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JNCI J Natl Cancer Inst (2017) 109(7): djw324

doi: 10.1093/jnci/djw324
First published online March 9, 2017
Article

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Limited Use of Adjuvant Therapy in Patients With Resected Gallbladder Cancer Despite a Strong Association With Survival

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Abstract

Background: There are no randomized data to guide clinicians treating patients with gallbladder cancer (GBC). Several retrospective studies reported the survival benefits of adjuvant radiotherapy (RT) and chemoradiation (CRT). In this paper, we examine whether these publications have impacted the utilization of adjuvant therapies and whether their survival benefits are evident in a contemporary cohort of patients.
Methods: Using the National Cancer Data Base, we identified 5029 patients diagnosed with T1-3N0-1 GBC and treated with surgical resection from 2005 to 2013. We described trends in receipt of adjuvant treatments for three time periods (2005–2007, 2008–2010, 2011–2013) and calculated three-year overall survival (OS) probabilities for 2989 patients treated in 2005–2010. All statistical tests were two-sided.
Results: The percentage of patients who received no adjuvant treatments was unchanged from 2005 to 2013. Adjuvant RT decreased from 4.2% to 1.7% ($P < .001$), adjuvant chemotherapy increased from 8.3% to 13.8% ($P < .001$), and adjuvant CRT remained stable at 15.9% ($P = .98$). Adjuvant treatments were associated with improved three-year OS, with adjusted hazard ratio of 0.47 (95% confidence interval [CI] = 0.39 to 0.58) for CRT, 0.77 (95% CI = 0.61 to 0.97) for chemotherapy, and 0.63 (95% CI = 0.44 to 0.92) for RT. Adjuvant CRT was associated with improved survival in all categories, except T1N0, and in patients with negative and positive margins.
Conclusion: Over the past decade there was no increase in the utilization of adjuvant therapies in the United States for patients with resected GBC. Adjuvant therapy is associated with statistically significantly improved three-year OS. This analysis should form the basis for current clinical recommendations and support future prospective trials.

Gallbladder cancer (GBC) is the most common biliary tract neoplasm in the United States, with approximately 11 420 new cases and 3710 deaths expected to occur in 2016 (1). Published studies demonstrate an overall five-year survival of only 5% to 15%. There are no randomized data guiding physicians in the treatment decision for patients diagnosed with GBC. The 2004 National Comprehensive Cancer Network (NCCN) guidelines recommended postoperative therapy with 5-FU-based chemoradiation (CRT) for resectable patients with greater than T1N0 disease (2). Since 2004, three retrospective publications using the Surveillance, Epidemiology, and End Results (SEER) database showed a survival benefit of adjuvant radiotherapy (RT) for patients with lymph node–positive (LN+) disease or T2 or greater primary tumor (3–5). Another analysis of this database demonstrated survival benefit of adjuvant CRT in the same patient population (6). A recently published analysis of the National Cancer Data Base (NCDB) on the outcomes of patients diagnosed with resected GBC and treated with adjuvant therapies between 1998 and 2006 showed a strong association between receipt of adjuvant therapies and improved survival (7).

Received: September 15, 2016; **Revised:** October 31, 2016; **Accepted:** December 6, 2016

Table 1. Descriptive characteristics of patients with resected T1-3N0-1 GBC and their tumor characteristics, by three diagnosis year periods*

Variable	2005–2007, % (n = 1530)	2008–2010, % (n = 1601)	2011–2013, % (n = 1898)
Age group, y			
18–49	5.9	7.8	5.8
50–64	26.2	25.1	26.6
65–79	42.3	42.3	42.1
≥80	25.6	24.7	25.4
Race/ethnicity			
NH white	62.1	63.9	63.1
NH black	13.3	13.2	15.3
Hispanic	11.6	11.6	11.3
Unknown/other	13.0	11.3	10.2
Comorbidity score			
0	64.5	65.2	62
1	24.7	22.9	25.9
≥2	10.8	11.9	12.1
Insurance			
Uninsured	3.4	4.4	4.5
Medicaid	4.7	7.4	6.5
Medicare	59.5	58.0	58.6
Private	29.9	27.7	28.4
Other/missing	2.5	2.5	2.1
Median income, $*			
<30 000	16.1	14.0	14.5
30 000–34 999	16.3	18.4	16.8
35 000–45 999	27.2	26.5	26.8
≥46 000	36.6	35.9	38.4
Missing	3.8	5.2	3.6
Median no high school diploma, %†			
≥29	20.5	18.4	20.8
20–28.9	23.6	23.5	21.9
14–19.9	21.6	22.0	21.1
<14	30.5	30.8	32.7
Missing	3.8	5.2	3.6
US region			
New England	5.5	5.4	4.5
Middle Atlantic	17.1	17.7	14.8
South Atlantic	21.6	22.7	22.1
East North Central	17.2	16.7	16.0
East South Central	5.9	5.3	5.2
West North Central	6.5	7.7	6.4
West South Central	9.5	10.4	11.0
Mountain	4.4	3.7	5.3
Pacific	12.2	10.4	14.8
AJCC TN category‡			
T1N0	17.5	16.1	16.6
T2N0	32.7	33.5	36.4
T3N0	19.2	17.7	17.3
T1-3N1	30.5	32.7	29.7
Tumor grade			
1	15.8	13.9	17.4
2	41.8	43.3	43.5
3	33.2	33.1	30.9
4	1.9	2.5	1.8
Missing	7.4	7.1	6.3
Margin status			
Margin negative	71.0	71.6	74.6
Margin positive	22.1	22.5	20.8
Unknown/other	6.9	5.9	4.7

*Area-level median household income quartiles from the 2000 US Census data. AJCC = American Joint Committee on Cancer; NH = non-Hispanic; TN = tumor node.
†Area-level quartiles for percentage of adults without a high school diploma from the US 2000 Census data.
‡Clinical stage used if pathologic stage was missing.

Despite these publications, the 2016 NCCN guidelines (8) have relaxed the recommendations, advocating for surgery to be followed by one of three options: adjuvant chemotherapy, adjuvant CRT, or observation. Because the previously published large national database analyses included patients treated a decade ago—until 2006—and did not evaluate the change in receipt of adjuvant treatments in the United States over time, our aim was to perform a contemporary analysis of the patterns of treatment over the past decade using the NCDB to determine the effect of previous national database retrospective publications and NCCN recommendations on the adjuvant treatments received by US patients, and to estimate the benefit of adjuvant therapies in the modern age. We also attempted to identify any barriers, whether patient related (such as insurance, income, ethnicity), or practice setting related (such as volume of patients seen at an institution), to receipt of adjuvant therapies.

Methods

Study Population

The NCDB, jointly sponsored by the American College of Surgeons and the American Cancer Society, is a national hospital-based oncologic outcomes database that derives its data from approximately 1500 Commission on Cancer–accredited programs in the United States. As such, the NCDB captures approximately 70% of incident cancers in the United States each year, making it one of the most powerful and generalizable cancer databases in the world (9). Ongoing validation of NCDB data accuracy and quality is performed through internal monitoring, site surveys, and data quality reviews (10). Data coding methods have been described previously (11).

We identified 8514 patients age 18 years or older who were diagnosed with a first primary American Joint Committee on Cancer (AJCC) T1-3N0-2 GBC and received all or part of their treatment at an accredited NCDB facility between January 1, 2005, and December 31, 2013. GBC cases include cancers with topography code of C23.9 and morphology codes of 8000-8152, 8154-8231, 8243-8245, 8250-8576, and 8980-8981, according to the third edition of the *International Classification of Disease for Oncology* (ICD-O-3) (12). Our analytic study population included 5029 patients after excluding 2243 patients who did not undergo surgical resection or for whom the status of surgical resection was unknown, 974 patients with stage IV disease, 17 patients with N2 disease, 231 patients who received neoadjuvant or unclassified treatment, and 20 patients with missing data for node status.

Treatment of all cases was analyzed using pathological stage (clinical stage was used if pathologic stage was missing) at the time of diagnosis. Management strategies for GBC include surgery, chemotherapy, RT, and combinations of these modalities. Information retrieved included type of surgery (local tumor excision, vs removal of gallbladder, vs removal of gallbladder in continuity with other organs), age (categorized as 18–49, 50–64, 65–79, ≥80 years), race/ethnicity (categorized as non-Hispanic [NH] white, NH black, Hispanic, or other/unknown), patient insurance (private, Medicaid, Medicare, uninsured, or other/missing), facility type (community cancer program, comprehensive community cancer program, teaching/research center, National Cancer Institute [NCI] program), facility volume (tertiles of facility case volume were ranked into low, medium, and high case volume by counting the number of cases treated at the facility by diagnosis year), geographical region of treatment facility (New England, Middle

Table 2. Percentage of patients with resected T1-T3N0-N1 GBC by type of treatment facility and adjuvant treatment received in three diagnosis year periods*

Variable	2005–2007, % (n = 1530)	2008–2010, % (n = 1601)	2011–2013, % (n = 1898)
Facility type			
Community cancer program	13.2	11.2	12.5
Comprehensive community cancer program	46.1	44.7	45.6
NCI/teaching/research center	33.5	36.8	34.6
Other programs	7.2	7.3	7.3
Facility case volume			
Low	39.7	37.9	32.5
High	60.3	62.1	67.5
Surgery type			
Local tumor excision	4.2	5.0	4.0
Simple/partial/total removal of gallbladder	84.7	83	84.3
Partial/total removal of gallbladder in continuity with other organs	11.1	12	11.7
Adjuvant treatments after surgery			
Surgery alone	71.6	71.0	68.6
Adjuvant CRT	15.9	15.1	15.9
Adjuvant chemotherapy	8.3	11.0	13.8
Adjuvant RT	4.2	2.9	1.7

*CRT = chemoradiotherapy; NCI = National Cancer Institute; RT = radiation therapy.

Atlantic, South Atlantic, East North Central, East South Central, West North Central, West South Central, Mountain, Pacific), educational attainment (<14.0%, 14.0%–19.9%, 20.0%–28.9%, ≥29.0%, missing, defined as the percentage of residents per ZIP code without a high school diploma), date of diagnosis, date of surgery, date chemotherapy started, date RT started, receipt of chemotherapy, receipt of RT, number of fractions, node status (negative, positive, not examined), tumor grade (1, 2, 3, 4, missing/unknown, using a four-grade system [13]), tumor size (≤2 cm, >2 cm to 5 cm, >5 cm), margin status (margin negative, margin positive, unknown/other), and comorbidity score (0, 1, ≥ 2, based on the sum of weighted Charlson-Deyo Score [14]). Adjuvant therapy was defined as any treatment administered within six months after diagnosis. For the trend analysis, all patients were grouped according to predetermined time periods of diagnosis: 2005–2007, 2008–2010, 2011–2013. For three-year survival analysis, data were limited to patients diagnosed with T1-3N0-1 GBC from 2005 to 2010 (n = 2989).

Statistical Analysis

We used SAS version 9.4 software (SAS Institute, Cary, NC) to perform the statistical analysis. We performed descriptive analysis to show patterns of adjuvant treatment using chi-square tests to test statistical significance for categorical variables and Cochran-Armitage trend test to determine trends over time in the use of adjuvant therapies for three time periods (2005–2007, 2008–2010, 2011–2013). Variables likely to be associated with receipt of adjuvant treatments and the type of adjuvant treatments were included in the multivariable logistic regression model. All-cause unadjusted three-year survival rates were calculated using the Kaplan-Meier method. Follow-up time for calculating survival rates was from date of diagnosis until end-of-study date (December 31, 2013), last contact date, or death, whichever occurred first. Cox proportional hazards models were used to estimate three-year risk of all-cause mortality and identify independent predictors of survival. Diagnosis age, TN category, grade, node status, comorbidity score, insurance status, and income violated the supremum proportional hazards assumption test and were included in strata statement of the model. Treatment was included in the model although it violated proportional hazard assumption. Statistical significance was considered when the two-sided *P* value was less than .05.

Results

Patient Demographics

There were no statistically significant differences in sociodemographic (age, ethnicity, insurance, income, or education) and clinical characteristics (comorbidity score) of patients among the three diagnosis periods (Table 1). The majority of patients (65.6%) diagnosed with T1-3N0-1 GBC were age 65 years and older. NH whites accounted for 63.1% of patients, and 63.8% had a comorbidity score of 0.

Tumor Characteristics

The quality of documentation of tumor characteristics has improved between the years of 2005 and 2013, with an apparent decrease in missing information on margin status ($P = .04$), tumor size ($P < .001$), and in percent of patients with unexamined lymph nodes ($P < .001$). No statistically significant changes in tumor characteristics (T category, N category, grade) were observed among the three diagnosis year cohorts (Table 1). The overall distribution of patients by TN categories was as follows: 16.7% T1N0, 34.4% T2N0, 18.0% T3N0, and 30.9% T1-3N1. Overall, 72.5% of patients who underwent surgery had margin-negative resection.

Patterns of Treatment

The majority of patients were treated at comprehensive community cancer programs (45.4%) and NCI/teaching/research

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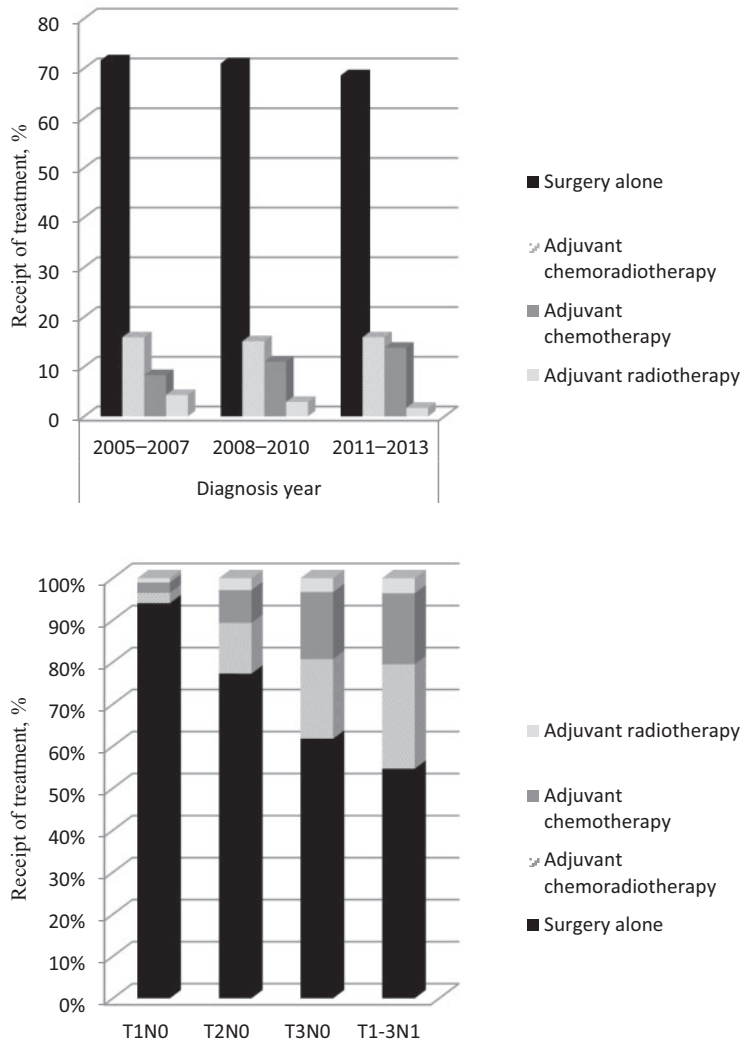

Figure 1. Trends in receipt of adjuvant therapies for patients with resected T1-3N0-1 gallbladder cancer in the United States by three time periods from 2005 to 2013 **(A)** and by tumor node category **(B)**.

centers (35.0%). The proportion of patients treated at facilities with low case volume status decreased from 39.7% during 2005–2007 to 32.5% during 2011–2013 (Table 2). Surgery rarely consisted of local tumor excision without gallbladder removal. The proportion of patients who received no adjuvant therapy after surgery for T1-3N0-1 trended down from 71.6% in years 2005–2007 to 68.6% in years 2011–2013 ($P_{trend} = .05$). The proportion of patients who received adjuvant RT following surgery decreased from 4.2% in 2005–2007 to 1.7% in 2011–2013 ($P_{trend} < .001$), with no statistically significant relationship between the type of surgery and the receipt of adjuvant RT (Supplementary Table 1, available online). At the same time, the receipt of adjuvant chemotherapy has increased from 8.3% to 13.8% ($P_{trend} < .001$) while receipt of adjuvant CRT remained stable at 15.9% through these years ($P_{trend} = .98$) (Figure 1A).

Patterns of Adjuvant Treatment by TN Category

Very few patients with T1N0 (5.9%) received adjuvant therapy after surgery, and this pattern did not change between 2005 and 2013 ($P_{trend} = .98$). Receipt of adjuvant therapies increased from 20.6% in 2005–2007 to 25.2% in 2011–2013 for patients with T2N0 disease ($P_{trend} = .05$). Adjuvant therapy was given to 38.5% of patients with T3N0 disease and to 45.5% of patients with T1-3N1 disease, with no statistically significant change across the three time periods ($P_{trend} = .87$ and .08, respectively) (Figure 1B).

Factors Associated With Receipt of Adjuvant Treatments

Patients who were older and had higher comorbidity scores were more likely not to receive any type of adjuvant therapy. Advanced stage, larger primary tumor size, and involvement of lymph nodes were associated with a higher likelihood of receiving some type of adjuvant therapy. Notably, regional differences impacted the receipt of adjuvant therapies, but social factors were not associated with adjuvant treatments (Table 3). Factors that were associated with receipt of adjuvant chemoradiation were younger age, being Hispanic, having a more advanced TN category, having positive lymph nodes, being treated at low case volume centers, as well as being treated in certain geographic regions (Supplementary Table 2, available online).

Table 3. Adjusted odds ratios predicting receipt of no adjuvant therapies for T1-T3N0-N1 resected gallbladder cancer*

Variable	OR (95% CI)
Race/ethnicity	
NH white (ref)	1.00
NH black	0.83 (0.68 to 1.03)
Hispanic	1.00 (0.78 to 1.28)
Other/missing/unknown	0.96 (0.77 to 1.19)
Diagnosis age group, y	
18–49 (ref)	1.00
50–64	1.19 (0.90 to 1.58)
65–79	1.76 (1.30 to 2.39)
≥80	5.73 (4.05 to 8.10)
Diagnosis year	
2005–2007 (ref)	1.00
2008–2010	1.08 (0.90 to 1.28)
2011–2013	0.85 (0.71 to 1.00)
AJCC TN category†	
T1N0 (ref)	1.00
T2N0	0.21 (0.15 to 0.28)
T3N0	0.10 (0.07 to 0.14)
T1-3N1	0.14 (0.08 to 0.25)
Margin status	
Negative (ref)	1.00
Positive	0.88 (0.74 to 1.04)
Other/unknown	1.12 (0.82 to 1.53)
Tumor grade	
1 (ref)	1.00
2	0.94 (0.75 to 1.17)
3	1.00 (0.80 to 1.26)
4	1.28 (0.77 to 2.14)
Missing	1.27 (0.90 to 1.80)
Tumor size, cm	
<2 (ref)	1.00
2–<5	0.79 (0.66 to 0.96)
≥5	0.73 (0.57 to 0.93)
Missing/unknown	0.86 (0.71 to 1.05)
Node status	
Negative (ref)	1.00
Positive	0.54 (0.33 to 0.89)
Not examined	1.14 (0.95 to 1.37)
Comorbidity score	
0 (ref)	1.00
1	1.11 (0.94 to 1.31)
≥2	1.39 (1.09 to 1.76)
Region	
East North Central (ref)	1.00
East South Central	1.54 (1.09 to 2.18)
Middle Atlantic	1.16 (0.91 to 1.47)
Mountain	1.77 (1.21 to 2.59)
New England	1.18 (0.83 to 1.68)
Pacific	1.82 (1.39 to 2.38)
South Atlantic	1.26 (1.01 to 1.57)
West North Central	1.10 (0.81 to 1.49)
West South Central	1.81 (1.37 to 2.40)
Facility category	
NCI/teaching/research center (ref)	1.00
Community cancer program	1.18 (0.92 to 1.53)
Comprehensive community cancer program	0.91 (0.78 to 1.08)
Other programs	1.02 (0.77 to 1.36)
Facility case volume	
High (ref)	1.00
Low	0.87 (0.75 to 1.02)
Insurance	
Private (ref)	1.00
Uninsured	1.17 (0.83 to 1.65)
Medicaid	1.30 (0.96 to 1.76)
Medicare	1.20 (0.97 to 1.47)
Other/missing	1.91 (1.16 to 3.16)
Median no high school diploma, %‡	
<14 (ref)	1.00
14–19.9	1.16 (0.95 to 1.42)
20–28.9	1.16 (0.92 to 1.45)
>29	1.05 (0.79 to 1.39)
Median income, $§	
≥46 000 (ref)	1.00
<30 000	1.05 (0.78 to 1.40)
30 000–34 999	1.12 (0.88 to 1.43)
35 000–45 999	1.10 (0.90 to 1.34)

*Adjusted for race/ethnicity, diagnosis age, diagnosis year, tumor node category, grade, tumor size, node status, margin status, comorbidity score, US region, facility case volume, facility category, insurance status, median no high school diploma, median income quartile. AJCC = American Joint Committee on Cancer; CI = confidence interval; NCI = National Cancer Institute; NH = non-Hispanic; OR = odds ratio; TN = tumor node.

†Clinical stage used if pathologic stage was missing.

‡Area-level quartiles for percentage of adults without a high school diploma from the US 2000 Census data.

§Area-level median household income quartiles from the 2000 US Census data.

Survival Outcomes

The three-year unadjusted all-cause survival rates were 38.7% (95% CI = 36.5 to 40.8), 43.0% (95% CI = 38.4 to 47.5), 28.6% (95% CI = 23.3 to 34.1), and 36.5% (95% CI = 27.2 to 45.8) among patients who received surgery alone, adjuvant CRT, adjuvant chemotherapy, and adjuvant RT, respectively (Figure 2). When compared with patients who did not receive any type of adjuvant treatments, adjusted hazard ratio (HR) for risk of death at three years was 0.47 for adjuvant CRT (95% CI = 0.39 to 0.58), 0.77 for adjuvant chemotherapy (95% CI = 0.61 to 0.97), and 0.63 for adjuvant RT (95% CI = 0.44 to 0.92) (Table 4). Positive surgical margin status carried more than twice the risk of death at three years, with a hazard ratio of 2.13 (95% CI = 1.81 to 2.50), when compared with negative surgical margin status. By TN categories, unadjusted three-year all-cause survival rates for patients undergoing no adjuvant therapies after surgery were as follows: 64.2% (95% CI = 59.6 to 68.4) for T1N0, 46.8% (95% CI = 43.1 to 50.3) for T2N0, 19% (95% CI = 15.0 to 23.4) for T3N0, and 16.7% (95% CI = 13.6 to 20.2) for T1-3N1 (Table 5). Among patients who underwent surgical margin-negative resection, the unadjusted three-year all-cause survival rate was 47.1% (95% CI = 44.5 to 49.5) in the absence of adjuvant therapies, whereas with surgical margin-positive resection this rate was 10.6% (95% CI = 7.8 to 13.9). The hazard ratios of survival for individual TN categories and margin status are listed in Table 6. Adjuvant CRT was associated with improved survival in all categories, except T1N0, and in patients with negative and positive margins.

Discussion

This analysis of the NCDB over the past decade demonstrated a strong association between receipt of adjuvant therapies after

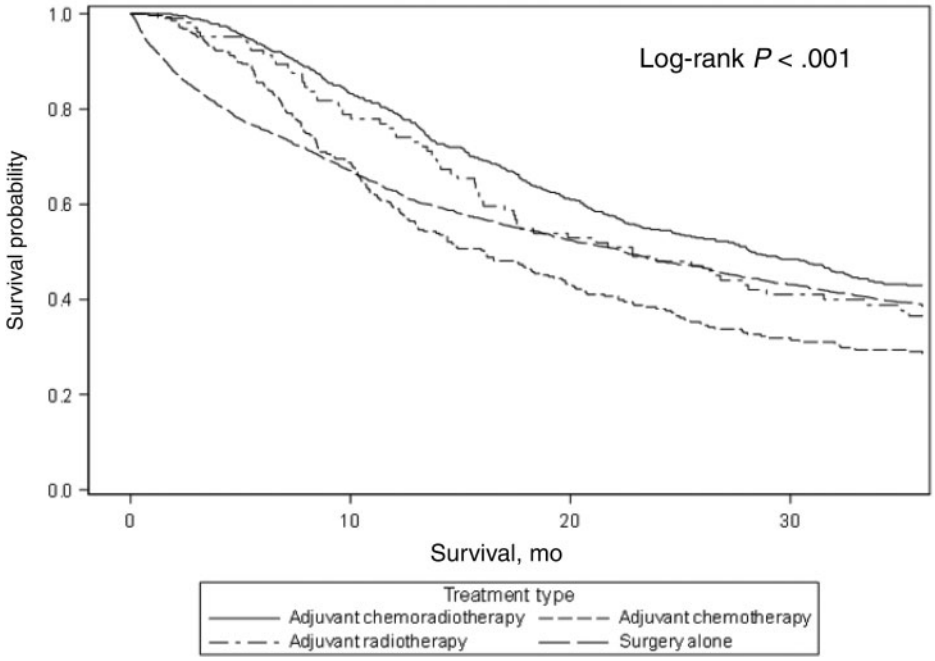

Figure 2. Probability of three-year survival for patients with T1-T3N0-1 resected gallbladder cancer by adjuvant treatment type in the United States (NCDB: 2005–2010). Two-sided *P* values were calculated using the log-rank test.

GBC resection and three-year overall survival. These findings validate older studies that analyzed large national data sets for outcomes in patients treated for GBC until 2006 (3–7,15). Our findings are also in line with a smaller contemporary retrospective series from 10 academic centers in the United States (16). In our study, the lowest hazard ratio for death at three years was associated with receipt of adjuvant CRT, although we did not compare different adjuvant therapies against each other, due to lack of statistical power. By category, adjuvant CRT was associated with better survival in all categories, except T1N0, where the number of patients who received adjuvant therapies was very low for any meaningful statistical analysis. The strong association of adjuvant CRT with overall survival can be explained by high risk of both local and distant disease recurrence in patients with even margin-negative resection of GBC.

Despite the published results of previous studies demonstrating association between improved survival and receipt of adjuvant therapy in resected GBC, we found that the past decade has not seen an increase in the utilization of adjuvant treatments in these patients. In the absence of randomized data, physicians must utilize evidence from large retrospective series to guide medical decisions. Our group has published two analyses of the SEER database, one in 2008 showing a strong association between adjuvant RT and overall survival for patients with node-positive or T2 or greater disease (3) and another in 2011 revealing a similar association with adjuvant CRT in the same group of patients (6). Two other groups have independently analyzed the SEER database and likewise confirmed a strong association of adjuvant RT with improved overall survival for patients with all stages, except stage I (4,5). A recent publication based on NCDB analysis of patients treated between 1998 and 2006 further confirmed the importance of adjuvant CRT (7). Unfortunately, our analysis of patterns of care shows no increase in utilization of adjuvant CRT between 2005 and 2013, a decrease in use of adjuvant RT, and a slight uptake of adjuvant chemotherapy over these years. The majority of US patients with resected gallbladder cancer still do not receive adjuvant therapies, even with locally advanced disease, such as T3N0 or T1-3N1, where three-year survival rates are only 19% and 17%, respectively, with surgery alone. Current NCCN guidelines may in part be responsible for the disconnect between published results from large national databases and lack of incorporation of this knowledge into clinical practice in the United States, as the current guidelines endorse a choice between observation, adjuvant chemotherapy, or adjuvant CRT, without giving support for adjuvant therapies to practicing clinicians (8).

It is important to note that complete surgical resection remains the only potentially curative treatment for primary adenocarcinoma of the gallbladder. In our analysis, we excluded patients who did not undergo surgery, but prior to exclusion we noted that almost 30% of US patients over the past decade with T1-3N0-1 disease were treated with nonsurgical modalities (definitive CRT, RT alone, or supportive care). This indicates that there may be a breakdown in referral for definitive surgery after GBC is diagnosed. Whether this is due to an incidental diagnosis of GBC made at cholecystectomy, comorbidities precluding major hepatic resection, or lack of clinical experience and knowledge regarding optimal surgical management of GBC among physicians facing an uncommon diagnosis remains unclear. What is known is that among patients who undergo curative resection, only 70% of patients in our analysis had R0 resection. For the remaining 30%, outcomes are poor, as patients had more than twice the risk of death at three years. While adjuvant treatments were associated with improved three-year all-cause survival rates in patients with both positive and negative margins, patients with negative margins and no adjuvant therapy had better unadjusted three-year survival (47%) than patients with positive margins and adjuvant treatments (22%). Hence, no currently available adjuvant therapy is able to make up for the presence of

Table 4. Adjusted hazard ratios of three-year survival for patients with resected T1-3N0-1 gallbladder cancer from 2005 to 2010*

Variable	HR (95% CI)
Treatment	
Surgery alone (ref)	1.00
Adjuvant CRT	0.47 (0.39 to 0.58)
Adjuvant chemotherapy	0.77 (0.61 to 0.97)
Adjuvant RT	0.63 (0.44 to 0.92)
Race/ethnicity	
NH white (ref)	1.00
NH black	1.10 (0.87 to 1.38)
Hispanic	0.83 (0.62 to 1.10)
Other/missing/unknown	0.92 (0.74 to 1.14)
Diagnosis year	
2005–2007 (ref)	1.00
2008–2010	1.10 (0.96 to 1.27)
Margin status	
Negative (ref)	1.00
Positive	2.13 (1.81 to 2.50)
Missing/unknown	1.61 (1.20 to 2.15)
Tumor size, cm	
<2 (ref)	1.00
2–<5	1.26 (1.03 to 1.53)
≥5	1.87 (1.46 to 2.39)
Missing/unknown	1.32 (1.08 to 1.61)
Comorbidity score	
0 (ref)	1.00
1	1.33 (1.27 to 1.40)
≥2	1.82 (1.70 to 1.95)
Region	
East North Central (ref)	1.00
East South Central	0.82 (0.59 to 1.13)
Middle Atlantic	0.76 (0.60 to 0.97)
Mountain	0.69 (0.47 to 1.01)
New England	0.93 (0.67 to 1.29)
Pacific	0.75 (0.57 to 0.97)
South Atlantic	0.84 (0.67 to 1.05)
West North Central	0.88 (0.65 to 1.18)
West South Central	0.60 (0.45 to 0.80)
Facility category	
NCI/teaching/research center (ref)	1.00
Community cancer program	1.19 (0.92 to 1.54)
Comprehensive community cancer program	1.33 (1.13 to 1.57)
Other programs	1.11 (0.84 to 1.48)
Facility case volume	
High (ref)	1.00
Low	1.13 (0.98 to 1.32)
Median no high school diploma, %†	
<14 (ref)	1.00
14–19.9	1.01 (0.83 to 1.23)
20–28.9	1.07 (0.86 to 1.33)
≥29	1.04 (0.78 to 1.38)

*Adjusted for all listed variables. Diagnosis age, tumor node category, grade, node status, comorbidity score, insurance status, and income were included in strata statement as they violated proportional hazard assumption; treatment was included in the model although it violated proportional hazard assumption. CI = confidence interval; CRT = chemoradiotherapy; HR = hazard ratio; NCI = National Cancer Institute; NH = non-Hispanic; RT = radiation therapy.

†Area-level quartiles for percentage of adults without a high school diploma from the US 2000 Census data.

Table 5. Probability of three-year survival for patients with resected gallbladder cancer by TN category and surgical margin status (NCDB: 2005–2010)*

Category/treatment	No.	3-y OS (95% CI), %
T1N0		
Adjuvant CRT	14	55.0 (27.8 to 76.8)
Adjuvant chemotherapy	11	45.5 (16.7 to 70.7)
Adjuvant radiotherapy	7	71.4 (25.8 to 92.0)
Surgery alone	471	64.2 (59.6 to 68.4)
T2N0		
Adjuvant CRT	118	61.2 (51.6 to 69.4)
Adjuvant chemotherapy	53	63.0 (48.3 to 74.6)
Adjuvant radiotherapy	34	43.7 (26.8 to 59.5)
Surgery alone	790	46.8 (43.1 to 50.3)
T3N0		
Adjuvant CRT	107	32.9 (24.1 to 42.0)
Adjuvant chemotherapy	74	20.0 (11.6 to 30.1)
Adjuvant radiotherapy	17	32.7 (12.2 to 55.2)
Surgery alone	345	19.0 (15.0 to 23.4)
T1-3N1		
Adjuvant CRT	226	37.3 (30.9 to 43.7)
Adjuvant chemotherapy	147	19.3 (13.1 to 26.3)
Adjuvant radiotherapy	47	27.4 (15.3 to 40.9)
Surgery alone	528	16.7 (13.6 to 20.2)
Negative margin, T1-3N0-1		
Adjuvant CRT	303	52.0 (46.1 to 57.6)
Adjuvant chemotherapy	177	37.4 (30.1 to 44.7)
Adjuvant radiotherapy	72	43.0 (31.2 to 54.2)
Surgery alone	1591	47.1 (44.5 to 49.5)
Positive margin, T1-3N0-1		
Adjuvant CRT	133	21.8 (15.1 to 29.3)
Adjuvant chemotherapy	89	9.1 (4.1 to 16.5)
Adjuvant radiotherapy	28	20.8 (8.2 to 37.5)
Surgery alone	410	10.6 (7.8 to 13.9)

*CI = confidence interval; CRT = chemoradiotherapy; OS = overall survival; TN = tumor node.

positive margins. Surprisingly, we did not observe a higher rate of patients with positive margins over the past decade receiving adjuvant treatments in our analysis.

When we explored the impact of individual adjuvant therapy in our contemporary NCDB analysis, we found that adjuvant chemotherapy alone was associated with improved OS only in node-positive patients. A previous NCDB analysis of patients treated until 2006 showed no benefit to adjuvant chemotherapy (7), whereas the recent retrospective analysis from 10 academic US institutions evaluating patients treated between 2000 and 2015 revealed an association between adjuvant chemotherapy and overall survival in multivariable analysis (16). NCDB does not collect information on the exact chemotherapy agents that patients in the United States received in the adjuvant setting, and it is possible that in the past patients were receiving chemotherapy that had limited activity in GBC. Indeed, a pooled analysis of 104 chemotherapy trials involving 1368 biliary cancer patients conducted in 1999–2006 suggested differences in clinical behavior and responsiveness to chemotherapy between GBC and other biliary tumors (17,18). Several phase II trials conducted in patients with GBC revealed that gemcitabine-based regimens have activity in this disease (18–20). Perhaps a higher proportion of patients

Table 6. Adjusted hazard ratios of three-year survival for patients with resected T1N0, T2N0, T3N0, and T1-3N1 gallbladder cancer from 2005 to 2010* by individual TN categories and surgical margin status and adjuvant treatments received

Category/treatment	HR (95% CI)
T1N0	
Surgery alone (ref)	1.00
Adjuvant CRT	1.94 (0.80 to 4.70)
Adjuvant chemotherapy	3.20 (1.25 to 8.18)
Adjuvant RT	1.63 (0.37 to 7.17)
T2N0	
Surgery alone (ref)	1.00
Adjuvant CRT	0.50 (0.36 to 0.69)
Adjuvant chemotherapy	0.70 (0.43 to 1.13)
Adjuvant RT	0.68 (0.42 to 1.11)
T3N0	
Surgery alone (ref)	1.00
Adjuvant CRT	0.57 (0.43 to 0.77)
Adjuvant chemotherapy	0.81 (0.60 to 1.11)
Adjuvant RT	0.46 (0.24 to 0.86)
T1-3N1	
Surgery alone (ref)	1.00
Adjuvant CRT	0.39 (0.30 to 0.49)
Adjuvant chemotherapy	0.71 (0.55 to 0.92)
Adjuvant RT	0.64 (0.41 to 0.98)
Margin negative	
Surgery alone (ref)	1.00
Adjuvant CRT	0.56 (0.44 to 0.70)
Adjuvant chemotherapy	1.02 (0.78 to 1.35)
Adjuvant RT	0.66 (0.43 to 1.01)
Margin positive	
Surgery alone (ref)	1.00
Adjuvant CRT	0.45 (0.34 to 0.59)
Adjuvant chemotherapy	0.78 (0.57 to 1.06)
Adjuvant RT	0.38 (0.24 to 0.62)

*Adjusted for race/ethnicity, diagnosis age, diagnosis year, tumor node category, margin status, grade, tumor size, node status, comorbidity score, US region, facility case volume, facility category, insurance status, median no high school diploma, median income. Treatment was included in the model, although it violated proportional hazard assumption. CI = confidence interval; CRT = chemoradiotherapy; HR = hazard ratio; RT = radiation therapy; TN = tumor node.

receiving gemcitabine in the modern era may explain the apparent difference between the NCDB analysis conducted in the old era and our current findings.

There were statistically significant changes in the AJCC TNM staging of GBC over the past decade (21). Individual definitions for T-category and N-category were not as affected as the grouping into overall stages. For this reason, our NCDB analysis focused on TN categories, which have not changed over the past decade, and we explicitly avoided using overall AJCC stages, which varied dramatically between 2005 and 2013 (data not shown).

We did not find any association between patient-related (such as insurance, income, race/ethnicity) or practice setting–related (such as volume of patients seen at an institution) factors and receipt of adjuvant therapies in our analysis, in contrast to our recent findings among US patients with locally advanced rectal cancer (22). This observation reinforces that medical knowledge, or lack thereof, is at the core of current practice patterns in the United States, and further research and education are critical for changing the outcomes for patients with GBC.

The NCDB is a comprehensive national oncologic outcomes database with detailed information on sociodemographic, tumor, hospital, and treatment characteristics (23). Several comparison studies have documented the validity of NCDB-based analysis (24,25). Despite these validation studies, several limitations to the current study require discussion. Although clinical and demographic characteristics of patients in the NCDB have been shown to be similar with patients in the SEER database (26), NCDB remains a hospital-based cancer registries database and the results may not be generalizable to the US population. Underreporting of receipt of chemotherapy and radiation therapy may occur as these therapies can be administered in the outpatient setting, which may make the data difficult to obtain. Additionally, NCDB does not collect information on types or combinations of chemotherapy drugs, provider/patient preferences, or individual socioeconomic factors that could influence receipt of treatment and survival outcome. Finally, we were unable to analyze GBC-specific mortality as the NCDB does not collect this information, which may not be reflective of treatment effectiveness but rather dependent on patient selection and thus susceptible to selection bias.

In a large national database, we have shown that over the past decade the uptake of adjuvant treatments has not improved in the United States, and more than 70% of patients do not receive adjuvant therapies. Further, the use of adjuvant therapies, particularly adjuvant CRT, is associated with improved overall survival for patients with resected GBC. In the absence of randomized data, large database retrospective cohort studies should be considered the foundation of current standards of care. This study and those that preceded it will certainly inform future guidelines, so that clinicians would be aware of a strong association between adjuvant therapies and overall survival in patients with resected GBC.

Funding

This work was supported by the American Cancer Society Intramural Research.

Notes

The funder had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The data used in the study are derived from a limited data set of the National Cancer Data Base (NCDB). The authors acknowledge the efforts of the American College of Surgeons, the Commission on Cancer, and the American Cancer Society in the creation of the National Cancer Data Base. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the authors.

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