



Adjuvant treatment for the elderly patient with resected gallbladder cancer: a SEER-Medicare analysis

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Background: In patients with resected gallbladder cancer (GBC), the role of adjuvant chemotherapy (aCT) remains ill-defined, especially in elderly patients. This study evaluates the value of aCT in elderly patients with GBC and assesses response according to tumor stage.

Methods: Patients of ≥ 65 years of age with resected GBC diagnosed from 2004–2015 were identified using a Surveillance, Epidemiology and End Results (SEER)/Medicare linked database. After propensity score matching, survival of patients treated with aCT was compared to survival of patients who did not receive aCT using Kaplan-Meier and Cox proportional hazards analysis.

Results: Of 2,179 patients with resected GBC, 876 (25%) received aCT. In the full cohort of 810 propensity-score matched patients, survival did not differ between patients treated with aCT (17.6 months) and without aCT (19.5 months, $P=0.7720$). Subgroup analysis showed that survival was significantly better after aCT in T3/T4 disease (12.3 vs. 7.2 months, $P=0.013$). Interaction analysis showed that benefit of aCT was primarily seen in combined T3/T4, node-positive disease (HR 0.612, $P=0.006$).

Conclusions: In this large cohort of elderly patients with resected GBC, aCT was not associated with increased survival. However, aCT may provide a survival benefit in T3/4, node-positive disease.

Keywords: Gallbladder cancer (GBC); chemotherapy; survival; elderly

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Introduction

Gallbladder cancer (GBC) has an extremely poor prognosis (1–4). In resected patients, recurrence rates are as high as 65%, and 5-year overall survival (OS) is only 15–30%

(5–7). Initial recurrence after resection is often locoregional, but distant relapse in the form of liver spread also occurs frequently (7,8). Adjuvant chemotherapy (aCT) or chemoradiotherapy (aCRT) could hypothetically grant a

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significant survival benefit by providing both locoregional and distant control.

Unfortunately, high-quality evidence regarding the benefit of aCT in GBC is sparse (9,10). Merely one prospective study, investigating gemcitabine and cisplatin as adjuvant treatment for GBC was conducted (11). However, only 100 patients were included and no sample size calculation was conducted. Hence, the only available prospective evidence consists of randomized controlled trials (RCTs) including patients with all forms of biliary tract cancer (BTC). Of these trials, only the BILCAP study (adjuvant capecitabine *vs.* observation alone) showed a statistically significant increase in survival in the per-protocol analysis alone (53 *vs.* 36 months, $P=0.028$) (8,12,13). Some have argued that the lack of apparent efficacy may be because aCT is only effective in patients with poor prognostic factors such as node-positive and R1 disease, a subgroup which was highly represented in the BILCAP trial (8). Moreover, one should exercise caution when extrapolating results of trial including all patients with BTC to patients with GBC alone, as BTC is a heterogeneous group of tumors with varying etiology, staging systems and molecular landscapes (8). Finally, studies show that there is a fundamental underrepresentation of especially geriatric patients in clinical trials, likely due to the utilization of stringent eligibility criteria (14,15). Consequently, outcomes of RCTs cannot necessarily be extrapolated to the increasingly frail and elderly general population (16,17). In order to improve external validity of clinical trials and provide clinicians with appropriate evidence for clinical decision making, experts have suggested supplementing RCT outcomes with data from observational cohorts.

Evidently, research specifically aimed at investigating the value of aCT in elderly patients with GBC is warranted. Population-based data provide an opportunity to analyze treatment and survival in a large number of patients and form a representative sample of the real-world population. Statistical methods such as propensity score matching can help to reduce the influence of treatment selection bias on results (18). We describe a propensity score-matched analysis of data from the Surveillance, Epidemiology and End Results (SEER) registry. The objective of this study was to determine the association of aCT in elderly GBC patients with survival and to identify clinically relevant subgroups of patients that may benefit from aCT. We present the follow article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-348/rc>) (19).

Methods

Data sources and study design

The SEER program is a population-based database maintained by the National Cancer Institute (NCI), encompassing approximately 34% of the population of the United States (<https://seer.cancer.gov>). Data provided by SEER can be supplemented by Medicare claims data in order to capture information not recoded by SEER, such as specific information on chemotherapy treatment. Medicare is a federally-funded health insurance program for citizens aged ≥ 65 years, with disabilities or end-stage renal disease (20). The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the University of Michigan Institutional Review Board and a waiver for informed consent was provided, given that SEER data is de-identified.

Study population

The cohort was created using data from the 2018 SEER-Medicare release. The cohort was restricted to patients diagnosed from 2004 to 2015. Patients with resected, non-metastatic GBC were included using site and histology codes from the International Classification of Disease for Oncology, Third Edition (ICD-O-3). Only patients with non-metastatic disease who underwent resection of the primary tumor site were included. Patients with Tis/T0 or Nx disease, overlapping lesions or uncommon histologies were excluded (Table S1). The cohort was limited to patients aged 65 years or older with Medicare part A and B coverage and no Health Maintenance Organization (HMO) enrollment during 12 months prior and 6 months after diagnosis (or until death) in order to assure completeness of Medicare claims.

Demographic and clinicopathologic variables

The following demographic variables were analyzed; age, race (White *vs.* Black *vs.* Asian/Pacific *vs.* Alaskan/native American), year of diagnosis, zip-code level percentage of residents with a high-school education (in quartiles), zip-code level median household income (in quartiles) and percentage living in poverty by zip-code. The number of Elixhauser comorbidities was derived from the outpatient and inpatient claims data (21,22).

Clinicopathological characteristics included for analysis were tumor location, differentiation grade, nodal status

(N0 vs. N+) and pT-stage. Tumor T, N and M stage were reported according to the 7th edition of the American Joint Committee on Cancer (AJCC)-staging manual (23).

Surgery, chemotherapy, and radiotherapy (RT) treatment identification

The date of surgery was identified using current procedural terminology (CPT) codes, healthcare common procedure coding system (HCPCS) codes, and international classification of diseases version 9 (ICD-9) procedure codes. Chemotherapy administration was identified using CPT codes, HCPCS codes and ICD-9 procedure codes. Oral equivalents of chemotherapeutic drugs were identified using National Drug Codes. RT was identified using CPT and revenue center codes for radiation therapy. All codes are available upon request to the authors.

Adjuvant treatment classification

Patients were classified into two groups according to the initial treatment strategy; aCT versus no aCT. aCT was defined as a claim for chemotherapy within six months of surgery, similar to other studies (24,25). A single claim for chemotherapy was used to reflect that a patient had received aCT. Claims for radiation therapy spanning ≥ 7 days were used to reflect that a patient had received RT.

Statistical analysis

Categorical variables were reported as counts with percentages and compared using the chi-squared test or Fisher's exact test, where appropriate. Numeric variables were reported as means with ranges and compared using the student's T-test or Mann-Whitney U test, where appropriate. The primary outcome of all analyses was OS. For all survival analyses, patients whom died within 30 days of surgery were excluded in order to correct for immortal-time bias. Sensitivity analysis in patients who survived >6 months was conducted to further reduce treatment selection and survivor bias since these patients may have had poor performance status or significant postoperative complications, resulting in a poor prognosis and potentially precluding them from receiving aCT. Survival was assessed using Kaplan-Meier curves and compared using the log-rank test. Missing data was classified as "unknown".

Propensity-score matching (PSM) was used to adjust for

treatment selection bias and compare OS of patients treated with aCT to that of patients with no aCT. The conditional probability of receiving chemotherapy (i.e., propensity score) was estimated using a multivariable logistic regression model including age, gender, education, median household income, Elixhauser score, tumor site, tumor size, tumor grade, pT/pN classification, tumor location and extent of lymph node resection. One-to-one nearest-neighbor PSM without replacement (caliper width 0.1) was then used to create a balanced cohort. Standardized mean differences were used to conduct balance diagnostics; all had a value of <0.1 , indicating good balance according to Austin *et al.* (18).

In the matched cohort, additional sensitivity analyses were conducted to investigate the association between N-classification and T-classification with treatment effect of aCT and survival. Cox-regression analysis modelling the interaction between N-classification, T-classification, differentiation grade, receipt of aCT and survival was conducted. To this end, patients were grouped according to pT/pN classification and differentiation grade. A model was composed using the combined stage/grade groups as an interaction term. A P value of <0.05 was considered statistically significant. All analyses were performed using SAS/STAT software, version 9.4 of the SAS system for Windows (Copyright © 2013, SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 31,465 patients with BTC was identified, of whom 2,179 patients had GBC, underwent resection and met the inclusion criteria (*Figure 1, Table 1*). Of these patients, 411 (19%) were treated with aCT. Median follow-up of patients alive at last follow-up was 54 months. Median age at diagnosis was 77 years, and most patients presented with AJCC T1/T2 (N=1,438, 66%) and N0 (N=1,653, 76%) disease.

Patients who received aCT were younger than patients that did not receive aCT. Patients that did receive aCT were diagnosed with more advanced tumors and more node-positive disease as opposed to patients that did not receive aCT. Adjuvant RT was more frequently administered in patients that received aCT compared to patients that did not receive aCT. After propensity score matching, 810 cases were matched: 405 patients with aCT and 405 patients who did not receive aCT. Baseline characteristics of the matched

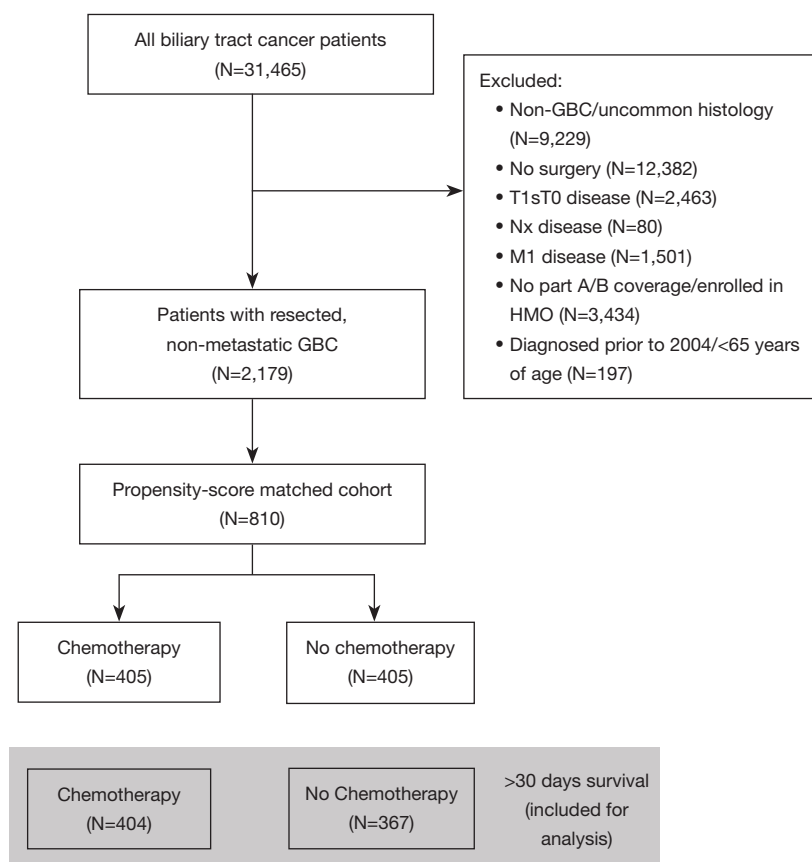


Figure 1 Flow diagram. GBC, gallbladder cancer.

cohort did not differ significantly between patients with and without aCT (Table 1, Table S2). Mean standardized difference in propensity score was 0.91 before matching and <0.1 across all variables after matching, indicating good balance (Figure S1).

Survival in patients with and without aCT before and after propensity score matching

In the unmatched cohort median OS was 18.0 months and 5-year survival was 27%. Median OS of patients that received aCT did not differ from survival in patients that did not receive aCT (aCT 17.7 months *vs.* no aCT 18.1 months, $P=0.284$).

In the matched cohort included for survival analysis ($N=772$), median OS was 18.3 months and 5-year survival was 28%. Survival did not differ between patients treated with aCT (17.6 months) compared to patients with no aCT (19.5 months, $P=0.7720$, Figure 2A). In adjusted Cox regression analysis, administration of chemotherapy was

not significantly associated with survival (HR 0.89, 95% CI: 0.74–1.08, $P=0.232$).

Subgroup analysis of survival in patients with and without chemotherapy according T-classification and N-classification

In the subgroup of patients with T1/T2 disease, no statistically significant difference between patients treated with aCT (29.2 months) and without aCT (51.8 months, $P=0.0984$, Figure 2B) was found. In T3/T4 disease, median OS in patients with aCT was 12.3 months, versus 7.2 months in patients without ($P=0.013$) (Figure 2B). When classifying patients according to N-stage (N0 and N1/N2), no difference in survival could be demonstrated between patients who did and did not receive aCT (Figure 2C).

Effect of different chemotherapy regimens

In uncorrected analysis, there was no significant ($P=0.542$)

Table 1 Baseline characteristics of resected patients with GBC, 2004–2015

Characteristic	Unmatched cohort			Matched cohort		
	No adjuvant therapy (N=1,768, 81%)	Adjuvant chemotherapy (N=411, 19%)	P value	No adjuvant therapy (N=405, 50%)	Adjuvant chemotherapy (N=405, 50%)	P value
Age, years			<0.001			0.586
65–70	210 (11.9%)	83 (20.2%)		100 (24.7%)	81 (20.0%)	
70–75	306 (17.3%)	126 (30.7%)		110 (27.2%)	122 (30.1%)	
75–80	385 (21.8%)	106 (25.8%)		100 (24.7%)	106 (26.2%)	
80–84	427 (24.2%)	63 (15.3%)		61 (15.1%)	63 (15.6%)	
85+	440 (24.9%)	33 (8.0%)		34 (8.4%)	33 (8.1%)	
Elixhauser comorbidity score			0.099			0.831
0–2	411 (23.2%)	103 (25.1%)		96 (23.7%)	100 (24.7%)	
3–4	485 (27.4%)	129 (31.4%)		136 (33.6%)	128 (31.6%)	
≥5	872 (49.3%)	179 (43.6%)		173 (42.7%)	177 (43.7%)	
Gender, male	538 (30.4%)	143 (34.8%)	0.086	144 (35.6%)	141 (34.8%)	0.833
Race			0.190			0.200
White	1,374 (77.7%)	336 (81.8%)		307 (75.8%)	331 (81.7%)	
Black	174 (9.8%)	27 (6.6%)		46 (11.4%)	27 (6.7%)	
Asian/pacific islander	78 (4.4%)	19 (4.6%)		17 (4.2%)	18 (4.4%)	
Hispanic	84 (4.8%)	17 (4.1%)		19 (4.7%)	17 (4.2%)	
Alaskan/native American	11 (0.6%)	<11 (0%)		<11 (0%)	<11 (0%)	
Other/unknown	47 (2.7%)	12 (2.9%)		16 (3.9%)	11 (2.7%)	
Tumor size			0.082			0.496
≤5 cm	926 (52.4%)	232 (56.4%)		211 (52.1%)	227 (56.0%)	
>5 cm	198 (11.2%)	53 (12.9%)		60 (14.8%)	52 (12.8%)	
Unknown	644 (36.4%)	126 (30.7%)		134 (33.1%)	126 (31.1%)	
pT stage			<0.001			0.899
T1	417 (23.6%)	39 (9.5%)		37 (9.1%)	39 (9.6%)	
T2	817 (46.2%)	165 (40.1%)		169 (41.7%)	165 (40.7%)	
T3	499 (28.2%)	185 (45.0%)		180 (44.4%)	180 (44.4%)	
T4	28 (1.6%)	21 (5.1%)		19 (4.7%)	20 (4.9%)	
Tx	<11 (0%)	<11 (0%)		<11 (0%)	<11 (0%)	
Regional lymph node surgery			<0.001			0.846
No nodes removed	1,080 (61.1%)	185 (45.0%)		183 (45.2%)	184 (45.4%)	
1–3 nodes	497 (28.1%)	152 (37.0%)		144 (35.6%)	151 (37.3%)	
4+ nodes	172 (9.7%)	<70 (<17.0%)		<75 (<18.5%)	<65 (<16.0%)	
Unknown	19 (1.1%)	<11 (0%)		<11 (0%)	<11 (0%)	

Table 1 (continued)

Table 1 (continued)

Characteristic	Unmatched cohort			Matched cohort		
	No adjuvant therapy (N=1,768, 81%)	Adjuvant chemotherapy (N=411, 19%)	P value	No adjuvant therapy (N=405, 50%)	Adjuvant chemotherapy (N=405, 50%)	P value
pN stage			<0.001			0.166
N0	1,468 (83.0%)	249 (60.6%)		266 (65.7%)	247 (61.0%)	
N+	300 (17.0%)	162 (39.4%)		139 (34.3%)	158 (39.0%)	
Differentiation grade			<0.001			0.525
Well	314 (17.8%)	49 (11.9%)		38 (9.4%)	49 (12.1%)	
Moderate	763 (43.2%)	161 (39.2%)		171 (42.2%)	159 (39.3%)	
Poor/undifferentiated	561 (31.7%)	178 (43.3%)		177 (43.7%)	174 (43.0%)	
Unknown	130 (7.4%)	23 (5.6%)		19 (4.7%)	23 (5.7%)	
Type of chemotherapy			<0.001			<0.001
Gemcitabine-based [†]	NA	135 (35.2%)		NA	134 (35.6%)	
Gemcitabine-cisplatin	NA	58 (14.1%)		NA	55 (13.6%)	
FU-based	NA	167 (40.6%)		NA	165 (40.7%)	
Other	NA	41 (10.0%)		NA	41 (10.1%)	
Timing of chemotherapy			<0.001			<0.001
Adjuvant	NA	384 (93.4%)		NA	378 (93.3%)	
Neo-adjuvant	NA	27 (6.6%)		NA	27 (6.7%)	
Radiotherapy (yes)	123 (7.0%)	178 (43.3%)		36 (8.9%)	176 (43.5%)	
Resection received [‡]			<0.001			<0.001
Cholecystectomy	1,712 (96.8%)	398 (96.5%)		386 (95.3%)	392 (96.8%)	
Liver resection	395 (22.3%)	133 (32.4%)		157 (38.8%)	130 (32.1%)	
Bile duct resection	117 (6.6%)	45 (10.9%)		51 (12.6%)	44 (10.9%)	
Pancreatic resection	<11 (0%)	<11 (0%)		<11 (0%)	<11 (0%)	
Lymph node resection	345 (19.5%)	115 (28.0%)		139 (34.3%)	112 (27.7%)	

Patients were matched on age, gender, Elixhauser comorbidity score, date of diagnosis, tumor size, pT- and pN stage, differentiation grade, education, income and poverty status. [†], 20 of these patients received 5-FU and gemcitabine; [‡], patients may have received multiple procedures which have been coded separately: i.e., a cholecystectomy and a liver resection as a second, separate procedure. GBC, gallbladder cancer.

difference in median OS between different aCT regimens; FU-based 20.5 months, gemcitabine-based 15.7 months, gemcitabine-cisplatin 16.7 months and other chemotherapy combinations 12.7 months. Adjusted multivariable analysis also did not show significant differences in survival between chemotherapy regimens (Table 2).

Interaction analysis of combined T-/N- classification and differentiation grade with aCT in the matched cohort

An association with superior OS after treatment with aCT was seen in patients with T4 disease (HR 0.475, 95% CI: 0.242–0.932), but not in patients with node-positive disease (HR 0.795, 95% CI: 0.598–1.057) (Table S3). Patients

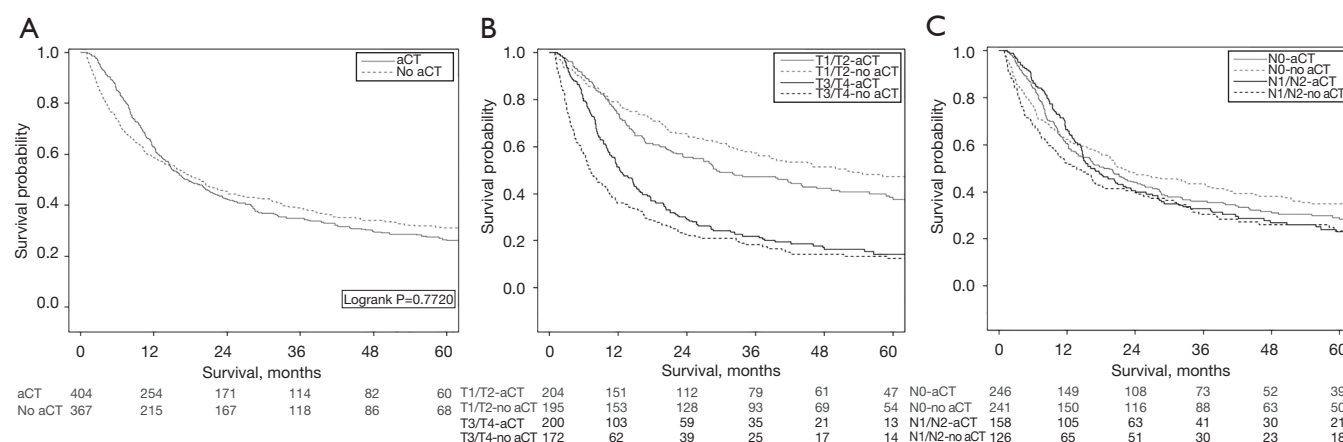


Figure 2 Survival curves of patients treated with and without aCT. (A) Survival of matched cohort excluding mortality <30 days (N=771, P=0.7720). (B) Survival of matched cohort excluding mortality <30 days, stratified by T-stage (N=399). Log rank P=0.0984 in T1/T2, aCT *vs.* no aCT. Log rank P=0.0129 in T3/T4 (N=372), aCT *vs.* no aCT. (C) Survival of matched cohort excluding mortality <30 days, stratified according to N stage. Log rank P=0.3150 in N0 (N=487), aCT *vs.* no aCT. Log rank P=0.2527 in N1/N2 (N=284), aCT *vs.* no aCT. aCT, adjuvant chemotherapy.

were grouped according to different combinations of T-classification (T1/T2 *vs.* T3/T4) and N-classification (N0 *vs.* N+) to analyze their interaction with chemotherapy and survival (Table 3). Multivariable analysis showed that aCT was only associated with longer OS in patients with a combination of T3/T4 and N+ disease (HR 0.61, 95% CI: 0.43–0.87, Table 3).

When including differentiation grade in the model, an association between administration of aCT and longer median OS was seen in patients with T3/T4, N+, poorly/undifferentiated disease (HR 0.43, Table S4).

Discussion

Tumor recurrence after resection of GBC occurs in up to 65% of patients and ultimately determines survival (7). Although RCTs show that aCT reduces recurrence rates in other cancers, robust evidence to support its use in GBCs has not existed. Given the conflicting results from single-institute series and absence of RCTs including GBC alone, we sought to inform this debate by performing an analysis of SEER registry data on elderly patients with resected GBC. In this propensity-score matched cohort survival was not significantly associated with receipt of aCT. However, subgroup analysis revealed that in patients with T3/T4, node-positive, poorly differentiated disease the administration of aCT was significantly associated with increased survival.

No high-quality RCTs investigating the value of aCT for GBC have been published. Therefore, treatment guidelines are based on the conflicting results of a few randomized trials investigating the efficacy of aCT in all forms of BTC. Of three high-quality trials completed recently, only the BILCAP trial (adjuvant capecitabine compared to observation alone) showed positive results in the per-protocol analysis alone (53 *vs.* 36 months, P=0.028) and not in the primary, intention to treat analysis (8,26). It is important to note that in the BILCAP trial, a relatively high number of patients with R1 resections (38%) or node-positive disease (46%) was included; both factors are known poor prognostic factors and are associated with increased response to chemotherapy (24,26,27). We aimed to delineate clinically relevant subgroups of GBC patients that may benefit from chemotherapy and found that chemotherapy may only be beneficial in patients with T3/T4, node-positive and poorly differentiated disease. In this study, aCT in patients with low-risk (i.e., T1/T2, node-negative, well-differentiated) disease even appeared to be negatively associated with median OS. This finding can potentially be attributed to the fact that patients with irradical resection are more frequently treated with chemotherapy. Since other studies show that irradical resection is a poor prognostic factor, we suggest that aCT for low-risk patients should potentially only be considered in case of positive resection margins (28).

After the aforementioned RCTs, the next highest

Table 2 Cox regression of prognostic factors for patients that received chemotherapy in the matched cohort

Factor	HR	95% CI	P value
Age (per year)	1.02	1.00–1.04	0.044
Elixhauser comorbidity score			
0–2	1		1
3–4	0.83	0.60–1.16	0.264
≥5	1.13	0.82–1.54	0.447
Differentiation grade			
Well	1		1
Moderate	1.16	0.78–1.72	0.478
Poor	1.40	1.01–1.81	0.094
Undifferentiated	1.30	0.64–2.27	0.386
Poverty indicator			
0–5%	1		1
5–10%	1.192	0.84–1.70	0.329
10–20%	1.341	0.95–1.90	0.099
>20%	1.096	0.74–1.62	0.647
Race			
White	1		1
Black	1.07	0.65–1.79	0.782
Asian/pacific islander	0.85	0.43–1.70	0.643
Hispanic	0.69	0.35–1.35	0.275
Alaskan/native American	0	0–1000.00	0.956
Year of diagnosis			
2004–2005	1		1
2006–2007	0.97	0.64–1.48	0.888
2008–2009	1.20	0.81–1.79	0.362
2010–2011	1.00	0.66–1.52	0.992
2012–2014	0.81	0.53–1.23	0.324
pN stage (yes vs. no)			
N0	1		1
N1/N2	1.58	1.13–2.20	0.008
pT stage			
T1	1		1
T2	1.37	0.87–2.16	0.171
T3	2.28	1.46–3.56	<0.001
T4	4.66	2.40–9.04	<0.001

Table 2 (continued)

Table 2 (continued)

Factor	HR	95% CI	P value
Tumor size			
≤5 cm	1		1
>5 cm	1.04	0.78–1.39	0.776
Radiotherapy (yes)	0.73	0.59–0.91	0.004
Type of chemotherapy			
Gemcitabine-based	1		
5FU-based	1.07	0.88–1.41	0.464
Gemcitabine-cisplatin	0.83	0.61–1.12	0.180
Other	1.37	0.98–1.90	0.110

HR, hazard ratio; CI, confidence interval.

Table 3 Interaction analysis between T-/N- classification and receipt of aCT and survival in patients who survived >30 and >180 days postoperatively

Group	aCT (N)	No aCT (N)	HR	95% CI	P value
T1/T2, N0					
>30 days	138	140	1.18	0.85–1.65	0.328
>180 days	124	122	1.32	0.90–1.94	0.155
T1/T2, N1/N2					
>30 days	66	55	1.27	0.79–2.06	0.324
>180 days	60	51	1.24	0.73–2.09	0.428
T3/T4, N0					
>30 days	108	101	0.92	0.67–1.26	0.583
>180 days	83	63	1.30	0.86–1.96	0.217
T3/T4, N1/N2					
>30 days	92	71	0.61	0.43–0.87	0.006
>180 days	78	35	1.03	0.65–1.63	0.911

aCT, adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.

level of evidence is a recent meta-analysis of 21 studies including 6,712 patients, of which 1,797 were treated with chemotherapy, RT or a combination of both (29). The meta-analysis showed a positive effect of adjuvant therapy in all patients with BTC (OR 0.74), contradicting our finding that aCT is only associated with improved median OS in patients with high-risk (i.e., T3/T4, N+) features. However, only one RCT was included and all other studies were retrospective, single-center experiences, which may be subject to selection and immortal-time bias. Additionally, a

large grade of heterogeneity was seen, and the authors were unable to report hazard ratios (adjusted for survival time) since many studies did not report actual survival times. Finally, a significant portion of the included studies had a high (>50%) rate of R1 resection or lymph-node positivity, explaining the high effect of aCT in their study. We used propensity score matching and exclusion of patients who deceased <30 days to account for both forms of bias, which may explain the lack of efficacy of aCT across the full cohort in our study.

Since the publication of the ABC-02 trial in 2010, gemcitabine and cisplatin (Gem-Cis) has been the regimen of choice in the treatment of locally advanced or metastatic GBC. (30-32). However, its efficacy has not been investigated in GBC alone, nor proven in the adjuvant setting (33,34). The only chemotherapeutic agent which has demonstrated to increase survival in resected patients compared to observation alone in a randomized controlled study is capecitabine (13). Most studies investigating other agents or combination regimens were single-arm studies or compared to observation alone and no studies have directly compared capecitabine to other commonly used agents. Therefore, it is difficult to establish whether other treatment regimens may be more effective than capecitabine. In the present study, after covariate adjustment all chemotherapeutic regimens (gemcitabine monotherapy, 5-FU, Gem-Cis or other combinations) were comparable in terms of association with median OS. This does not necessarily mean that no significant difference in efficacy between these regimens exists. New evidence shows that the expression of specific molecular profiles may be associated with extremely good response to certain forms of (targeted) therapy (35,36). Future research should focus on identifying specific molecular profiles and their association with response to chemotherapy.

There is no randomized evidence available regarding the use of adjuvant RT, alone or in combination with chemotherapy. In the aforementioned meta-analysis, chemotherapy alone appeared to be more effective in reducing the risk of death (HR 0.39 compared to surgery alone) than chemoradiotherapy (HR 0.61) (29). However, in patients with R1 disease adjuvant RT was associated with significantly better survival (HR 0.33). Our data shows that in patients treated with chemotherapy, additional radiation appeared to provide a survival benefit. However, only 212 patients received RT in our cohort and the majority of irradiated patients (83%) received concurrent chemotherapy, potentially providing significant bias. Therefore, we feel that our data are of insufficient quality to provide definitive recommendations on the use of adjuvant RT. Similarly, no randomized evidence on the efficacy of neoadjuvant chemotherapy is available. A very small number of patients in our cohort received neoadjuvant chemotherapy (N=27). Due to statistical limitations, no separate analyses investing patients treated with neoadjuvant chemotherapy were conducted.

The primary limitation of this study is the non-random allocation of treatment. PSM and exclusion of subjects

whom were deceased within 30 days of surgery were used to limit the impact of selection bias and immortal time bias. Secondly, SEER does not register margin status after resection, which may be both a marker of disease biology and a risk factor for recurrence. The inability to correct for margin status is a significant confounding factor. Since chemotherapy is more likely to be administered to patients with positive resection margins, it is likely that the efficacy of aCT may be underestimated in this study as a positive resection margin is a significant predictor for poor survival (37,38). Finally, it is possible that the use of oral chemotherapeutic agents, especially capecitabine, is not fully captured because not all patients had Part D coverage. However, if anything this likely leads to an underestimation of treatment efficacy.

This study has multiple strengths. Primarily, this study provides insight into the outcomes of a uniquely large cohort of elderly GBC patients treated with aCT. Due to the use of population-based data and the inclusion of elderly patients with comorbidities, this paper provides an excellent reflection of contemporary clinical practice and outcomes of patients with GBC. Specifically, median age of GBC patients in Western countries is 72 and only 29% of patients is under 65 years of age (39,40). Median age of patients included in the BILCAP trial was 62 and virtually all patients had a WHO performance status of 0 or 1. In our cohort the median age was 77 and patients had multiple comorbidities, which may more accurately reflect the average GBC patient. In contrast to most retrospective and registry studies that do not include information on patient comorbidity, we used Medicare claims data to calculate the Elixhauser comorbidity score. This method is viable to assess and correct for performance status in statistical models (41,42). Finally, we were able to compare different chemotherapeutic regimens.

Conclusions

These data show that aCT may provide a survival benefit in high-risk elderly patients with advanced GBC, including T3/T4 tumors and node-positive disease. Future research efforts should focus on improving the selection of GBC patients who might have a higher likelihood of benefit from adjuvant treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-348/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-348/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the University of Michigan Institutional Review Board and a waiver for informed consent was provided, given that SEER data is de-identified.

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Table S1 Location codes

Code	Location/histology
Location	
C22.0	Liver ^a
C22.1	Intrahepatic bile duct ^b
C23.9	Gallbladder
C24.0	Extrahepatic bile duct ^c
Histology	
8000	Neoplasm, malignant
8001	Tumor cells, malignant
8010	Carcinoma, NOS
8020	Carcinoma, undifferentiated, NOS
8050	Papillary carcinoma, NOS
8052	Papillary squamous cell carcinoma
8070	Squamous cell carcinoma, NOS
8140	Adenocarcinoma, NOS
8141	Scirrhus adenocarcinoma
8144	Adenocarcinoma, intestinal type
8145	Adenocarcinoma, diffuse type
8160	Cholangiocarcinoma
8162	Klatskin tumor
8210	Adenocarcinoma in adenomatous polyp
8211	Tubular adenocarcinoma
8260	Papillary adenocarcinoma
8480	Mucinous adenocarcinoma
8481	Mucin producing adenocarcinoma
8560	Adenosquamous carcinoma
8570	Adenocarcinoma with squamous metaplasia
8576	Hepatoid adenocarcinoma

^a, combined with histology code 8160 recoded to proximal cholangiocarcinoma and 8160 to intrahepatic cholangiocarcinoma; ^b, combined with histology code 8162 recoded to proximal cholangiocarcinoma; ^c, use site-specific factor 25 to differentiate between proximal and distal cholangiocarcinoma. NOS, not otherwise specified.

Table S2 Additional patient characteristics used for PSM

	No adjuvant therapy (N=1,768)	Adjuvant chemotherapy (N=411)	P value	No adjuvant chemotherapy (N=405)	Adjuvant chemotherapy (N=405)	P value
Percentage >24 years old with high school education						
1 st quartile	453 (25.6%)	99 (24.1%)	0.66	93 (23.0%)	98 (24.2%)	0.88
2 nd quartile	452 (25.6%)	108 (26.3%)		107 (26.4%)	106 (26.2%)	
3 rd quartile	412 (23.3%)	106 (25.8%)		98 (24.2%)	103 (25.4%)	
4 th quartile	451 (25.5%)	98 (23.8%)		107 (26.4%)	98 (24.2%)	
Median household income ^a						
1 st quartile	449 (25.4%)	101 (24.6%)	0.89	92 (22.7%)	99 (24.4%)	0.89
2 nd quartile	427 (24.2%)	104 (25.3%)		100 (24.7%)	102 (25.2%)	
3 rd quartile	438 (24.8%)	106 (25.8%)		114 (28.1%)	105 (25.9%)	
4 th quartile	453 (25.6%)	100 (24.3%)		99 (24.4%)	99 (24.4%)	
Poverty						
<5%	368 (20.8%)	88 (21.4%)	0.38	85 (21.0%)	86 (21.2%)	0.95
5–10%	455 (25.7%)	116 (28.2%)		106 (26.2%)	112 (27.7%)	
10–20%	512 (29.0%)	124 (30.2%)		127 (31.4%)	124 (30.6%)	
>20%	414 (23.4%)	81 (19.7%)		86 (21.2%)	81 (20.0%)	

^a, 2 missing values. PSM, propensity-score matching.

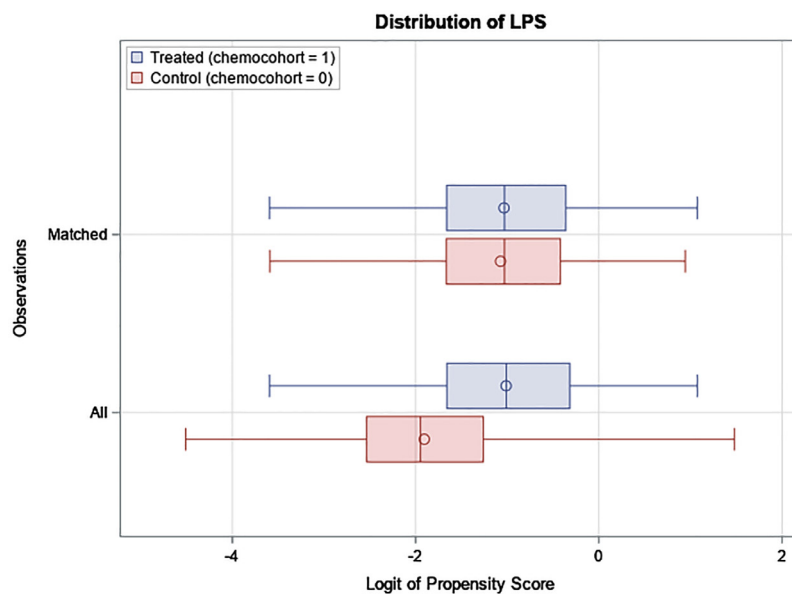


Figure S1 Distribution of the Logit propensity score (LPS), before and after matching.

Table S3 Adjusted interaction between receipt of chemotherapy and T/N-classification in the matched cohort in patients with survival >30 days postoperatively

Factor	HR	95% CI	P value
pN-stage stratified according to receipt of chemotherapy (yes vs. no)			
N0	1.017	0.799–1.293	0.893
N1/N2	0.795	0.598–1.057	0.115
pN-stage stratified according to receipt of chemotherapy (yes vs. no)			
T1	1.466	0.777–2.767	0.238
T2	1.179	0.868–1.600	0.292
T3	0.791	0.615–1.018	0.069
T4	0.475	0.242–0.932	0.031

Table S4 Adjusted interaction analysis between T-/N- classification, differentiation grade, receipt of aCT and survival in patients with survival >30 days postoperatively

Group	aCT (N)	No aCT (N)	HR	95% CI	P value
T1/T2, N0					
Well/moderate	85	86	1.31	0.86–1.98	0.207
Poor/undifferentiated	53	54	1.03	0.61–1.74	0.906
T1/T2, N1/N2					
Well/moderate	32	29	1.30	0.67–2.51	0.441
Poor/undifferentiated	34	26	1.35	0.68–2.70	0.393
T3/T4, N0					
Well/moderate	47	47	1.05	0.65–1.69	0.845
Poor/undifferentiated	61	54	0.81	0.54–1.23	0.323
T3/T4, N1/N2					
Well/moderate	43	33	0.86	0.51–1.43	0.555
Poor/undifferentiated	49	38	0.43	0.27–0.68	<0.001

aCT, adjuvant chemotherapy.