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

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ABSTRACT

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.

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 liver segments 4b and 5 with locoregional lymph node dissection [4]. For those presenting with evidence of a resectable mass prior to cholecystectomy, this requires an en bloc 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 χ^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 what we considered 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

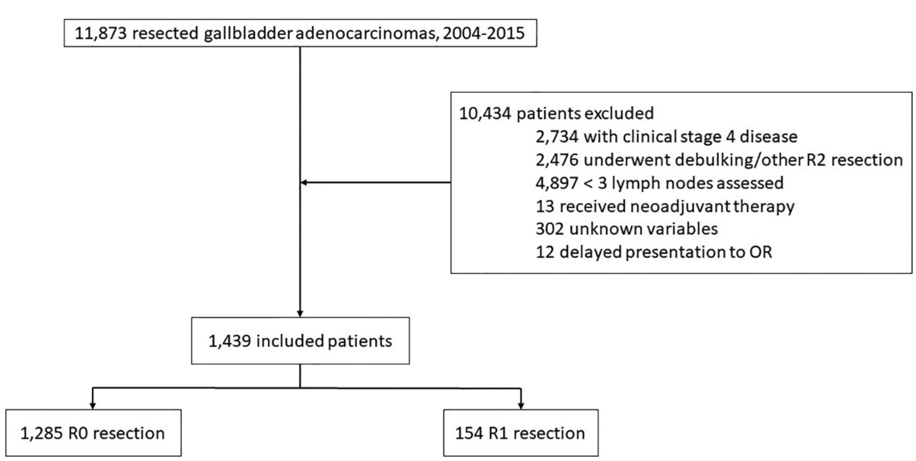

Fig 1. Patient selection map showing numbers of records excluded for each criteria.

Table 1
Univariate comparison of patient cohorts prior to propensity matching

Characteristic	*R0*	*R1*	P
n	1285	154	
Age (%)			.005
<50 y	99 (7.7)	5 (3.2)	
50–70 y	707 (55.0)	73 (47.4)	
>70 y	479 (37.3)	76 (49.4)	
Sex = F (%)	914 (71.1)	109 (70.8)	1.000
Race (%)			.457
White	999 (77.7)	125 (81.2)	
Black	190 (14.8)	17 (11.0)	
Other	96 (7.5)	12 (7.8)	
Insurance status (%)			.023
Private	492 (38.3)	44 (28.6)	
Government	757 (58.9)	108 (70.1)	
Uninsured	36 (2.8)	2 (1.3)	
Facility type (%)			.479
Community program	58 (4.5)	7 (4.5)	
Comprehensive community program	385 (30.0)	38 (24.7)	
Academic/research program	638 (49.6)	79 (51.3)	
Integrated network program	204 (15.9)	30 (19.5)	
Income quartile (%)			.163
<25%	249 (19.4)	26 (16.9)	
25%–50%	267 (20.8)	24 (15.6)	
50%–75%	316 (24.6)	49 (31.8)	
>75%	453 (35.3)	55 (35.7)	
Charlson–Deyo comorbidity index (%)			.432
0	909 (70.7)	102 (66.2)	
1	275 (21.4)	35 (22.7)	
2	63 (4.9)	12 (7.8)	
3+	38 (3.0)	5 (3.2)	
Surgery type = radical resection (%)	291 (22.6)	46 (29.9)	.057
Tumor size (%)			<.001
<3 cm	673 (52.4)	53 (34.4)	
3–6 cm	470 (36.6)	71 (46.1)	
>6 cm	142 (11.1)	30 (19.5)	
Grade (%)			.005
Well differentiated	186 (14.5)	12 (7.8)	
Moderately differentiated	659 (51.3)	70 (45.5)	
Poorly differentiated	431 (33.5)	69 (44.8)	
Undifferentiated	9 (0.7)	3 (1.9)	
Analytic stage (%)			<.001
1	237 (18.4)	6 (3.9)	
2	497 (38.7)	38 (24.7)	
3	463 (36.0)	71 (46.1)	
4	88 (6.8)	39 (25.3)	
Lymph nodes harvested (%)			.006
3–6	706 (54.9)	66 (42.9)	
6+	579 (45.1)	88 (57.1)	
Lymph nodes positive (%)			<.001
0	714 (55.6)	38 (24.7)	
0–3	437 (34.0)	74 (48.1)	
3+	134 (10.4)	42 (27.3)	
Radiotherapy (%)			.028
No	885 (68.9)	92 (59.7)	
Yes	400 (31.1)	62 (40.3)	
Chemotherapy (%)			.077
No	644 (51.1)	65 (42.2)	
Yes	641 (49.9)	89 (57.8)	

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%, $P = .028$). 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. 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%, $P = .006$).

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], $P < .001$) were all statistically less likely to undergo R0 resection than those who were younger, had more well differentiated histology, and had smaller tumors (Table 2).

Table 2
Mutivariable logistic regression identifying factors associated with receipt of R0 resection

	OR	*Lower*	*Higher*	P
Age (ref = <50 y)				
50–70 y	0.52	0.17	1.23	.176
>70 y	0.35	0.11	0.86	.036
Sex (ref = male)	0.98	0.66	1.43	.919
Race (ref = white)				
Black	1.41	0.82	2.54	.234
Other	0.98	0.53	1.96	.945
Insurance status (ref = private)				
Government	0.77	0.50	1.16	.214
Uninsured	1.47	0.42	9.38	.607
Charlson–Deyo comorbidity score (ref = 0)				
1	0.87	0.57	1.34	.507
2	0.56	0.29	1.15	.092
3+	0.96	0.39	2.95	.944
Income quartile (ref = <25%)				
25%–50%	1.22	0.67	2.24	.514
50%–75%	0.71	0.42	1.20	.208
>75%	0.96	0.56	1.59	.865
Facility type (ref = community cancer)				
Comprehensive community cancer	1.31	0.51	2.98	.544
Academic/research	0.96	0.38	2.09	.917
Integrated network cancer program	0.88	0.33	2.07	.788
Grade (ref = well differentiated)				
Moderately differentiated	0.65	0.33	1.20	.195
Poorly differentiated	0.47	0.23	0.87	.024
Undifferentiated	0.20	0.05	1.01	.031
Tumor size (ref = <3 cm)				
3–6 cm	0.52	0.35	0.77	.001
>6 cm	0.37	0.22	0.62	.000
Surgery type (ref = simple resection)	0.82	0.56	1.22	.322

Cox Proportional Hazards Analysis. We performed Cox proportional hazards analysis to identify factors associated with OS. This model adjusted for margin status, patient age, sex, race, insurance, comorbidity index, patient income, adjuvant chemotherapy, adjuvant radiotherapy, facility type, extent of resection, analytic stage, histopathologic grade, and tumor size (Table 3). Patient age > 70 years (HR 1.27, CI [0.91, 1.77]), government insurance (HR 1.22, CI [1.02, 1.46]), Charlson–Deyo comorbidity index of 3+ (HR 1.55, CI [1.06, 2.27]), advanced analytic stage (stage 3 HR 2.02, CI [1.58, 2.58]), undifferentiated histopathologic grade (HR 6.74, CI [3.40, 13.36]), tumor size >3 cm (HR 1.46, CI [1.25, 1.71]), and microscopically positive surgical margins (HR 2.24, CI [1.83, 2.74]) were independently associated with increased risk of all-cause mortality. Patient income >75%ile (HR 0.71, CI [0.57, 0.87]), receipt of chemotherapy (HR 0.81, CI [0.67, 0.98]), and treatment at an academic center (HR 0.59, CI [0.43, 0.81]) were independently associated with improved OS.

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).

Table 3
Cox proportional hazards analysis identifying factors associated with OS

Characteristic	*HR*	*Lower*	*Higher*	P
Margin status (ref = R0)	2.24	1.83	2.74	.000
Age (ref = <50 y)				
50–70 y	1.00	0.73	1.36	.988
>70 y	1.27	0.91	1.77	.160
Sex (ref = male)	0.84	0.72	0.99	.034
Race (ref = white)				
Black	1.00	0.81	1.25	.970
Other	0.77	0.57	1.03	.081
Insurance status (ref = private)				
Government	1.22	1.02	1.46	.026
Uninsured	1.26	0.77	2.08	.357
Charlson–Deyo comorbidity score (ref = 0)				
1	1.15	0.97	1.38	.115
2	1.17	0.86	1.61	.321
3+	1.55	1.06	2.27	.022
Income quartile (ref = <25%)				
25%–50%	0.87	0.69	1.10	.246
50%–75%	0.94	0.75	1.16	.557
>75%	0.71	0.57	0.87	.001
Chemotherapy (ref = no)	0.81	0.67	0.98	.027
Radiotherapy (ref = no)	0.91	0.75	1.11	.346
Facility type (ref = community cancer)				
Comprehensive community cancer	0.75	0.55	1.04	.081
Academic/research	0.59	0.43	0.81	.001
Integrated network cancer program	0.73	0.52	1.02	.065
Surgery type (ref = simple resection)	1.16	0.99	1.37	.072
Analytic stage (ref = 1)				
2	1.40	1.10	1.78	.006
3	2.02	1.58	2.58	.000
4	2.96	2.19	4.00	.000
Grade (ref = well differentiated)				
Moderately differentiated	1.61	1.24	2.09	.000
Poorly differentiated	2.28	1.74	2.99	.000
Undifferentiated	6.74	3.40	13.36	.000
Tumor size (ref = <3 cm)				
3–6 cm	1.46	1.25	1.71	.000
>6 cm	2.07	1.66	2.57	.000

Table 4
Univariate comparison of patient cohorts post-propensity matching.

Characteristic	*R0*	*R1*	P
n	154	154	
Age (%)			.776
<50 y	6 (3.9)	5 (3.2)	
50–70 y	67 (43.5)	73 (47.4)	
>70 y	81 (52.6)	76 (49.4)	
Sex = F (%)	111 (72.1)	109 (70.8)	.900
Race (%)			.755
White	120 (77.9)	125 (81.2)	
Black	21 (13.6)	17 (11.0)	
Other	13 (8.4)	12 (7.8)	
Insurance status (%)			.760
Private	48 (31.2)	44 (28.6)	
Government	105 (68.2)	108 (70.1)	
Uninsured	1 (0.6)	2 (1.3)	
Facility type (%)			.962
Community program	8 (5.2)	7 (4.5)	
Comprehensive community program	36 (23.4)	38 (24.7)	
Academic/research program	77 (50.0)	79 (51.3)	
Integrated network program	33 (21.4)	30 (19.5)	
Income quartile (%)			.926
<25%	28 (18.2)	26 (16.9)	
25%–50%	22 (14.3)	24 (15.6)	
50%–75%	53 (34.4)	49 (31.8)	
>75%	51 (33.1)	55 (35.7)	
Charlson–Deyo comorbidity index (%)			.578
0	95 (61.7)	102 (66.2)	
1	37 (24.0)	35 (22.7)	
2	12 (7.8)	12 (7.8)	
3+	10 (6.5)	5 (3.2)	
Surgery type = radical resection (%)	45 (29.2)	46 (29.9)	1.00
Tumor size (%)			.465
<3 cm	43 (27.9)	53 (34.4)	
3–6 cm	79 (51.3)	71 (46.1)	
>6 cm	32 (20.8)	30 (19.5)	
Grade (%)			.794
Well differentiated	9 (5.8)	12 (7.8)	
Moderately differentiated	77 (50.0)	70 (45.5)	
Poorly differentiated	66 (42.9)	69 (44.8)	
Undifferentiated	2 (1.3)	3 (1.9)	
Analytic stage (%)			.770
1	6 (3.9)	6 (3.9)	
2	37 (24.0)	38 (24.7)	
3	79 (51.3)	71 (46.1)	
4	32 (20.8)	39 (25.3)	
Radiotherapy (%)			.908
No	90 (58.4)	94 (59.7)	
Yes	64 (41.6)	62 (40.3)	
Chemotherapy (%)			.817
No	62 (40.3)	65 (42.2)	
Yes	92 (59.7)	89 (57.8)	

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 that had 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,

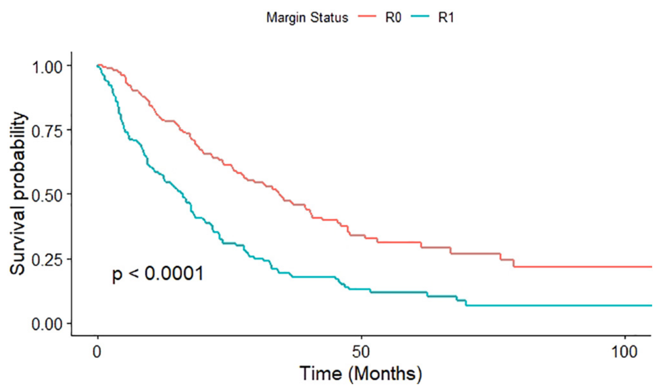

Fig 2. Kaplan–Meier survival curve comparing OS between propensity-matched cohorts.

tumor size greater than 3 cm and poorly differentiated histology were both independently associated with a 50% reduction in the probability of achieving R0 resection. Although histologic grade is beyond the control of the clinical care team and is infrequently known prior to surgery, we do feel that the findings around tumor histology and tumor size have the potential to drive clinical decision making in important ways. Locoregional and systemic therapies including chemotherapy, immunotherapy, brachytherapy, and/or external beam radiotherapy given prior to surgery would be expected to offer potential to reduce both the size and local infiltration of large, high grade tumors and facilitate R0 resection. There is currently little evidence to support the use of neoadjuvant therapy in this disease [6]. Our findings at the very least suggest that there is a need to more formally study the potential benefits of neoadjuvant therapy in gallbladder cancer.

Prior retrospective analyses have been limited in their ability to define the magnitude of the association between margin of resection and survival as these have generally included small numbers of patients with histologically positive surgical margins. One recent retrospective analysis attempting to model survival in resected gallbladder adenocarcinoma identified a strong association between margin positivity and risk of death. This study included a total of 164 patients with 6 resected to positive margins [7]. A second study evaluating the effect of bile spillage on survival identified an association between a positive hepatic margin and/or failure to perform a hepatic resection and both progression-free survival and OS [8]. This study was likewise limited by a small total patient population ($n = 66$) and small number of patients with positive surgical margins ($n = 26$). These small numbers make adjusting for relevant determinates of OS, like age, pathologic stage, and comorbid disease, practically impossible and effectively limit any effort to draw conclusions regarding the importance of the surgical margin using these studies. Older retrospective analyses have reached similar conclusions—that margin is associated with survival—but again suffer from the same limitations [9–11].

In contrast to previous studies, we use a large national data set to study 1,439 patients, 154 of whom underwent margin positive resection. We exclude patients who underwent inadequate lymph node assessment, defined as fewer than 3 nodes assessed, to ensure that we were able to appropriately adjust for stage in our analyses. The larger sample size in this study allowed us to develop propensity-matched cohorts and better control for potential confounding. These advantages would be expected to afford a more accurate assessment of the value of R0 resection in gallbladder adenocarcinoma and improve the applicability of our results compared to previous analyses. The propensity-matched analysis also provides an estimate of the duration of improvement in OS associated with R0 resection. This estimate of duration would be expected to facilitate clinical applicability of the modeling in that it would be an easier number for patients to understand and thereby appreciate the importance of extended resection required to achieve negative margins.

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 complication type or severity, including details on specific postoperative 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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