared with previous studies. In contrast, other studies have found that the increased morbidity and mortality of such aggressive resections suggests that these procedures should not be standard of care but should only be done when necessary to clear locally invasive tumors.[9] In our series, there was no intraoperative or perioperative mortality and no reoperations. Therefore, the extent of aggressive surgical resection should be determined on a case-to-case basis, examining the anatomy and distribution of disease in each individual as well as the expertise at the institution.

This study did not demonstrate a survival benefit for those who received adjuvant therapy. In fact, this study actually suggests that survival probability was better in patients who did not receive adjuvant therapy. This is because patients who were chosen to have adjuvant therapy had higher stages of disease, whereas patients with lower stages of disease did not require chemotherapy. However, as a result of the small sample size of patients undergoing adjuvant therapy, further studies should be conducted to confirm this finding. It should also

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be noted that many of the patients in this study continued follow-up at their local institution and factors contributing to the decision to undergo adjuvant therapy postsurgery are unknown. A study from Memorial Sloan-Kettering Cancer Center also did not demonstrate a survival benefit to adjuvant therapy based on median survival time.[10] Because there is no standard recommendation for adjuvant chemo- or radiation therapy, there may be significant variation in treatment agents, dosage, and total number of cycles between patients, leading to the inconclusive results of this study. Further studies should be conducted to elucidate the effectiveness of chemotherapy in gallbladder cancer management and determine standardized treatment.

In 10 of 42 patients (24%), laparoscopy diagnosed disseminated disease, which had not been seen on preoperative imaging studies. Published rates of unsuspected disseminated disease for gallbladder cancer range from 7 to 37 per cent.[11, 12] Given the paucity of data, the exact role of laparoscopy remains to be determined.

These data should be interpreted with caution, because there were various limitations in this study. There was a relatively small number of subjects included in this study with a small number of patients represented in each tumor stage. It should also be noted that the median length of follow-up for this study was 20.1 months. This may not have been enough time to allow recurrences to present in late-stage patients (Stage III and Stage IV).

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## References

1. Memon MA, Anwar S, Shiwani MH, Memon B. Gallbladder carcinoma: a retrospective analysis of twenty-two year experience of a single teaching hospital. Int Semin Surg Oncol. 2005; 2:6. [PubMed: 15774016]
2. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol. 2003; 4:167–76. [PubMed: 12623362]
3. Edge, SB.; Byrd, DR.; Compton, CC., et al. AJCC Cancer Staging Manual. 7th. New York, NY: Springer Verlag; 2010.
4. Fong Y, Wagman L, Gonen M, et al. Evidence-based gallbladder cancer staging: changing cancer staging by analysis of data from the NCD. Ann Surg. 2006; 243:767–74. [PubMed: 16772780]
5. Zaydfudim V, Feurer ID, Wright JK, Pinson CW. The impact of tumor extent (T stage) and lymph node involvement (N stage) on survival after surgical resection for gallbladder adenocarcinoma. HPB. 2008; 10:420–7. [PubMed: 19088928]
6. Foster JM, Hoshi H, Gibbs JF, et al. Gallbladder cancer: defining the indications for primary radical resection and radical re-resection. Ann Surg Oncol. 2007; 14:833–40. [PubMed: 17103074]
7. Dixon E, Vollmer CM, Sahajpal A, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer. Ann Surg. 2005; 241:385–94. [PubMed: 15729060]
8. Konstantinidis IT, Deshpande V, Genevay M, et al. Trends in presentation and survival for gallbladder cancer during a period of more than 4 decades. Arch Surg. 2009; 144:441–7. [PubMed: 19451486]
9. D'Angelica M, Dalal KM, DeMatteo RP, et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol. 2009; 16:806–16. [PubMed: 18985272]

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10. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol. 2008; 98:485–9. [PubMed: 18802958]

11. Butte JM, Gonen M, Allen PJ, et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. HPB. 2011; 13:463–72. [PubMed: 21689230]

12. Agrawal S, Sonawane RN, Behari A, et al. Laparoscopic staging in gallbladder cancer. Dig Surg. 2005; 22:440–5. [PubMed: 16479113]

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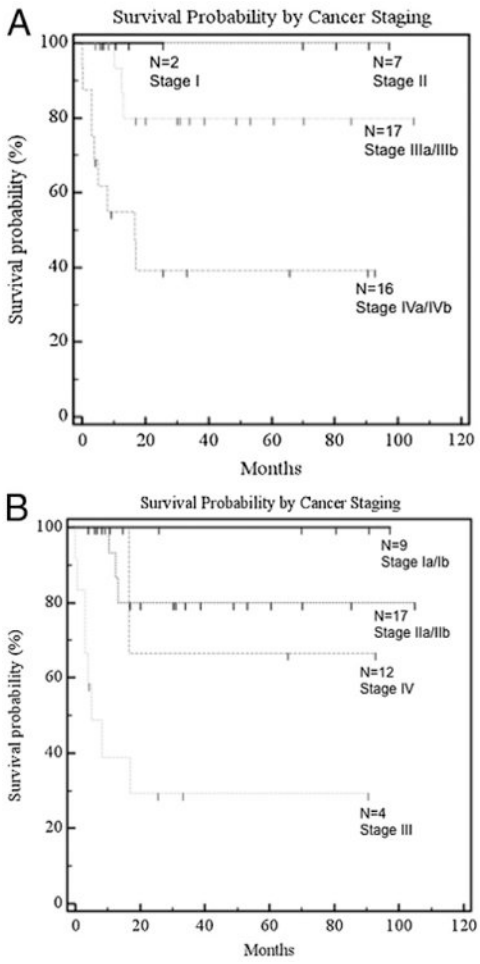


**Fig. 1.**

(*A*) Survival probability by 7th edition American Joint Committee on Cancer (AJCC) staging criteria. (*B*) Survival probability by 6th edition AJCC staging criteria.

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## Table 1
### Univariate Analysis of Variables as it Affects Survival Probability

| | Probability of Survival 5-year (95% CI) | *P* Value of Log-rank Test | Hazard Ratio (95% CI) |
|---|---|---|---|
| Gender | | | |
| Male | 0.47 (0.12–0.76) | 0.0722 | 2.87 (0.86–9.56) |
| Female | 0.73 (0.53–0.86) | | 1.0 |
| Race | | | |
| Asian | 0.50 (0.06–0.84) | 0.1931 | 2.82 (0.73–10.93) |
| Hispanic | 0.78 (0.36–0.94) | | 0.74 (0.15–3.57) |
| White | 0.68 (0.45–0.84) | | 1.0 |
| Other | 1.0 | | 0.0 |
| AJCC 7th edition staging | | | |
| 1 | 1.0 | 0.0075 | 0.0 |
| 2 | 1.0 | | 0.0 |
| 3a and 3b | 0.80 (0.61–0.99) | | 1.0 |
| 4a and 4b | 0.39 (0.28–0.76) | | 4.75 (1.28–17.64) |
| T stage | | | |
| 1 | 1.0 | 0.0199 | 0.0 |
| 2 | 0.94 (0.63–0.99) | | 1.0 |
| 3 | 0.63 (0.23–0.86) | | 5.58 (0.58–53.65) |
| 4 | 0.42 (0.17–0.66) | | 12.06 (1.05–96.64) |
| N stage | | | |
| 0 | 0.75 (0.49–0.89) | 0.2335 | 1.0 |
| 1 | 0.70 (0.42–0.86) | | 1.04 (0.3–3.6) |
| 2 | 0 | | 3.56 (0.68–18.52) |
| M stage | | | |
| 0 | 0.68 (0.49–0.81) | 0.7921 | 1.0 |
| 1 | 0.67 (0.05–0.95) | | 0.76 (0.1–5.89) |
| Positive lymph nodes | | | |
| 0 = not involved | 0.77 (0.53–0.90) | 0.3691 | 1.0 |
| 1 = involved | 0.58 (0.31–0.77) | | 1.68 (0.53–5.3) |
| Liver involvement | | | |
| 0 = no liver involvement | 0.83 (0.63–0.92) | 0.0100 | 1.0 |
| 1 = liver Involvement | 0.36 (0.11–0.63) | | 4.04 (1.28–12.74) |
| Adjuvant therapy | | | |
| 0 = not involved | 0.70 (0.49–0.84) | 0.9662 | 1.0 |
| 1 = involved | 0.61 (0.26–0.83) | | 0.97 (0.29–3.24) |
| N2 *vs* M1 | | | |
| N2 | NE | 0.1730 | 4.61 (0.41–51.31) |
| M1 | 0.67 (0.05–0.95) | | 1.0 |
| Time between laparoscopic cholecystectomy and curative operation (days) | Not applicable | 0.1562 | 1.0 (1.00–1.01) |

CI, confidence interval; AJCC, American Joint Committee on Cancer; NE, No Estimate.

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