Is positive histologic surgical margin associated with overall survival in patients with resectable gallbladder cancer?☆

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A B S T R A C T
Background: Achieving microscopically negative (R0) surgical margins in gallbladder cancer often requires a partial hepatectomy with associated risk of morbidity and potential to delay adjuvant therapy. Prior studies on the importance of margin status in resectable gall bladder cancer include small numbers of patients with positive (R1) resection margins and are underpowered.

Methods: We queried the National Cancer Database to identify patients undergoing resection of gallbladder adenocarcinoma between 2004 and 2015. Patients presenting with metastatic disease, those who received neoadjuvant therapy, and those with fewer than 3 lymph nodes assessed were excluded. 1:1 propensity score matching was used to develop cohorts undergoing either R0 or R1 resection, matched for demographic, pathologic, and facility characteristics. Kaplan–Meier analysis was used to assess the association between margin status and overall survival.

Results: A total of 1,439 patients met inclusion criteria; 1,285 underwent R0 and 154 underwent R1 resection. On Kaplan–Meier analysis of propensity-matched cohorts, patients undergoing R0 resection had a median overall survival that was 18 months longer than those undergoing R1 resection (34.6 ± 2.0 months vs 16.3 ± 1.7 months. P < .001).

Conclusion: In patients presenting with resectable gallbladder adenocarcinoma, margin-negative resection is associated with significant improvement in overall survival.

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INTRODUCTION
Adenocarcinoma of the gallbladder is a nearly uniformly lethal malignancy. The 5-year overall survival (OS) rate is estimated at less than 5%, and overall length of disease-specific survival is 6 months [1]. This prognosis is due in large part to timing of presentation. Cancer-related symptoms develop late in the course of the disease. Approximately 75% of patients present after their tumors have infiltrated locally or spread distantly, precluding resection [2]. Early-stage cancers present rarely as pathologic findings in patients undergoing cholecystectomy for symptomatic cholelithiasis or as incidental findings on imaging done for vague abdominal symptoms.

For patients that do present at early pathologic or clinical stages, expert consensus panels, including the National Comprehensive Cancer Network, recommend resection to microscopically negative (R0) margins and an appropriate lymph node dissection [3–5]. For patients with disease discovered incidentally at the time of cholecystectomy, optimal surgical clearance and staging require a revisional resection of the gallbladder and adjacent liver segments with portal node dissection [4]. Both operations are associated with risk of significant morbidity and potential to delay adjuvant systemic treatment [5]. This is of particular clinical relevance given the tendency for these cancers to have subclinical systemic dissemination at the time of presentation when systemic therapies are an essential component of effective treatment [4].

Few studies evaluate the association between margin status and survival in patients undergoing resection for gallbladder cancer. Most of the evidence supporting R0 resection in these patients comes from single-institution retrospective case series with limited numbers of patients undergoing resection to positive margins [7–11]. Although these studies do identify an association between margin status and survival,

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the small number of patients with positive resection margins makes it difficult to adjust for nonpathologic determinates of survival and thus to measure the true impact of margin status on survival.

In the current analysis, we used the National Cancer Database (NCDB) to conduct a propensity-matched comparison of patients undergoing microscopically margin positive (R1) resection for gallbladder adenocarcinoma to a contemporaneous cohort undergoing R0 resection in an effort to better define the importance of resection margin in patients presenting with localized gallbladder cancer.

METHODS

Data Source and Patient Selection. The NCDB is a nationally represented oncology registry jointly administered by the American Cancer Society and the American College of Surgeons. The database contains records on an estimated 34 million cancer patients and captures an estimated 70% of malignancies diagnosed annually in the United States from approximately 1,500 hospitals accredited by the Commission on Cancer.

We queried the NCDB for records of adult patients undergoing curative-intent surgical resection of primary gallbladder cancer between 2004 and 2015. Patients with a second primary malignancy, those presenting with metastatic disease (clinical stage 4), those receiving neoadjuvant therapy, those with fewer than 3 lymph nodes assessed, those receiving resection to grossly positive (R2) margins, those with delayed presentation (>30 weeks) to the operating room, and those with missing data for variables to be used in our modeling were excluded from analysis. Patients with fewer than 3 lymph nodes assessed were excluded in an effort to ensure that individuals included in the analysis had accurate pathologic staging.

Variable Coding. Overall survival was defined as the time from diagnosis to death (due to any cause). Patient age was categorized as <50, 50–70, and >70 years. Tumor size was stratified into three categories: <3, 3–6, and >6 cm. The extent of tumor resection was classified as either simple or radical. Simple resections included any operation not requiring resection of an adjacent organ. Radical resections involved en bloc removal of one or more adjacent organs. Adjuvant treatment was defined as therapy given within the 3 months following primary surgical resection, per NCDB coding definitions. Analytic stage was used for all analyses. Analytic stage is defined and reported by the NCDB. It is an integration of all factors used for clinical and pathologic staging and is meant to provide the most accurate representation of the stage of a patient's disease taking both clinical and pathologic features into account. The sixth and seventh editions of the AJCC Cancer Staging Manual were used to determine disease stage depending on the time of diagnosis, as captured by the NCDB.

Statistical Analysis. Univariate comparisons of demographic, clinical, and histopathologic characteristics were made using $\chi^2$ and Student t tests where appropriate. Multivariable logistic regression was used to identify factors associated with R0 resection. Multivariable Cox proportional hazards modeling was used to identify factors associated with OS. Patients receiving R0 resection were then 1:1 propensity matched using the “nearest neighbor” method without replacement to those undergoing resection to microscopically positive (R1) margins. Propensity scores for each patient were generated from a multivariable logistic regression model adjusting for age, sex, insurance status, patient income, Charlson–Deyo comorbidity index, extent of resection, histopathologic grade, analytic stage, adjuvant radiotherapy, and adjuvant chemotherapy. Variables included in our models were chosen a priori as those thought most likely to be determinates of clinical outcome. Overall survival profiles for the matched cohorts were compared using the Kaplan–Meier method, and statistical significance was determined by log-rank test.

Statistical analyses were performed in R v3.6.0 (The R Foundation for Statistical Computing). All tests were 2-sided using a P value < .05. This project was approved by the Stritch School of Medicine, Loyola University Chicago Institutional Review Board.

RESULTS

Patient Selection. A total of 11,873 patients underwent surgical resection of gallbladder adenocarcinoma between 2004 and 2015. Of those, 1,439 records met inclusion criteria. A total of 1,285 (89.3%) underwent R0 resection; 154 (10.7%) underwent an R1 resection. Figure 1 represents our selection map. The most common reason for patients to be excluded from our analysis was that they underwent substandard lymph node assessment. A total of 4,897 (41.2%) patients underwent assessment of fewer than 3 lymph nodes.

Univariate Comparison of Demographics, Histopathology, and Clinical Outcomes. Table 1 displays the univariate unadjusted comparison of demographics, treatment, and histopathologic characteristics and clinical outcomes for patients undergoing R0 and R1 resection. Patients who underwent R0 resection tended to be younger (66.3 ± 0.3 vs 69.5 ± 0.8 years, P = .005) and were more likely to have private insurance (38.3% vs 28.6%, P = .023) than those undergoing R1 resection. Patients undergoing R0 resection had smaller average tumor sizes (3.34 ± 0.07 vs 4.34 ± 0.28 cm, P < .001), were less likely to have tumors of advanced histopathologic grade (poorly differentiated: 33.5% vs 44.8%, P = .005), and

![Patient selection map showing numbers of records excluded for each criteria.](image-url)
were more likely to have tumors of lower analytic stage (stage 1: 18.4% vs 3.9%, \( P < .001 \)) than those who underwent R1 resection. Patients undergoing R0 resection were less likely to receive adjuvant radiotherapy (31.1% vs 40.3%, \( P = .28 \)). There were no statistically significant differences between patients undergoing R0 and R1 resections with regard to timing of either adjuvant radiation (116.5 ± 63.6 vs 108.6 ± 62.8 days, \( P = .372 \)) or chemotherapy (88.6 ± 50.1 vs 78.7 ± 43.4 days, \( P = .083 \)). Patients undergoing R0 resection were also more likely to have node-negative disease (55.6% vs 24.7%, \( P < .001 \)) and to have less than 6 lymph nodes harvested (54.9% vs 42.9%, \( P = .006 \)).

### Cox Proportional Hazards Analysis
We performed Cox proportional hazards analysis to identify factors associated with OS. This model adjusted for age, sex, insurance status, patient income, Charlson–Deyo comorbidity index (CCI), facility type, histologic grade, tumor size, and extent of resection. On this analysis, patient age, histologic grade, and tumor size were associated with likelihood of undergoing R0 resection. Patients older than 70 years (OR 0.35, CI [0.11, 0.86]; \( P = .036 \)), those with undifferentiated histology (OR 0.20, CI [0.05, 1.01]; \( P = .031 \)), and those with tumor sizes greater than 6 cm (OR 0.37, CI [0.22, 0.62], \( P < .001 \)) all were statistically less likely to undergo R0 resection than those who were younger, had more well differentiated histology, and had smaller tumors (Table 2).

### Propensity-Matched Cohort Analysis of OS
All 154 patients undergoing R1 resection were then 1:1 propensity matched for age, demographics, comorbid disease state, histologic grade, analytic stage, and receipt of adjuvant therapies to 154 patients undergoing R0 resection. After matching, there were no statistically significant differences between cohorts (Table 4). On Kaplan–Meier analysis of matched cohorts, patients undergoing an R0 resection demonstrated median OS that was 18 months longer than those undergoing R1 resection (34.6 ± 2.0 vs 16.3 ± 1.7 months, \( P < .001 \); Fig 2).

### Multivariable Logistic Regression Identifying Factors Associated with R0 Resection
We performed multivariable logistic regression to identify factors independently associated with R0 resection. This model adjusted for age, sex, insurance status, patient income, Charlson–Deyo comorbidity index (CCI), facility type, histologic grade, tumor size, and extent of resection. On this analysis, patient age, histologic grade, and tumor size were associated with likelihood of undergoing R0 resection. Patients older than 70 years (OR 0.35, CI [0.11, 0.86]; \( P = .036 \)), those with undifferentiated histology (OR 0.20, CI [0.05, 1.01]; \( P = .031 \)), and those with tumor sizes greater than 6 cm (OR 0.37, CI [0.22, 0.62], \( P < .001 \)) all were statistically less likely to undergo R0 resection than those who were younger, had more well differentiated histology, and had smaller tumors (Table 2).
A clear surgical margin may be indicated in selected patients who are involved by the cancer (stomach, right colon, and common bile duct) to extensive en bloc resection of organs adjacent to the gallbladder and incholecystectomy is warranted. This result also suggests that a more extensive en bloc resection of organs adjacent to the gallbladder and involved by the cancer (stomach, right colon, and common bile duct) to a clear surgical margin may be indicated in selected patients who are deemed fit to tolerate such extended resections.

**DISCUSSION**

In this study, we used a large national cancer registry to evaluate the effect of achieving R0 resection on OS for patients presenting with localized gallbladder cancer. Patients undergoing R0 resection tended to be younger and were more likely to have private insurance than those undergoing R1 resection. We performed multivariable logistic regression to identify factors associated with R0 resection. In this analysis, we identified advanced patient age, undifferentiated histologic grade, and larger tumor size as factors independently associated with decreased risk-adjusted odds of achieving R0 margins. We then performed Cox proportional hazards analysis to identify factors associated with OS. Positive surgical margins were associated with significantly worse survival in this model, with a hazard ratio of 2.24. Propensity matching was then used to determine the association between margin status and the duration of survival. On this analysis, patients undergoing R0 resection demonstrated an OS that was 18 months longer than that of patients undergoing R1 resection.

Our primary finding has important implications for patients presenting with resectable gallbladder cancer. We find that R0 resection is associated with an 18-month improvement in OS, independent of analytic stage. This result suggests that performing an interval partial hepatectomy to clear the surgical margin in patients who have gallbladder carcinoma discovered incidentally at the time of a laparoscopic cholecystectomy is warranted. This result also suggests that a more extensive en bloc resection of organs adjacent to the gallbladder and involved by the cancer (stomach, right colon, and common bile duct) to a clear surgical margin may be indicated in selected patients who are deemed fit to tolerate such extended resections.

There are several other findings worth noting. On univariate comparison of patients undergoing R0 vs R1 resection, patients undergoing R0 resection tended to be younger and were more likely to have private insurance. On multivariable analysis, advanced age continued to be associated with lower odds of R0 resection, although insurance status was not. We believe that these findings reflect a natural selection bias in the providers, with surgeons being more likely to pursue more aggressive resection in younger patients and in those who are insured. It is also possible that younger patients and those with insurance were more likely to present with less advanced disease. Socioeconomic status (SES) has great potential to impact extent of disease at presentation and, thus, resection margin by affecting a patient's ability to access healthcare resources. Although that relationship did not reach significance in our adjusted analyses, further study in effort to more formally evaluate the relationship between SES, surgical approach, resection margin, and clinical outcome would be warranted.

On multivariable analysis evaluating factors associated with R0 resection, we found that tumor size and poorly differentiated histology were associated with margin status. In our final risk-adjusted model,
Our analysis has several limitations. This is a retrospective review of a large data set and is thus subject to both selection bias and omitted variable bias. We have matched our cohorts for analytic disease stage, but the NCDB does not capture detail on local–regional extent of tumor. It may be that histologic margin is simply a marker for more advanced disease and that our results overstate the value of R0 resection as applied to patients with resectable gallbladder cancer by comparing patients undergoing R0 resection to a cohort of patients with disease that is technically unresectable/disseminated. The NCDB does not capture granular information on adjuvant treatment, including the type of therapy used and the length of time given/number of doses given. This precludes any effort to adjust for the amount of systemic therapy patients with R1 resection margin received relative to that received by those undergoing R0 resection. The NCDB does not contain data on disease recurrence. For this reason, we are unable to draw conclusions on disease-specific survival or recurrence-free survival. We would hypothesize that the survival benefit identified here is due to improved disease clearance, but without data on site, nature, and timing of recurrence, we are unable to formally test this hypothesis. The NCDB does not capture more granular clinical data on the nature of resection. There are discrete codes for radical resection and enucleation, but there is no detail on which organ(s) or which segments of the liver were removed with the gallbladder. Because of this, it is not possible to evaluate the impact of extended resections on either margin status or OS in an organ-specific fashion. The NCDB also does not contain detail on how the gallbladder carcinoma was diagnosed. For this reason, we may be evaluating a cohort that includes patients with disease discovered incidentally at the time of cholecystectomy done for symptomatic gallstones. We are unable to determine the proportion of patients for whom the cancer is detected incidentally. We have attempted to control for this as best possible by eliminating patients with fewer than 3 nodes sampled and adjusting for stage of disease. The NCDB is also lacking specific detail on sites of margin positivity. Margin status is defined only as negative, microscopically positive (R1), or grossly positive (R2) with no granular information on which specific margins were positive. For this reason, we are unable to comment on patterns or distributions of sites of margin positivity. The NCDB does not capture information on complications or postoperative functional health. For this reason, we have limited ability to understand potential costs associated with the extended resections required to achieve negative margins and may thus, again, overstate the potential value of R0 resection. In spite of these limitations, the use of this data set allows for an analysis of a number of patients undergoing R1 resection far surpassing that in any study available in the literature today and affords a more robust ability to adjust for potential confounding determinates of survival.

In conclusion, despite limitations inherent in studies using nationally accruing data, our analysis demonstrates a survival benefit for margin negative (R0) resection in patients presenting with resectable gallbladder cancer. These findings suggest that more extensive resections to provide clear margins in patients generally fit for such procedures are justified.

Author Contribution

Dr. Baker and Mr. Littau had full access to all data in the study and take responsibility for the integrity and accuracy of data analysis.

Conception & design: Dr. Baker, Mr. Littau.

Data acquisition: Dr. Baker, Dr. Luchette, Mr. Littau.

Analysis and interpretation: all authors.

Drafting the manuscript/critical revision: all authors.

Final approval: all authors.

Conflict of Interest

The authors have no conflicts of interest to disclose.
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Ethics Approval

This research was conducted under Exempt status as determined by the Loyola University Chicago Institutional Review Board (IRB #214433).

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