Original Article

Therapeutic response analysis for patients with adenosquamous carcinoma of the gallbladder: data analysis based on the Surveillance, Epidemiology, and End Results (SEER) database

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Background: Adenosquamous carcinoma of the gallbladder (GBASC) is a rare histological variant without defined appropriate clinical measures.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, data on a cohort of patients with GBASC were collected from 21 cancer registries between 1975 and 2018. We used Kaplan-Meier analysis to evaluate the effectiveness of different treatment regimens on patients with GBASC. Then we used Cox proportional hazards regression method to determine the prognostic factors for cancer-specific survival (CSS) of GBASC patients.

Results: A total of 388 patients with GBASC were identified: 80 patients diagnosed as early stage and 308 patients diagnosed as advanced stage. For early-stage GBASC, radical lymph node dissection improved the CSS significantly; for advanced-stage GBASC, radical surgery, nonradical surgery, lymph node dissection, chemotherapy, and radiotherapy improved the CSS significantly. Surgery, lymph node dissection, radiation, chemotherapy, age, race, and the American Joint Committee on Cancer (AJCC) stage were the independent risk factors for the CSS of GBASC patients.

Conclusions: Radical intraoperative lymph node dissection provided a survival benefit for patients with early-stage GBASC, whereas chemotherapy and radiotherapy provided no significant benefit; surgical treatment, more complete lymph node dissection, radiotherapy, and chemotherapy provided survival benefits for patients with advanced GBASC. The prognosis for GBASC patients is affected by the factors of surgery, lymph node dissection, radiation, chemotherapy, age, race, and the AJCC stage.

Keywords: Gallbladder carcinoma; adenosquamous; cancer-specific survival (CSS); treatment; survival analysis

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Introduction

Cancer of the gallbladder is the most prevalent type of malignancy affecting the biliary tract, with annual incidence ranging from 0.35/100,000 to 3.0/100,000 worldwide (1). More than 90–95% of cases of gallbladder cancer (GBC) are caused by the most common histologic subtype, adenocarcinoma (AC), which has been extensively researched regarding its clinicopathologic features and

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survival outcomes (2,3), while adenosquamous/squamous cells (2–10%) and undifferentiated cells (2–7%) constitute the remaining number of cases (4-7).

There is presently no standardized definition for adenosquamous carcinoma of the gallbladder (GBASC), and it is regularly recognized in the literature as having tumors with both glandular and squamous features. Several criteria were employed in various studies to determine the extent of squamous differentiation, including any squamous component (8), more than 10% squamous differentiation (9-11), more than 25% squamous differentiation (4), and more than 30% squamous differentiation (5,6). It is common for researchers to include squamous differentiation in the GBASC cohort since there are much fewer cases of GBASC than there are of mixed-difference tumors in the breasts and pancreas (12). For this study, we thus defined GBASC as including any component of squamous differentiation.

Due to the rarity of GBASC, only a few studies have explored the efficacy of different treatment modalities and the prognostic factors of patients with GBASC, and of those that were conducted, most were single-center case studies while a few were population studies (4-6,13-17). In the available research, GBASC was observed to be more prevalent in women (4,13) and was associated with greater tumor size (6,9,13,14,17-19), poor differentiation (13-15,17), shorter survival (13,14), an advanced stage at presentation (5,6,13), more aggressive invasiveness to adjacent viscera (6), and inconsistent findings with regard to other distant organs and lymph node metastasis (5,8,15-17). In terms of the therapy modality, surgical resection, especially radical surgery, was considered the effective treatment for patients with GBASC (5,6,8,13,17), while chemotherapy and radiotherapy could also improve the prognosis to some extent (13). Although some of these correlations are well-supported or consistent across the research, some issues related to GBASC still need to be addressed: owing to the rarity of GBASC, the research to evaluate the treatment response of patients with GBASC was dearth, and the most appropriate clinical measures for treating patients with GBASC in the different stages must be determined; moreover, the clinicopathological variables associated with prognosis of GBASC were still unclear.

Researchers searched the Surveillance, Epidemiology, and End Results (SEER) database for information on a large number of patients with GBASC, and conducted a retrospective study on the cohort of them to examine the curative benefits of the various treatment options for patients with GBASC at various stages and to investigate the risk factors affecting the prognosis of GBASC to assist physicians in determining clinical decisions about these patients' treatment. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1292/rc).

Highlight box

Key findings

- The therapeutic benefit of different treatment for patients with GBASC was assessed, and the optimal clinical measures for GBASC patients was determined.

What is known and what is new?

- GBASC is a rare subtype of gallbladder carcinoma, with different clinical characteristics from those of GBAC.
- A larger sample size of GBASC patient was analyzed, the therapeutic response and the prognostic factors of GBASC patients were determined.

What is the implication, and what should change now?

- Intraoperative lymph node dissection during surgery is preferred when treating patients with early-stage GBASC; surgical treatment (particularly radical surgery), lymph node dissections that are more comprehensive, radiotherapy, and chemotherapy are optimal treatments for advanced patients with GBASC. Surgery, lymph node dissection, radiation, chemotherapy, age, race, and AJCC stage can be used as prognostic factor for GBASC patients.

Methods

Data source

The SEER program of the National Cancer Institute (NCI) was constructed from 21 population-based cancer registries to provide information on roughly 34.6% of the US population. In this study, an independent cohort of GBASC patients was retrieved, and all the relevant demographic and clinical characteristics were reviewed and noted by trained investigators who were blind to the predictor variables of our research. The records of patient survival information were not determined by the subjective judgment of blinded investigators but depended on the death certificates. Data on patients with a primary cancer site inside the gallbladder were extracted using topographical codes from the *International Classification of Diseases for Oncology, 3rd edition* (ICD-O-3: C23.9) using SEER Stat 8.4.0. Only patients diagnosed between the year 1975 and 2018 with the ICD-O-3 histology/behavior codes 8070/3, 8071/3, 8074/3, 8560/3, and 8570/3 were included

in this study to concentrate on the GBASC. During the follow up, the cancer data collection was periodically performed by identifying patients in the medical institution, and cancer registries pulled cancer information from the medical records. All patients were followed up until they were dead or to the date of last follow-up in November 2020, any lost to follow-up case was exclude from the study. Stage I and stage II were considered early stages as per the American Joint Committee on Cancer (AJCC) staging concept of 2004, whereas stage III and stage IV were considered advanced stages. Only patients with a diagnosis confirmed by positive histology at pathological analysis or positive exfoliative cytology were included. Patients with any of the following conditions were excluded: (I) GBASC as secondary cancer; (II) patients without definitive information on pathological type, degree of differentiation, or metastasis; (III) incomplete patient follow-up information; and (IV) patients with autopsy confirmation. To increase the authority and generalizability of our study, the maximum quantity of patient information in the database that met the above-mentioned criteria was included. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Demographic and clinical features including gender (male, female), age (65 years old), ethnicity (American Indian/Alaska Native, Asian or Pacific Islander, Black, White), family status (divorced, married, single), extent of operation (no surgery, radical surgery, nonradical surgery), lymph node dissection (removal of 1 to 3 regional lymph nodes, 4 or more regional lymph nodes, none), receipt of chemotherapy (yes, no), receipt of radiotherapy (yes, no), cancer grade (well differentiated; moderately differentiated; poorly differentiated; undifferentiated, anaplastic), pathological primary tumor T stage (T1–T2, T3–T4), M stage (M0, M1), and N stage (N0, N1) according to the *AJCC Cancer Staging Manual*, *6th edition*, life expectancy and cause of death could be discerned from data in the SEER database. Cases with the above information missing were excluded from analysis. In this paper, "radical surgery" refers to the whole excision of the gallbladder with resection in continuity (partial or total removal) with adjacent organs, whereas "nonradical surgery" refers to the removal of the gallbladder alone. According to National Comprehensive Cancer Network guideline, individuals older than 65 years old can be categorized into elder population, thus we used 65 years old as cutoff point of age (20). We selected cancer-specific survival (CSS) as the outcomes of interest, and it was calculated from diagnosis to death or to the date of last follow-up; only GBASC-related fatalities were deemed occurrences, whereas other deaths and survivors were censored.

Due to the huge difference in clinicopathological features between early stage and advanced stage of the carcinoma, our therapeutic analysis was stratified by tumor stage. Pearson chi-squared analysis was employed to test and compare the clinical differences between patients with early-stage and advanced-stage GBASC. The Kaplan-Meier curve, the 1-, 2-, and 3-year CSS rate, and median survival were calculated using Kaplan-Meier analysis to predict the CSS of patients with GBASC with regard to different therapeutic mode. Limited to the low mortality of some cohorts in the sample, some data on median survival and 95% confidence intervals (CIs) were not available. The log-rank test was used to examine the differences between the curves.

Cox proportional hazards models were used to identify the independent prognostic variables. Univariate Cox regression was performed to reveal the potential predictors for patients with GBASC. Statistically significant variables identified by univariate Cox regression were selected for the multivariate Cox regression. Following Harrell's rule (the number of events should be at least 10 times greater than the number of covariates), the potential predictors were included in the analysis (21). Multivariate Cox proportional hazards models were then created to evaluate independent variables with stepwise regression based on the minimum Akaike information criterion, and the hazard ratios (HRs) and 95% CIs of the independent prognostic factors associated with CSS in patients with GBASC were generally assumed. A forest map was used to visualize the efficiency of all independent variables in the analysis. Statistical analysis was performed using R software (version 4.6.3; The R Foundation of Statistical Computing, USA).

Results

Demographic and clinical characteristics

The overall sample size included 388 SEER-Medicare patients diagnosed with GBASC between the year 1975 and 2018. In all, 312 patients had died of GBASC at the time of analysis, the median follow-up time was 15.2 months, and the longest follow-up period was 165 months. Among the samples, 80 patients were classified as early stage,

and 308 patients were classified as advanced stage. The majority of patients with GBASC were older patients, with a marital status of married or single, in both the early stage and advanced stage, and without significant differences between the two stages. A greater proportion of females (75.6%) and White individuals (76.3%) was found in the advanced stage when compared with the early stage (60.0% and 68.8%, respectively) (P<0.001 for both). Among the treatment options, nonradical surgery was used in almost all patients from the early stage (92.5%) and part of patients from the advanced stage (62.3%), while radical surgery was performed mainly in later-stage disease patients (23.4%; P<0.001). The remaining treatment modalities shared similar distributions between the two stages: lymph node dissection was performed in half of the patients, and chemotherapy and radiotherapy were used to treat fewer than one-eighth of the patients with GBASC, respectively. A significant difference in pathological differentiation existed between the patients of two stages: moderately differentiated carcinoma constituted half of the early-stage patients (51.3%), while poorly differentiated carcinoma was observed in most of the patients with advanced GBASC (59.7%; P<0.001; *Table 1*). Compared to patients with advanced GBASC, patients with early-stage GBASC (median survival: 21 *vs.* 6 months, P<0.001) had substantially longer overall survival (*Figure 1*, *Table 2*).

Comparative efficacy of the different therapeutic approaches

The survival rates associated with GBASC for each of the treatment regimens at various stages of illness were calculated using Kaplan-Meier analysis. The impact of the surgery method on the early-stage patients with GBASC was not analyzed, mainly because of the uncoordinated samples between groups. The log-rank test of the Kaplan-Meier curves for the GBASC cohort at the early disease stage indicated that the lymph node dissection improved the CSS significantly only when more than 4 lymph nodes were removed. The 1-, 2-, and 3-year CSS for patients with more than 4, 1–3, and 0 lymph nodes dissected were 94.7% *vs.* 69.2% *vs.* 45.1%, 73.7% *vs.* 43.3% *vs.* 30.1%, and 73.7% *vs.* 43.3% *vs.* 30.1%, respectively (P<0.001). In the evaluation regarding the treatment efficacy of chemotherapy and radiotherapy for patients with early-stage GBASC, the log-rank test of the survival curves demonstrated no significant difference in CSS (chemotherapy: P=0.500; radiotherapy: P=0.100), indicating that chemotherapy and radiotherapy did not exert a curative effect on the early-stage group (*Figure 2*, *Table 2*).

Compared with early-staged patients, the characteristic of the relative efficacy of therapeutic approaches for patients with GBASC identified at an advanced stage altered. Radical surgery was associated with the highest CSS, followed by nonradical surgery, and then no surgery. The 1-, 2-, and 3-year CSS for patients who had radical surgery, nonradical surgery, and no surgery was 44.5% *vs.* 24.7% *vs.* 2.3%, 19.7% *vs.* 9.5% *vs.* 0%, and 13.8% *vs.* 7% *vs.* 0%, respectively (P<0.001). This suggests surgery, especially radical surgery, is a crucial treatment method for advanced patients with GBASC. Among the patients with operative treatment, GBASC-related mortality was associated with the execution of lymph node dissection but not with the number of dissected lymph nodes. The 1-, 2-, and 3-year CSS for patients with more than 4, 1–3, and 0 lymph nodes dissected was 48.2% *vs.* 31.6% *vs.* 14.6%, 24.0% *vs.* 9.5% *vs.* 5.7%, and 17.4% *vs.* 7.6% *vs.* 3.6%, respectively (P<0.001), indicating the additional removal of lymph did not confer equal benefit. The survival benefit of chemotherapy and radiotherapy on advanced patients with GBASC was also obvious: CSS was much improved, and the difference was significant. The 1-, 2-, and 3-year CSS for patients who were and were not given chemotherapy was 38.5% *vs.* 14.8%, 12.2% *vs.* 9.9%, and 7.6% *vs.* 7.4%, respectively (P<0.001). The 1-, 2-, and 3-year CSS for patients who were and were not given radiotherapy was 66.3% *vs.* 14.0%, 25.1% *vs.* 6.0%, and 22.8% *vs.* 1.4%, respectively (P<0.001). Unlike early-stage patients, terminally ill patients were sensitive to chemotherapy and radiotherapy (*Figure 3*, *Table 2*). There was a statistically significant difference in the predicted advantages of survival between any two-way comparisons that had not previously been made between the different modalities. (i.e., P<0.050 for any comparison).

Identification of independent prognostic factors of CSS in patients with GBASC

The prognostic factors for CSS in those with GBASC were examined using univariate and multivariate Cox regression analysis. As per the univariate Cox regression, age, race, marital status, surgery, lymph nodes dissection, chemotherapy, radiotherapy, and TNM stage were associated with the CSS of patients with GBASC. Based on the statistically significant factors identified by the multivariate Cox regression analysis described above, multivariate Cox regression further confirmed 9 variables, including older age (≥65 *vs.* <65 years old: HR =1.41; 95%

Table 1 Demographic and therapeutic characteristics of the patients diagnosed with GBASC

Patient variables	Advanced stage (n=308)	Early stage (n=80)	Overall (n=388)	P
Age, n (%)				0.178
<65 years old	124 (40.3)	25 (31.3)	149 (38.4)	
≥65 years old	184 (59.7)	55 (68.8)	239 (61.6)	
Sex, n (%)				0.008
Female	233 (75.6)	48 (60.0)	281 (72.4)	
Male	75 (24.4)	32 (40.0)	107 (27.6)	
Race, n (%)				0.004
White	235 (76.3)	55 (68.8)	290 (74.7)	
American Indian/Alaska Native	4 (1.3)	0 (0.0)	4 (1.0)	
Asian or Pacific Islander	45 (14.6)	8 (10.0)	53 (13.7)	
Black	24 (7.8)	17 (21.3)	41 (10.6)	
Marital status, n (%)				0.794
Divorced	23 (7.5)	5 (6.3)	28 (7.2)	
Married	153 (49.7)	43 (53.8)	196 (50.5)	
Single	132 (42.9)	32 (40.0)	164 (42.3)	
Surgery, n (%)				<0.001
No surgery	44 (14.3)	0 (0.0)	44 (11.3)	
Nonradical surgery	192 (62.3)	74 (92.5)	266 (68.6)	
Radical surgery	72 (23.4)	6 (7.5)	78 (20.1)	
Lymph node dissection, n (%)				0.494
0	166 (53.9)	47 (58.8)	213 (54.9)	
1–3	73 (23.7)	14 (17.5)	87 (22.4)	
≥4	69 (22.4)	19 (23.8)	88 (22.7)	
Chemotherapy, n (%)				0.119
No	164 (53.2)	51 (63.8)	215 (55.4)	
Yes	144 (46.8)	29 (36.3)	173 (44.6)	
Radiotherapy, n (%)				0.382
No	240 (77.9)	58 (72.5)	298 (76.8)	
Yes	68 (22.1)	22 (27.5)	90 (23.2)	
Grade, n (%)				<0.001
Well differentiated	4 (1.3)	8 (10.0)	12 (3.1)	
Moderately differentiated	110 (35.7)	41 (51.3)	151 (38.9)	
Poorly differentiated	184 (59.7)	31 (38.8)	215 (55.4)	
Undifferentiated, anaplastic	10 (3.2)	0 (0.0)	10 (2.6)	

GBASC, adenosquamous carcinoma of the gallbladder.

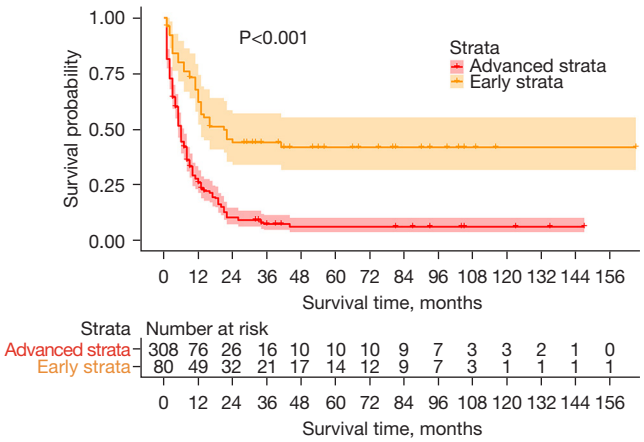

Figure 1 CSS of patients with GBASC in the early and advanced stages. The median survival for patients with early-stage GBASC was 21 months while that for patients with advanced-stage GBASC was 6 months. CSS, cancer-specific survival; GBASC, adenosquamous carcinoma of the gallbladder.

CI, 1.10–1.80; P=0.007), Asian or Pacific Islander descent (*vs.* White: HR =0.65; 95% CI, 0.44–0.96; P=0.031), radical surgery (*vs.* no surgery: HR =0.42; 95% CI, 0.26–0.67; P<0.001), nonradical surgery (*vs.* no surgery: HR =0.37; 95% CI, 0.25–0.54; P<0.001), 1–3 lymph nodes dissected (HR =0.66; 95% CI, 0.48–0.91; P=0.012), more than 4 lymph nodes dissected (HR =0.58; 95% CI, 0.40–0.83; P=0.003), chemotherapy (*vs.* no chemotherapy: HR =0.67; 95% CI, 0.51–0.88; P=0.003), radiotherapy (*vs.* no radiotherapy: HR =0.65; 95% CI, 0.46–0.91; P=0.011), T3–T4 stage (*vs.* T1–T2: HR =1.68; 95% CI, 1.27–2.21; P<0.001), M1 stage (*vs.* M0: HR =2.55; 95% CI, 1.94–3.34; P<0.001), and N1 stage (*vs.* N0: HR =1.71; 95% CI, 1.29–2.27; P<0.001) as independent predictors for the CSS of patients with GBASC (*Table 3*, *Figure 4*). Similar to Kaplan-Meier analysis, multivariate Cox regression analysis revealed that the type of treatment received by GBASC patients was a prognostic factor. The sample size, number of events and

Table 2 The 1-, 2-, and 3-year CSS and the median CSS for patients with GBASC as stratified by AJCC stage and treatment regimen

AJCC stage	Treatment	1-year survival, %	2-year survival, %	3-year survival, %	Median survival (months)	95% CI	P
Early stage	Including all treatment	62.20	44.00	41.80	21	13–NA	<0.001
Advanced stage	Including all treatment	25.90	10.30	7.30	6	5–7	
Early stage	≥4 lymph nodes dissection	94.70	73.70	73.70	NA	NA–NA	<0.001
Early stage	1–3 lymph nodes dissection	69.20	43.30	43.30	22	11–NA	
Early stage	No lymph node dissection	45.10	30.10	30.10	12	7–21	
Early stage	Chemotherapy	65.50	33.60	33.60	16	13–NA	0.500
Early stage	No chemotherapy	60.40	51.10	51.10	NA	11–NA	
Early stage	Radiotherapy	54.50	27.30	27.30	13	12–41	0.100
Early stage	No radiotherapy	65.70	51.60	51.60	NA	14–NA	
Advanced stage	Radical surgery	44.50	19.70	13.80	11	9–16	<0.001
Advanced stage	Nonradical surgery	24.70	9.50	7.00	6	5–7	
Advanced stage	No surgery	2.30	0.00	0.00	2	1–3	
Advanced stage	≥4 lymph nodes dissection	48.20	24.00	17.40	12	9–16	<0.001
Advanced stage	1–3 lymph nodes dissection	31.60	9.50	7.60	8	7–11	
Advanced stage	No lymph node dissection	14.60	5.70	3.60	4	3–5	
Advanced stage	Chemotherapy	38.50	12.20	7.60	10	8–12	<0.001
Advanced stage	No chemotherapy	14.80	9.90	7.40	3	2–4	
Advanced stage	Radiotherapy	66.30	25.10	22.80	17	13–20	<0.001
Advanced stage	No radiotherapy	14.00	6.00	1.40	4	3–5	

CSS, cancer-specific survival; GBASC, adenosquamous carcinoma of the gallbladder; AJCC, American Joint Committee on Cancer; CI, confidence interval; NA, not applicable.

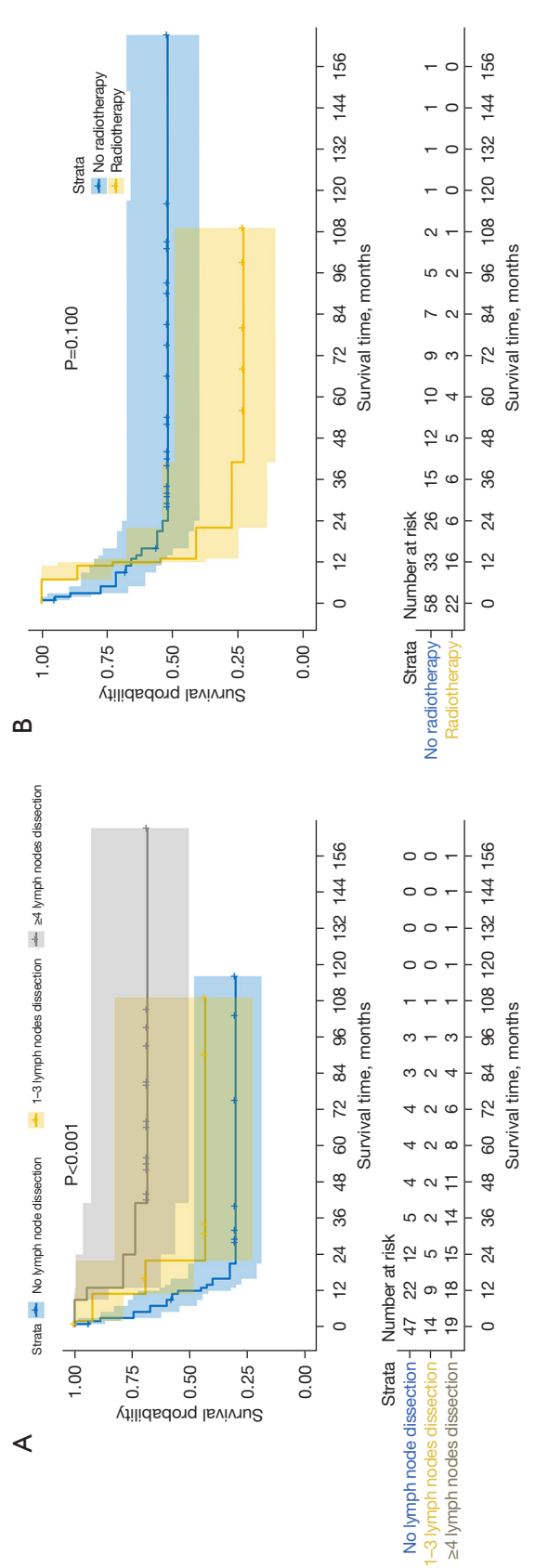

Figure 2 CSS of patients with early-stage GBASC according to treatment regimens, with the significantly effective therapeutic approaches including lymph node dissection during surgery. (A) CSS for patients with early-stage GBASC with surgery stratified by the lymph node dissection during the surgery. (B) CSS for patients with early-stage GBASC stratified by radiotherapy. (C) CSS patients with early-stage GBASC stratified by chemotherapy. CSS, cancer-specific survival; GBASC, adenosquamous carcinoma of the gallbladder.

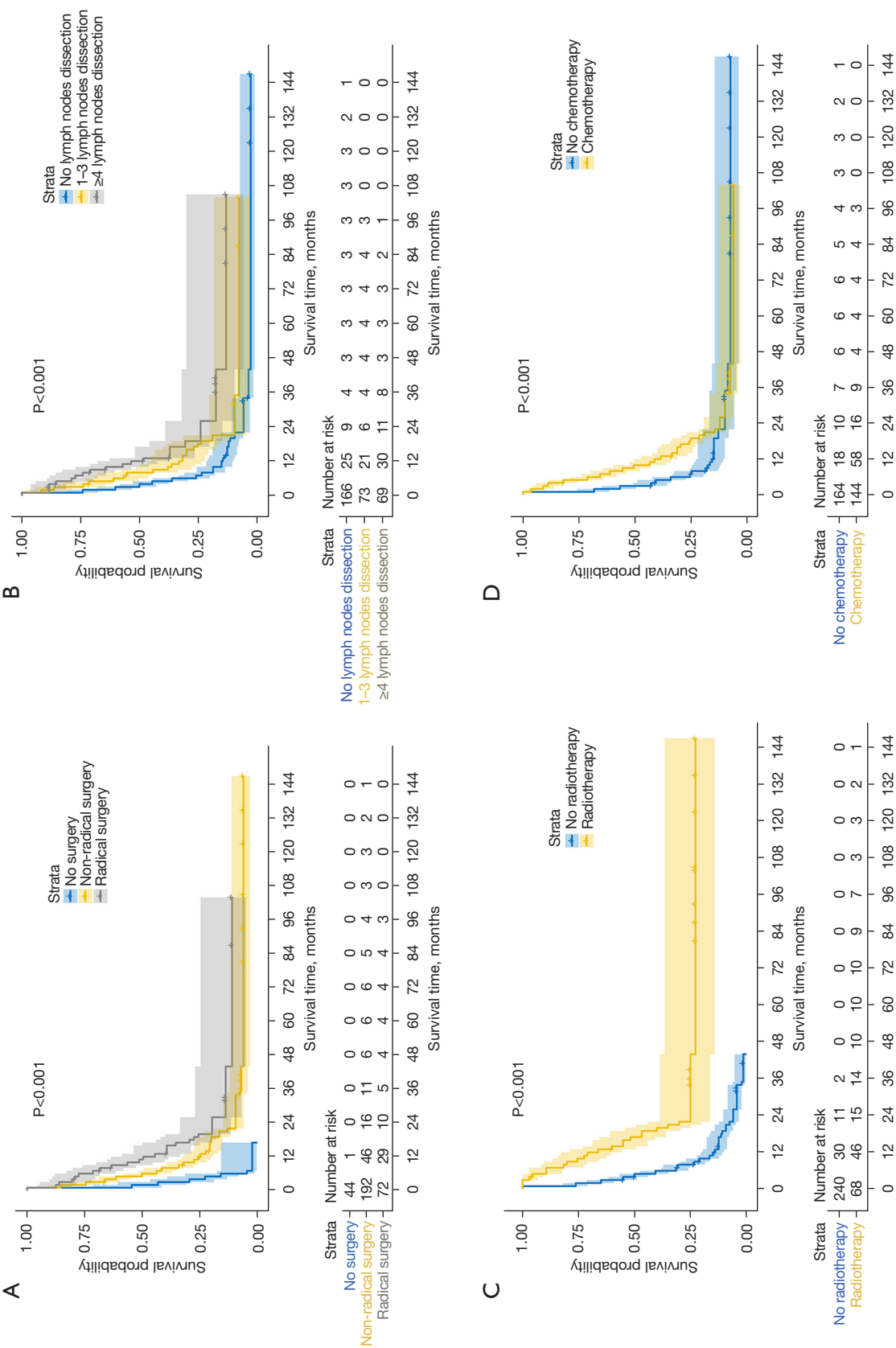

Figure 3 CSS of patients with advanced-stage GBASC according to treatment regimens, with the significantly effective therapeutic approaches including surgery, lymph node dissection during surgery, radiotherapy, and chemotherapy. (A) CSS for patients with advanced-stage GBASC stratified by surgery. (B) CSS for patients with advanced-stage GBASC with surgery stratified by the lymph node dissection during surgery. (C) CSS for patients with advanced-stage GBASC stratified by radiotherapy. (D) CSS for patients with advanced-stage GBASC stratified by chemotherapy. CSS, cancer-specific survival; GBASC, adenosquamous carcinoma of the gallbladder.

Table 3 Univariate and multivariate analysis on CSS in the entire GBASC cohort

Patient variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age						
<65 years old	Reference			Reference		
≥65 years old	1.42	0.70–1.73	<0.001	1.41	1.10–1.80	0.007
Race						
White	Reference			Reference		
American Indian/Alaska Native	1.52	0.57–4.11	0.406	2.63	0.95–7.30	0.064
Asian or Pacific Islander	0.66	1.53–0.46	0.021	0.65	0.44–0.96	0.031
Black	1.26	0.89–1.77	0.187	1.34	0.93–1.92	0.114
Sex						
Male	Reference					
Female	0.82	0.64–1.06	0.137			
Marital status						
Divorced	Reference					
Single	1.57	1.01–2.44	0.046			
Married	1.18	0.76–1.82	0.464			
Surgery						
No surgery	Reference			Reference		
Radical surgery	0.21	0.14–0.31	<0.001	0.42	0.26–0.67	<0.001
Nonradical surgery	0.24	0.17–0.34	<0.001	0.37	0.25–0.54	<0.001
Lymph node dissection						
0	Reference			Reference		
1–3	0.62	0.47–0.82	<0.001	0.66	0.48–0.91	0.012
≥4	0.38	0.28–0.51	<0.001	0.58	0.40–0.83	0.003
Chemotherapy						
No	Reference			Reference		
Yes	0.70	0.56–0.88	0.002	0.67	0.51–0.88	0.003
Radiotherapy						
No	Reference			Reference		
Yes	0.45	0.34–0.59	<0.001	0.65	0.46–0.91	0.011
Grade						
Well differentiated	Reference					
Moderately differentiated	1.21	0.61–2.39	0.579			
Poorly differentiated	1.59	0.82–3.11	0.173			
Undifferentiated, anaplastic	3.29	1.33–8.14	0.010			

Table 3 (*continued*)

Table 3 (*continued*)

Patient variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
T						
T1–T2	Reference			Reference		
T3–T4	1.79	1.40–2.29	<0.001	1.68	1.27–2.21	<0.001
M						
M0	Reference			Reference		
M1	3.13	2.46–3.99	<0.001	2.55	1.94–3.34	<0.001
N						
N0	Reference			Reference		
N1	1.34	1.06–1.70	0.015	1.71	1.29–2.27	<0.001

CSS, cancer-specific survival; GBASC, adenosquamous carcinoma of the gallbladder; HR, hazard ratio; CI, confidence interval.

HR in each analysis were also calculated (*Table 4*).

Discussion

According to earlier research, GBASC is an uncommon histological variation that accounts for 2% to 10% of all GBCs (6,7). Due to the scarcity of GBASC, large clinical trials on it are difficult to conduct, resulting in little clinical evidence on its clinicopathological characteristics, survival outcomes, and treatment responses. Most related research that has focused on GBASC has been in the form of small-sample studies or data-based analyses. For instance, Murimwa *et al.* (13) and Akce *et al.* (14) characterized the clinical features of GBASC by comparing it to gallbladder adenocarcinoma (GBAC) using the National Cancer Database and SEER. According to the available literature, when compared with patients with GBAC, patients with GBASC have a larger tumor size, poorly differentiated tumors, and worse survival. These data suggests that GBASC should be explored separately rather than as a part of GBAC with no pathological subtype recognition. Previous studies identified the characteristics of GBASC relative to those of GBAC; however, there is limited research focused on the treatment response and prognostic factors; furthermore, most patients with GBASC in the previous studies were not staged for analysis, limiting the generalizability and reliability of findings (6,13,14,16). We performed the current retrospective investigation to obtain a deeper understanding of GBASC.

Our result demonstrated that most patients with GBASC were older and White, more often female, and more likely to present with advanced clinical stage. For patients in the early GBASC stage, most underwent nonradical surgery with a tumor grade of moderately or poorly differentiated, and only a few received chemotherapy or radiotherapy. Treatment modalities of patients with advanced GBASC differed from those at the early stage, with a relatively higher rate of radical surgery, chemotherapy, and radiotherapy.

Similar to previous studies, our study found that surgical excision remained the most effective treatment for curing or improving the prognosis of GBASC. Murimwa *et al.* (13) reported that the median survival time for patients with GBASC who received surgical removal was substantially longer than for those who did not. Additionally, Oohashi *et al.* (8) indicated that patients with GBASC who received radical resection were considerably more likely to survive than were those who merely underwent initial tumor excision. Similarly, Song *et al.* (5) reported a higher 1-year survival of patients with advanced GBASC when R0 resection was performed. Our studies also demonstrated a better survival rate in patients with advanced GBASC who underwent surgery and lymph node dissection. However, the efficacy of surgery is largely based on clinical staging and the applied surgical procedures; when considering the patients at an early stage, a similar survival benefit was found in both radical surgery and primary tumor resection. This result suggests that the range of surgery for patients with early-stage GBASC could be appropriately reduced so that patients can be guaranteed some surgical benefit with less trauma, while more radical surgery for patients with advanced GBASC can enable patients to achieve the longest

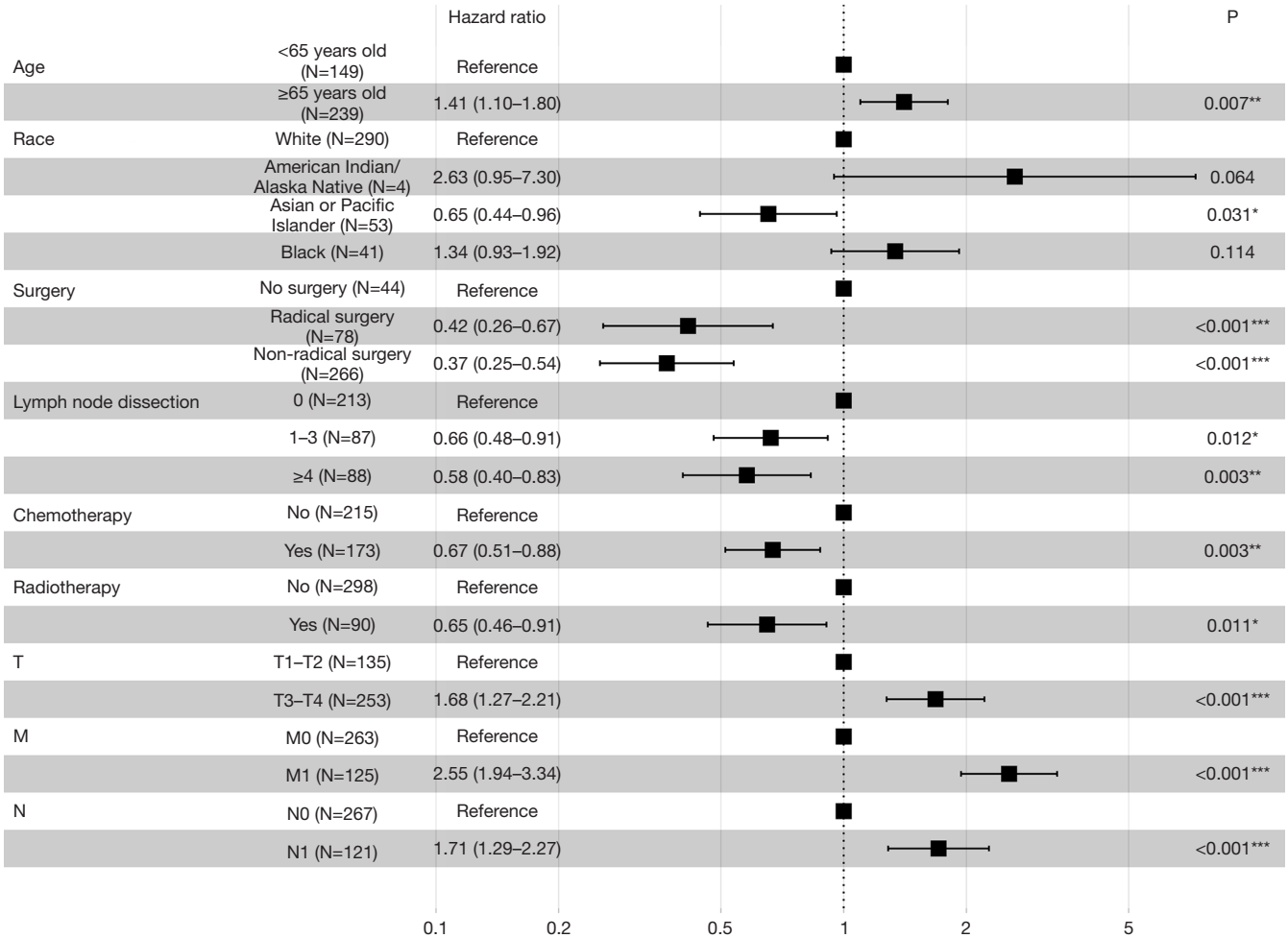

Figure 4 Forest map for HRs, 95% CIs, and P value of each independent prognostic factor associated with the CSS of patients with GBASC. *, P value less than 0.05; **, P value less than 0.01; ***, P value less than 0.001. HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; GBASC, adenosquamous carcinoma of the gallbladder.

survival.

As the basis of biliary cancer treatment, adjuvant systemic therapy has been problematic for patients with GBC due to a dearth of clinical trials focused on this disease, with this being worse in GBASC for its even lower incidence (2,22,23). Akce *et al.* (14) established a connection between increased survival with receipt of adjuvant systemic therapy in patients with GBASC. However, the lack of inclusion of nontreatment variables in the group limits the reliability of the findings. Murimwa *et al.* (13) found chemotherapy and chemoradiation to be independent prognostic variables for patients with GBASC, and the administration of adjuvant chemoradiation treatment was related to good overall mortality in resected patients with GBASC. Still, these two studies above did not maintain separate data for patients at different stages, and thus their results are less convincing.

The current study assessed the efficacy of systemic medication by carrying out a subgroup analysis of patients with GBASC at various stages. We found that chemotherapy and radiation therapy had no significant impact on the survival time of patients with early-stage GBASC, while advanced-stage GBASC patients had a significantly improved survival time when treated with radiotherapy or chemotherapy. Unfortunately, because SEER does not record the specifics of the systemic chemotherapy and radiotherapy that were provided, our findings are not as detailed or definitive as they could be. GBC is a disease that has no clinical trials to help clinicians make decisions about

Table 4 The sample size and number of events in each analysis for multivariate Cox analysis

Patient variables	Multivariate Cox analysis			
	Sample size (%)	Number of events	HR (95% CI)	P
Age				
<65 years old	149 (76.51)	114	Reference	
≥65 years old	239 (82.95)	198	1.41 (1.10–1.80)	0.007
Race				
White	4 (100.00)	4	Reference	
American Indian/Alaska Native	53 (64.15)	34	2.63 (0.95–7.30)	0.064
Asian or Pacific Islander	41 (92.68)	38	0.65 (0.44–0.96)	0.031
Black	290 (81.38)	236	1.34 (0.93–1.92)	0.114
Surgery				
No surgery	44 (100.00)	44	Reference	
Nonradical surgery	266 (79.70)	212	0.37 (0.25–0.54)	<0.001
Radical surgery	78 (71.79)	56	0.42 (0.26–0.67)	<0.001
Lymph node dissection				
0	213 (88.73)	189	Reference	
1–3	87 (79.31)	69	0.66 (0.48–0.91)	0.012
≥4	88 (61.36)	54	0.58 (0.40–0.83)	0.003
Chemotherapy				
No	215 (75.81)	163	Reference	
Yes	173 (86.13)	149	0.67 (0.51–0.88)	0.003
Radiotherapy				
No	298 (82.89)	247	Reference	
Yes	90 (72.22)	65	0.65 (0.46–0.91)	0.011
T				
T1–T2	135 (69.63)	94	Reference	
T3–T4	253 (86.17)	218	1.68 (1.27–2.21)	<0.001
M				
M0	263 (72.24)	190	Reference	
M1	125 (97.60)	122	2.55 (1.94–3.34)	<0.001
N				
N0	267 (78.28)	209	Reference	
N1	121 (85.12)	103	1.71 (1.29–2.27)	<0.001

HR, hazard ratio; CI, confidence interval.

the appropriateness and type of adjunctive treatment. In the absence of clinical trials, physicians will have to make these decisions based on tumor characteristics, such as tumor differentiation, margin status, and the size or involvement of adjacent tissues.

In addition to treatment-related factors like surgery, lymph node dissection, radiation therapy, and chemotherapy, our analysis showed that patients with GBASC who were younger, of Asian or Pacific Islander descent, or with a lower AJCC stage had a better CSS. Specifically, the AJCC T stage acted as an essential factor for patients with GBASC, mainly due to the robust capabilities of the proliferation of the tumor. According to Leigh *et al.* (17), patients with GBASC had bigger tumors (58 *vs.* 28 mm), greater liver infiltration (73% *vs.* 37%), and a higher rate of advanced AJCC stage (73% *vs.* 52%) than did those with GBAC (4,8,16). In line with the aforementioned studies, we discovered that patients with GBASC had a bulky disease presentation (60 mm). According to Charbit *et al.* (24), the squamous carcinoma component of tumors, which develops twice as rapidly as does the AC component, is most likely responsible for the cancer's very aggressive biological features (the doubling times are 81 and 166 days, respectively). Some scholars believe that enhanced proliferating cell nuclear antigen action in the squamous component of GBASC might contribute to the higher rate of progression as shown by bigger, locally progressed tumors; this would explain the incidence of bulky tumors and surrounding organ contacts in patients with GBASC and thus make T stage an important prognostic indicator for patients with GBASC (25).

The prognostic significance of distant metastases and lymph node involvement in GBC is well documented. However, the lymph node distribution pattern in GBASC remains unknown. Murimwa *et al.* (13) and Kim *et al.* (6) reported a much higher prevalence of lymphovascular invasion in GBASC than AC, indicating that a squamous histological element of GBC denotes a locally infiltrative disease with a higher risk of lymphatic dispersion. On the contrary, Kalayarasan *et al.* (16) found lower rates of nodal metastases and theorized that GBASC has a low ability to spread to other parts of the body because it enters directly through the gallbladder wall instead of through the lymphatic system. Oohashi *et al.* (8) reached the same conclusion. In our investigation, we discovered a low prevalence of lymph node involvement in 31% of all patients with GBASC as well as less than 50% in advanced patients with GBASC, suggesting that tumors are scattered by direct extension with fewer lymph node metastases.

In our present study, the comparison of different treatment modalities of patients with GBASC from the SEER database indicated that the differences in therapeutic effects could be significant between AJCC stages. The survival of patients with GBASC in early stages could benefit from more thorough lymph node dissection (more than 4), while advanced patients showed better survival when treated with surgery (both radical surgery and nonradical surgery), lymph node dissection during surgery, and chemotherapy and radiotherapy. Multivariate Cox regression also revealed that the aforementioned therapy modalities, as well as age, race, M stage, and N stage, were independent prognostic markers for all patients with GBASC in terms of CSS. The result provides some information for clinicians to reconsider in formulating a treatment strategy for patients with GBASC, and the prognostic factors may also help these patients receive personalized survival assessment.

Consideration should be given to the following limitations when interpreting the results of this investigation. First, the only information concerning the surgery was the procedure that was completed, and the SEER did not provide an information on the condition of the surgical margin. Aside from the type of surgery, achieving negative microscopic margins (R0 resection) was found to be the most important driver of surgical results in early GBASC. Furthermore, the lack of information on chemotherapy and radiotherapy protocols in SEER hindered our assessment of the efficacy of systematic treatment for GBASC. Moreover, the significance of neoadjuvant chemo/radiotherapy for patients with GBASC remains unclear. A clarification of the exact routine of systematic therapies, the order of surgery and systematic therapy, and the integrated treatment modalities is required to better comprehend the therapeutic response in GBASC. However, this study improves upon past case-series' reporting for such uncommon malignancies with a larger sample size but with the tradeoff of less clinical data. Despite these limitations, our study has yielded convincing findings with implications for diagnosing and treating GBASC.

Conclusions

Intraoperative lymph node dissection may prolong the survival of patients with early-stage GBASC; surgical treatment (particularly radical surgery), lymph node dissections that are more comprehensive, radiotherapy, and chemotherapy may provide substantially improved

survival benefits for patients with advanced GBASC. GBASC patient prognosis is influenced by independent risk variables, including surgery, lymph node dissection, radiation, chemotherapy, age, race, and AJCC stage.

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Footnote

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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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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