European Review for Medical and Pharmacological Sciences 2023; 27: 10016-10030

A nomogram predicting the outcome of gallbladder cancer patients with different target organ metastases

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Abstract. – OBJECTIVE: Gallbladder cancer (GBC) is a highly aggressive malignancy that is associated with a high mortality rate globally. Unfortunately, distant metastases are often detected at the time of diagnosis. Therefore, we investigated the survival outcomes of gallbladder cancer patients with different metastases targeting organs, analyzed their prognosis, and explored their hidden clinical value.

PATIENTS AND METHODS: Through data screening, a total of 398 patients with GBC with different target organ metastases were analyzed retrospectively, including patients with solitary bone metastasis, solitary liver metastasis, solitary lung metastasis, and multiple organ metastases. The survival results of different variables were plotted as Kaplan-Meier survival curves. Univariate and multivariate Cox regression models were used to screen study variables and identify independent prognostic factors. Finally, a nomogram was established to systematically evaluate the prognosis of patients with multiple organ metastasis.

RESULTS: In the patient cohort, thirteen (3.3%) had solitary bone metastasis, 290 (72.9%) had solitary liver metastasis, 22 (5.5%) had solitary lung metastasis, and 73 (18.3%) had multiple organ metastases (including liver, lung, bone and brain metastases). Multivariate Cox analysis showed that the overall survival (OS) of patients with solitary lung metastasis was significantly better than that of patients with other organ metastasis ($p = 0.038$), while the difference in tumor cancer-specific survival (CSS) of this factor was not statistically significant ($p > 0.05$). Surgery and chemotherapy were independent prognostic protective factors for OS and CSS. The OS-related models exhibited a C-index of 0.74 (95% CI: 0.71-0.77), while the CSS-related models showed a slightly lower C-index of 0.73 (0.70-0.76). Both the OS- and CSS-related clinical prediction models had good accuracy.

CONCLUSIONS: This study shows that different target organ metastases may affect the OS of patients with distant metastatic GBC. Patients receiving palliative surgery, primary site resection, radical surgery, and chemotherapy have significant survival benefits in terms of OS and CSS.

Key Words:
Target organ metastasis, Gallbladder cancer, Prognosis, Nomogram.

Introduction

Malignant tumors of the biliary tract include the hilar bile duct, common hepatic duct, and common bile duct, among which gallbladder cancer (GBC) is the most common, and it is also one of the common tumors of the digestive tract. Its onset is insidious, and its development is rapid. When diagnosed, the tumor is often in its late stage. High malignancy and poor prognosis are the characteristics of GBC, which are also the difficulties that clinicians need to face and solve[1,2]. The treatments for GBC vary according to its stage. Early cholecystectomy is the best way to cure this cancer. For patients with advanced GBC, surgical treatment may not be the most preferred benefit option depending on their physical conditions. At present, there are few chemotherapy regimens for such patients, and there is no effective treatment for advanced patients. Patients at an advanced stage have a dismal prognosis, with a 5-year survival rate of approximately 10% or even lower[3]. There are few reports on distant metastasis of GBC, mainly case reports[4].

Gallbladder cancer commonly spreads to the liver not only due to its anatomical proximity but also because of the liver's abundant blood flow. In addition to the liver, gallbladder cancer often metastasizes to the lungs, brain, bones, colorectum, and even the gums[5-9]. This mode of metastasis presents a huge challenge for clinical treatment. Recently, more and more literature has focused on GBC patients with distant metastasis, but there is still a lack of a comprehensive evaluation of such patients. It is urgent to explore the influence of different metastatic hab-

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its of gallbladder carcinoma on survival outcomes. Therefore, the purpose of this paper was to explore a representative population of patients with distant metastasis of GBC, tap the hidden prognostic value of this information, and provide additional plans and thoughts for clinical work.

Patients and Methods

Research Design

We searched the Surveillance, Epidemiology and End Results database (SEER) and included eligible cases in our study. It covers almost all types of cancer, including the incidence and prevalence of different types of cancer in different geographical locations and their mortality rates. The patient variables were screened by SEER * Stat software (Version 8.4.0.1). The following inclusion criteria were applied: (1) be diagnosed with GBC by ICD-0-3 (Third Edition of the International Classification of Diseases for Oncology). (2) Patients with distant, isolated target organ metastasis or multiple target organ metastases at the time of diagnosis. (3) Information on chemoradiotherapy, specific tumor grade, and marital status. (4) Patients with primary gallbladder cancer. Exclusion criteria: (1) a primary tumor elsewhere. (2) Patients without a clear description of the surgical procedure. (3) Patients without complete information about their survival status.

Information on the Variables

In the variable of distant metastasis, we included isolated bone metastasis, isolated liver metastasis, isolated lung metastasis, and multiple target organ metastasis. Simultaneous presence of two or more bone, liver, lung, and/or brain metastases is referred to as multiple target organ metastases. The study did not collect isolated brain metastasis patients but combined them with patients who had metastases in other organs.

The surgical information included no surgical treatment, palliative surgery, total resection of the primary site, and radical surgery (per SEER database official procedure coding guidelines). In the SEER database, palliative surgery-related variables include local tumor destruction, local tumor resection, simple resection of the primary site, and tumor reduction surgery. In this paper, these variables were unified into palliative surgery.

With regard to the tumor pathological grading of the patients, we included well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated. In this paper, they are referred to as different grades (I, II, III, and IV). Overall survival (OS) and cancer-specific survival (CSS), as two important outcome endpoints in the SEER database, will be included in this study as outcome events for analysis, respectively.

In addition, age, gender, race, radiotherapy information, chemotherapy information, and marital status were also included information.

Statistical Analysis

Fisher's test or a Chi-square test was used to make a preliminary difference comparison for all variables in this study. Kaplan-Meier survival analysis curves were drawn to compare survival differences associated with some variables, and log-rank tests were used. All variables were included in the univariate and multivariate Cox analysis to screen out independent factors affecting the prognosis, and a forest plot was drawn to display the results visually. According to the current clinical experience and decision-making, some results of single-factor and multi-factor Cox analysis were included in the construction of the nomogram. At the same time, calibration curves were plotted for 1, 2, and 3-year intervals to demonstrate the model's reliability. The C-index was used to evaluate the effectiveness of the model. R software (version 4.2.1, Vienna, Austria) was used for all data analysis. The statistical significance level was set at $p < 0.05$.

Results

Population Information

The study included a cohort of 398 patients. Among them, 102 (25.6%) were younger than 60 years old, and 296 (74.4%) were older than 60 years old. There were 121 (30.4%) male and 277 (69.6%) female. There were 13 (3.3%) with solitary bone metastasis, 290 (72.9%) with solitary liver metastasis, 22 (5.5%) with solitary lung metastasis, and 73 (18.3%) with multiple target organ metastasis. In terms of tumor pathological grading, there were 24 (6.0%) Grade I, 141 (35.4%) Grade II, 214 (53.8%) Grade III, and 19 (4.8%) Grade IV. In terms of treatment information, 169 (42.5%) did not receive surgery, 61 (15.3%) received palliative surgery, 139 (34.9%) received total resection of the primary site, and 29 (7.3%) received radical surgery. Only 34 (8.5%) received radiotherapy, and 364 (91.5%) did not receive radiotherapy; 208 (52.3%) received chemotherapy, and 190 (47.7%) did not receive chemotherapy. All of the included patient variable information is summarized in Table I.

Table I. Baseline table related to basic information.

Characteristic	Total (n = 398)	*p*-value
Age (n,%)		0.623
< 60 years	102 (25.6)	
≥ 60 years	296 (74.4)	
Sex (n, %)		0.999
Male	121 (30.4)	
Female	277 (69.6)	
Ethnicity (n, %)		0.794
White	287 (72.1)	
Black	54 (13.6)	
Other	57 (14.3)	
Grade (n,%)		0.104
Grade I	24 (6.0)	
Grade II	141 (35.4)	
Grade III	214 (53.8)	
Grade IV	19 (4.8)	
Surgical operation (n, %)		0.677
Non-surgical treatment	169 (42.5)	
Palliative procedure	61 (15.3)	
Total surgical removal of primary site	139 (34.9)	
Radical surgery	29 (7.3)	
Radiotherapy (n, %)		0.250
No/Unknown	364 (91.5)	
Yes	34 (8.5)	
Chemotherapy (n, %)		< 0.001
No/Unknown	190 (47.7)	
Yes	208 (52.3)	
Distant metastasis (n, %)		0.810
Bone	13 (3.3)	
Liver	290 (72.9)	
Lung	22 (5.5)	
Multiple metastases	73 (18.3)	
Marital status (n, %)		0.488
Married	231 (58.0)	
Single	60 (15.1)	
Divorced	33 (8.3)	
Widowed	74 (18.6)	

Survival Differences

Figure 1 depicts the OS curves for patients who underwent chemotherapy, radiotherapy, and surgery. Patients receiving chemotherapy had a better median OS than those not receiving chemotherapy (8 months *vs.* 2 months). This is still the case with radiotherapy. Patients receiving radiotherapy can also obtain a longer median OS:11 months. In terms of surgery, patients who did not receive surgery had the shortest median OS, which was only 3 months, while patients who received radical surgery had the longest median OS, 8 months. The median OS of patients receiving palliative surgery with total primary site resection was 5 months ($p < 0.001$).

In Figure 2, the pathological grade of the tumor is shown. The patients with high and medium differentiation had better median OS: 7 months and 8 months. The poorly differentiated and undifferentiated patients had poor median OS of 3 and 4 months, respectively ($p = 0.002$). Figure 2 also shows the survival finale of the cohort with distant metastasis. Patients with solitary pulmonary metastasis had the longest median OS: 9

Figure 1. Survival analysis of the OS patients with chemotherapy conditions (**A**), radiotherapy conditions (**B**), and surgical conditions (**C**).

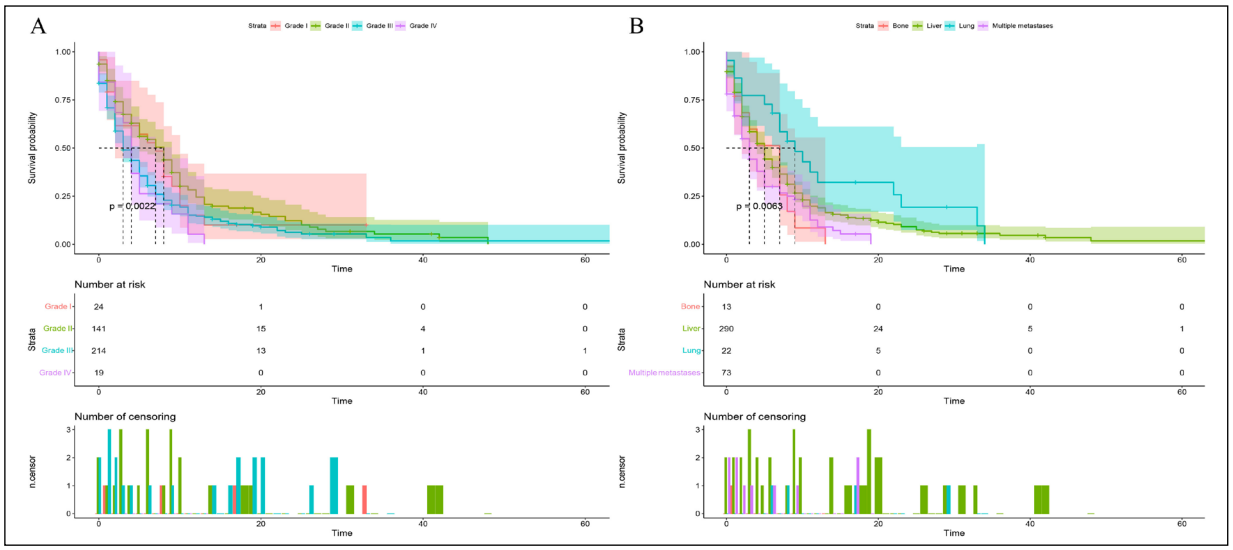

Figure 2. Survival analysis of the patients' OS with tumor grades (**A**) and different target organ metastases (**B**).

months. The patients with solitary bone metastasis and solitary liver metastasis followed with 7 months and 5 months, respectively. The median OS of patients with multiple target organ metastases was the worst, only 3 months ($p = 0.006$).

Cox Regression Analysis

All variables in this study were analyzed by single-factor analysis according to the patients' OS and CSS. The findings of the variable analysis with respect to patients' OS are presented in Table II. Surgical information, chemotherapy, radiotherapy, distant metastasis, and marital status stood out from the single-factor analysis. These factors were included in the multivariate analysis. Palliative surgery, total resection of the primary site, radical surgery, chemotherapy, and solitary pulmonary metastasis were independent protective prognostic factors of OS in these patients ($p < 0.05$). For CSS, we also con-

Table II. Univariate and multivariate analysis based on OS of patients. HR: Hazard ratio CI: Confidence interval.

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (n,%)				
< 60 years	1			
≥ 60 years	1.12 (0.88 - 1.43)	0.369		
Sex (n, %)				
Female	1			
Male	0.99 (0.79 - 1.24)	0.925		
Ethnicity (n, %)				
White	1			
Black	0.85 (0.62 - 1.17)	0.316		
Other	0.95 (0.70 - .1.28)	0.722		
Grade (n, %)				
Grade I	1			
Grade II	0.86 (0.53 - 1.38)	0.533		
Grade III	1.29 (0.82 - 2.05)	0.274		
Grade IV	1.57 (0.83 - 2.94)	0.163		
Surgical operation (n, %)				
Non-surgical treatment	1		1	
Palliative procedure	0.77 (0.56 - 1.06)	0.109	0.65 (0.47 - 0.90)	0.010
Total surgical removal of primary site	0.64 (0.50 - 0.81)	< 0.001	0.56 (0.43 - 0.72)	< 0.001
Radical surgery	0.52 (0.34 - 0.79)	0.003	0.40 (0.26 - 0.62)	< 0.001
Radiotherapy (n, %)				
No/Unknown	1		1	
Yes	0.51 (0.34 - 0.76)	0.001	0.73 (0.48 - 1.11)	0.137
Chemotherapy (n, %)				
No/Unknown	1			
Yes	0.34 (0.28 - 0.43)	< 0.001	0.32 (0.25 - 0.40)	< 0.001
Distant metastasis (n, %)				
Bone	1		1	
Liver	0.74 (0.41 - 1.32)	0.304	0.64 (0.36 - 1.16)	0.145
Lung	0.45 (0.22 - 0.96)	0.038	0.42 (0.20 - 0.89)	0.024
Multiple metastases	1.05 (0.57 - 1.96)	0.859	0.81 (0.43 - 1.51)	0.506
Marital status (n, %)				
Married	1		1	
Single	1.06 (0.77 - 1.44)	0.730	0.86 (0.62 - 1.19)	0.357
Divorced	1.13 (0.76 - 1.68)	0.541	1.36 (0.91 - 2.04)	0.133
Widowed	1.45 (1.10 - 1.91)	0.009	1.12 (0.84 - 1.49)	0.451

Table III. Univariate and multivariate analysis based on CSS of patients.

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (n,%)				
< 60 years	1			
≥ 60 years	1.13 (0.88 - 1.44)	0.351		
Sex (n, %)				
Female	1			
Male	0.98 (0.78 - 1.24)	0.878		
Ethnicity (n, %)				
White	1			
Black	0.85 (0.62 - 1.17)	0.316		
Other	0.87 (0.63 - 1.19)	0.379		
Grade (n, %)				
Grade I	1			
Grade II	0.89 (0.55 - 1.45)	0.649		
Grade III	1.32 (0.82 - 2.12)	0.251		
Grade IV	1.56 (0.82 - 2.97)	0.179		
Surgical operation (n, %)				
Non-surgical treatment	1		1	
Palliative procedure	0.78 (0.57 - 1.08)	0.141	0.66 (0.47 - 0.92)	0.014
Total surgical removal of primary site	0.64 (0.50 - 0.82)	< 0.001	0.55 (0.43 - 0.71)	< 0.001
Radical surgery	0.54 (0.35 - 0.83)	0.005	0.40 (0.26 - 0.62)	< 0.001
Radiotherapy (n, %)				
No/Unknown	1		1	
Yes	0.53 (0.35 - 0.79)	0.002	0.81 (0.54 - 1.22)	0.318
Chemotherapy (n, %)				
No/Unknown	1		1	
Yes	0.36 (0.29 - 0.44)	< 0.001	0.32 (0.25 - 0.40)	< 0.001
Distant metastasis (n, %)				
Bone	1			
Liver	0.80 (0.44 - 1.47)	0.479		
Lung	0.51 (0.24 - 1.09)	0.081		
Multiple metastases	1.05 (0.55 - 2.00)	0.883		
Marital status (n, %)				
Married	1			
Single	1.08 (0.79 - 1.48)	0.630	0.86 (0.63 - 1.19)	0.369
Divorced	1.14 (0.76 - 1.70)	0.536	1.29 (0.85 - 1.94)	0.231
Widowed	1.49 (1.12 - 1.96)	0.006	1.12 (0.84 - 1.49)	0.453

ducted single-factor and multi-factor analysis (Table III). Surgical treatment, chemotherapy, radiotherapy, and marital status were screened out by the single-factor analysis and included in the multi-factor analysis. Multivariate analysis showed that surgical treatment and chemotherapy were protective prognostic factors of CSS. Figures 3 and 4 show the multi-factor analysis of the OS and CSS-related variables in the form of a forest plot.

Clinical Prediction Model

The important variables from the analyses were used to construct the patient's OS and CSS-related nomographs, and the impact of each variable on the patient's prognosis was displayed intuitively. A clinical prediction model was established to predict the OS and CSS at 1, 2, and 3 years. The results suggest that surgical treatment and chemotherapy are related to better OS and CSS, while solitary

lung metastasis is only related to better OS (Figures 5 and 6).

Calibration Curve and C-Index

Figures 7 and 8 show the calibration curve of the OS related to the CSS clinical prediction model, which shows the good consistency of the model. The C-index was calculated and used to evaluate the accuracy of the new model. The model's C-index for OS was found to be 0.74 (95% CI: 0.71-0.77), while the CSS correlation model exhibited a C-index of 0.73 (95% CI: 0.70-0.76). Both OS and CSS-related clinical prediction models had good accuracy.

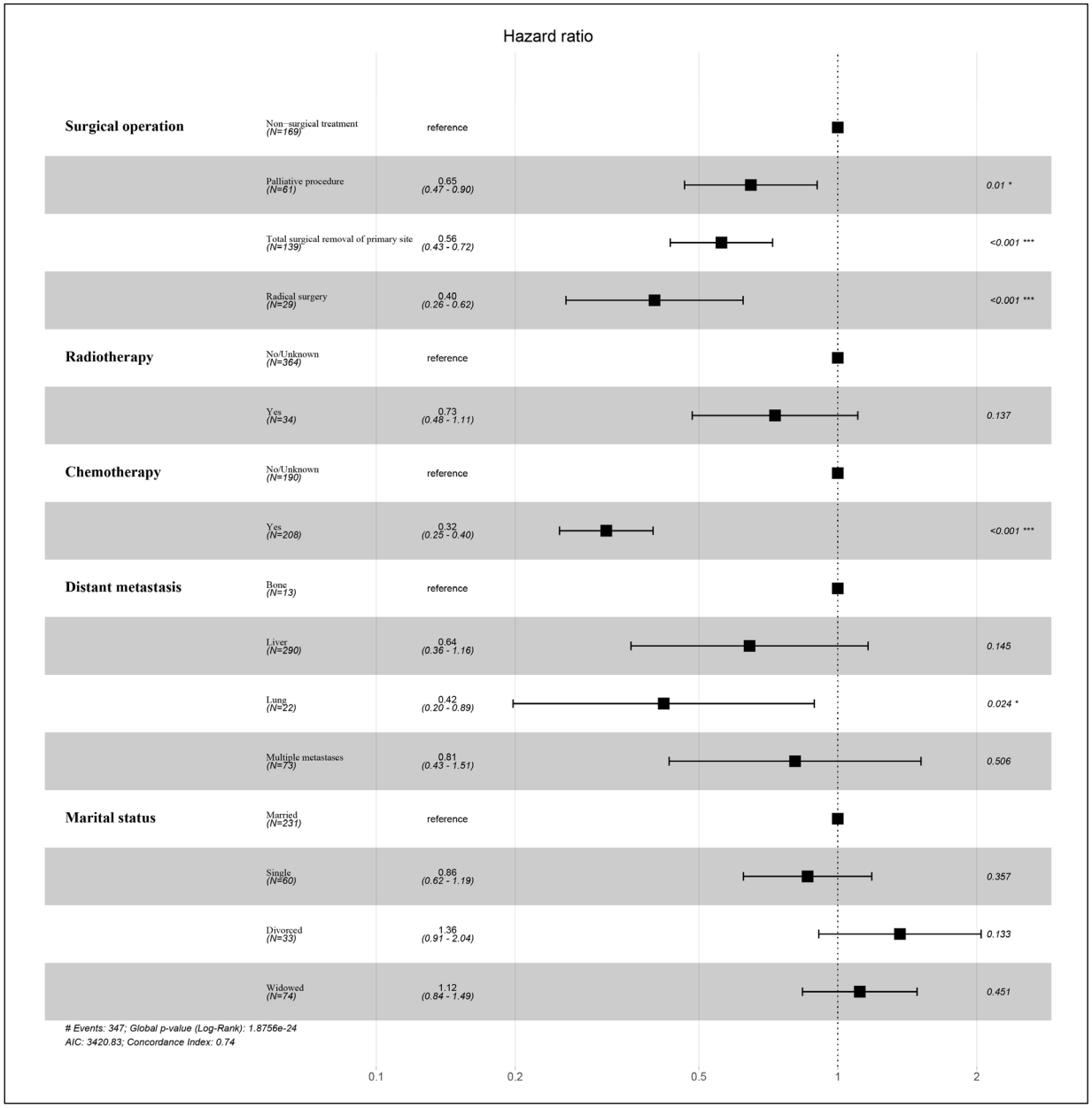

Figure 3. Visualization of the OS in patients with multivariate Cox regression analysis. *represents the significance of the *p*-value.

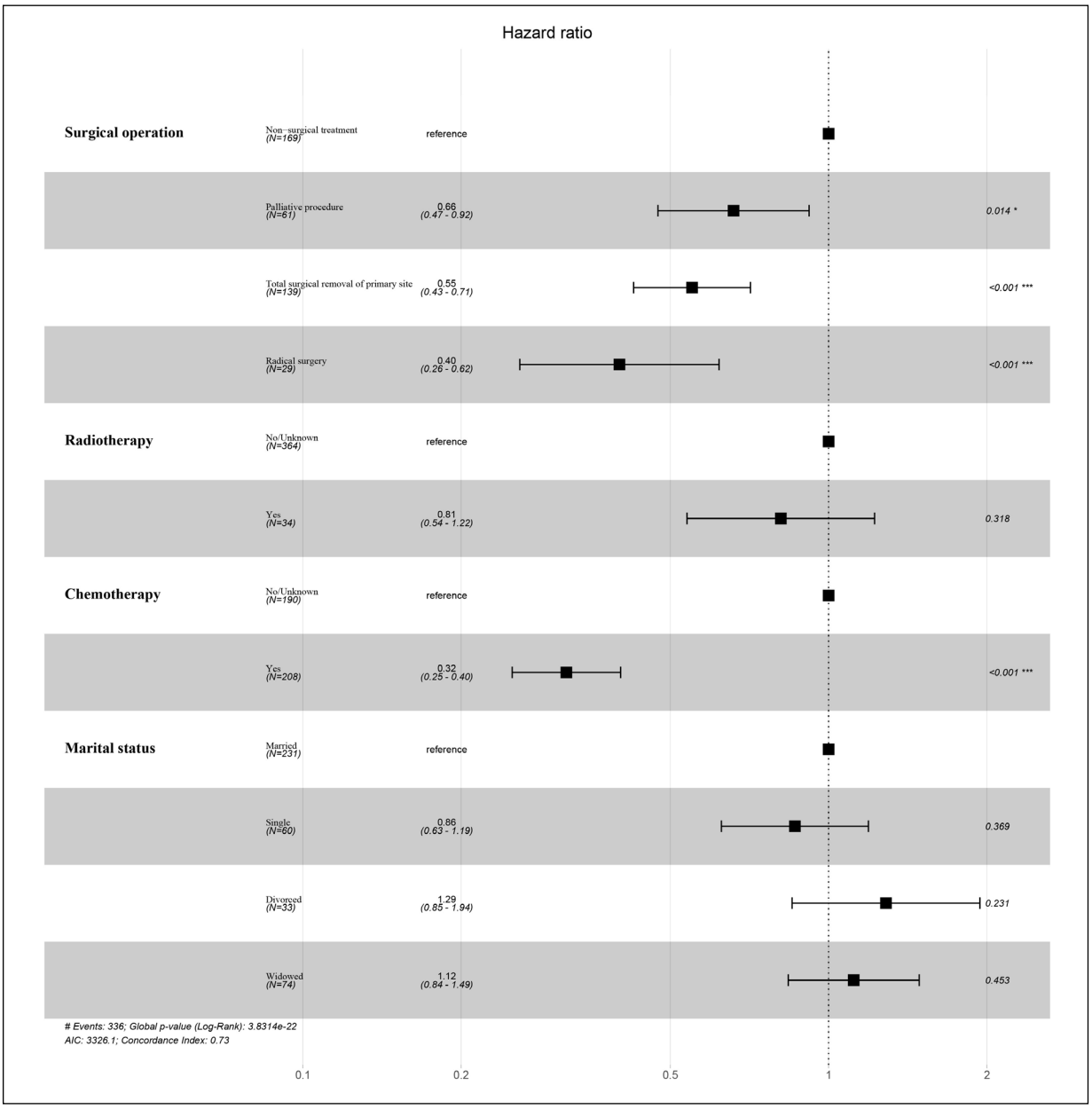

Figure 4. Visualization of the CSS in patients with multivariate Cox regression analysis. *represents the significance of the *p*-value.

Discussion

GBC has a high degree of malignancy and mortality, and there is a lack of effective interventions in clinical practice[10]. Once metastasis occurs, the patient's life may be limited. According to a research report[11], there are approximately 10,000 new cases and 3,000 deaths worldwide every year from GBC. Only a few patients have surgical indications[12]. In this study, 290 of 398 patients (72.9%) had isolated liver metastases, which was the largest compared to the other three modalities. It is well-known that liver metastasis is one of the most common sites of distant metastasis of GBC[13]. A retrospective multicenter study pointed out that surgery combined with postoperative chemotherapy may be one of the best treatment methods for patients with liver metastasis and GBC[14].

For intrahepatic cholangiocarcinoma, retrospective studies[15] have suggested a poor prognosis for bone metastases. In this study, 13 (3.3%)

patients had bone metastasis. For GBC, previous studies on bone metastasis are mostly case reports, including micrometastasis and cases combined with brain metastasis[16]. PET/CT is able to identify suspicious bone metastases and is one of the best methods to determine the locations for performing tissue biopsy[17]. Some genetic tests can also assist in detecting micrometastasis, such as the *CEA*, *CK19*, and *CK20* genes. Identifying related subtype genes may be a direction of future research[4,18].

In this study, 73 (18.3%) patients had multiple target organ metastases. They had the worst median OS of 3 months. For patients with this kind of advanced tumor, multidisciplinary joint diagnosis and treatment and adjuvant treatment have become the means of prolonging the survival of patients[19].

In this study, 22 patients (5.5%) had solitary pulmonary metastasis. A case report[20] suggested that *RCAS1* is one of the indicators of a poor prognosis for such patients because it occurs in both GBC and lung cancer. After performing univariate and multivariate analysis, it was found that isolated pulmonary metastasis is an independent protective factor for OS. However, it is not related to the patient's CSS. After analyzing the reasons, we suggest the following points: (1) This study required that the relevant information of the included patients must be complete, including specific surgical methods, radiotherapy, chemotherapy,

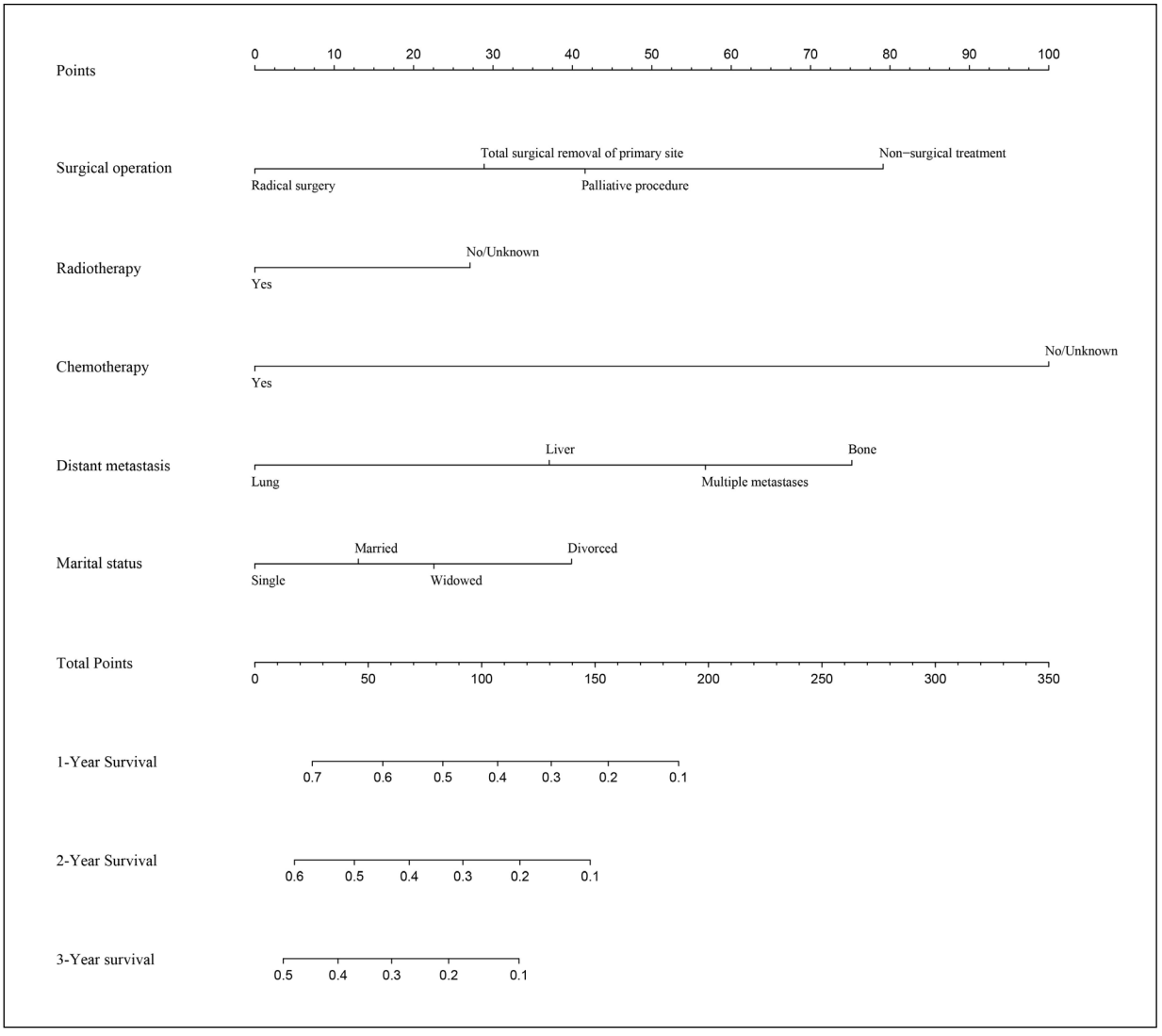

Figure 5. Prognostic nomograms for OS of patients.

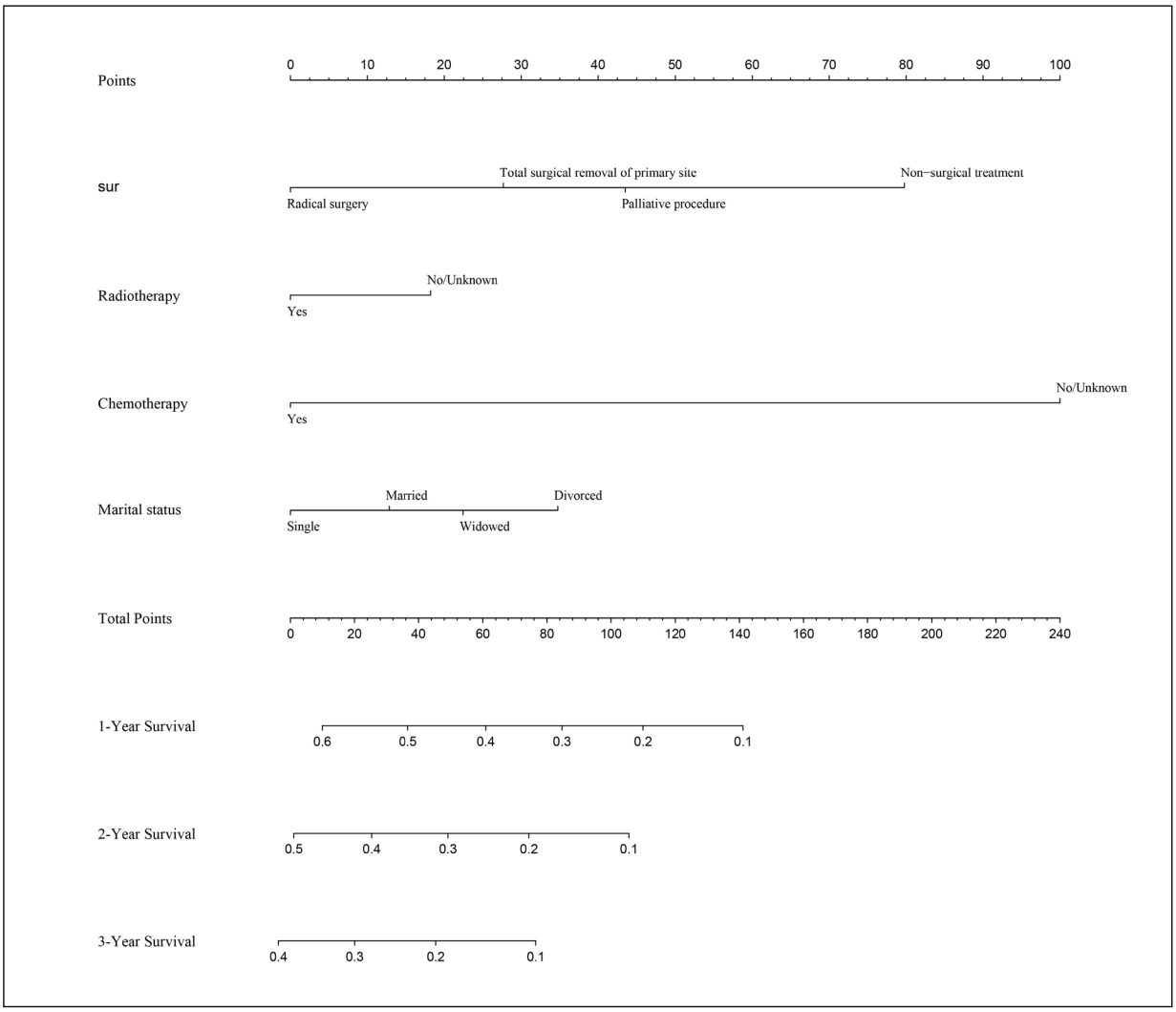

Figure 6. Prognostic nomograms for CSS of patients.

etc. After screening, except for isolated liver metastasis, the number of patients with other target organ metastases was small, which increased the uncertainty of the outcomes of this research investigation. (2) In this study, the patients with isolated lung metastasis were older, and they may have other basic diseases or systemic diseases that may affect their CSS and contribute to shorter survival.

In terms of surgery, we have made a more in-depth discussion than in previous literature. Since ancient times, whether advanced GBC should be treated by surgery and what kind of surgery should be performed have been debated by many scholars. Up to now, surgical treatment is still the only treatment that could be curative. Although treatments are available, the patients' mortality rate remains high, and the problem of rapid recurrence needs to be addressed. It is important to carefully consider the patient's treatment plan in a step-by-step manner. At present, some clinical retrospective studies[21] indicate that radical surgery is the best way to prolong the survival of patients with early GBC. For patients with advanced stage, palliative surgery is sometimes not inferior to radical surgery. At the same time, lymph node dissection and R0 resection are also important prognostic factors. In this study, the forest plot (Figures 3 and 4) and the nomogram (Figures 5 and 6) both suggested that radical surgery is the best choice. Total primary site resection and palliative surgery can prolong the OS and CSS of patients, which provides more treatment options for patients with distant metastasis. If the distant

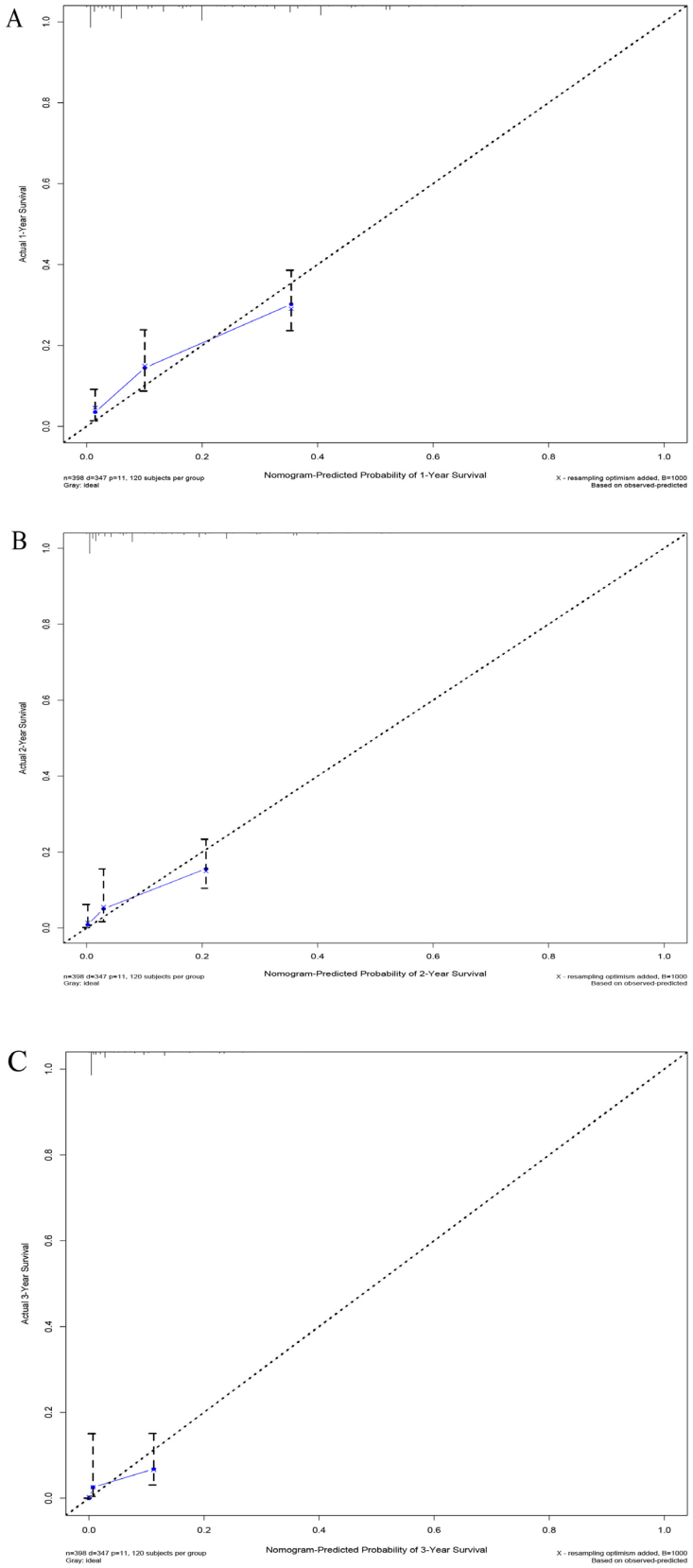

Figure 7. Calibration curves for OS predictions at 1 (**A**), 2 (**B**), and 3 (**C**) years.

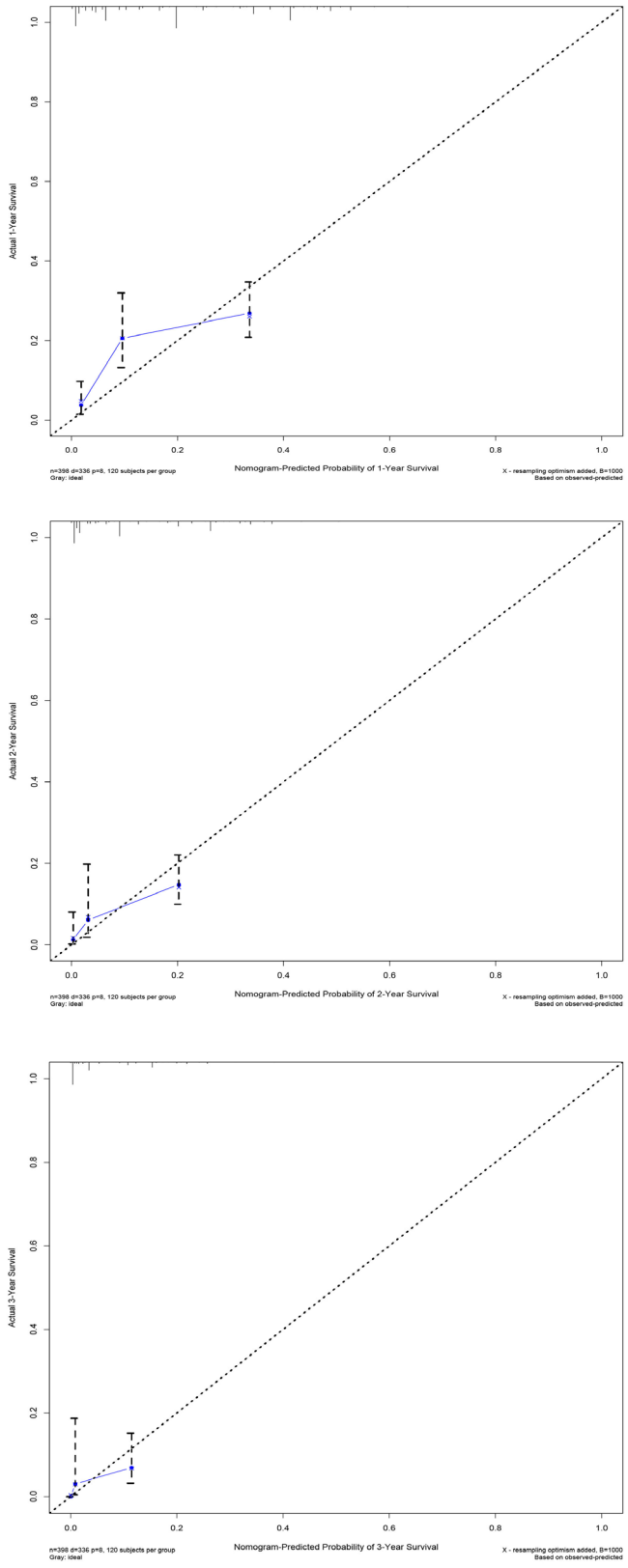

Figure 8. Calibration curves for CSS predictions at 1, 2, and 3 years.

metastasis cannot be removed, in addition to palliative surgery, total resection of the primary site may benefit the patient. In addition, increasing numbers of surgical methods have also entered the stage. In addition to traditional laparotomy, radical laparoscopic surgery and robotic surgery start from the perspective of minimally invasive surgery, and their advantages are gradually being highlighted[23]. Multidisciplinary team discussions are becoming more and more important in the treatment of cancer patients at a time when new crown pneumonia is prevalent. Therefore, we should re-discuss the timing and indications of surgery in terminally ill patients to maximize their survival benefits.

In some cases, for some patients with distant metastasis of GBC who have lost the opportunity of surgery, multidisciplinary combined treatment and adjuvant treatment are often required. In terms of chemotherapy, after different phase III clinical trials, gemcitabine combined with cisplatin or oxaliplatin was finally selected as the first-line chemotherapy scheme for patients with GBC[23]. Despite significant life extension potential, the approach has obvious side effects. Immunotherapy and targeted therapy have also been developed gradually. Immune agents such as pembrolizumab and nivolumab have shown efficacy. Compared with chemotherapy, immunotherapy has fewer side effects, most of which are immune-mediated thyroid dysfunction, liver dysfunction, rash, diarrhea, etc. Vascular endothelial growth factor (*VEGF*) has been the core and focus of targeted therapy, and the *HER2*, *MAPK* (*RAS*/*RAF*/*MEK*/*ERK*) and *PI3K*/*AKT*/*mTOR* pathways have also been gradually targeted. However, it has been reported that *CA19-9* and *PD-L1* may be predictors of poor prognosis in patients with GBC. These additional targets provide more possibilities for patients with advanced GBC. The role of non-coding RNA in the growth and development of different cancers has also been explored and has the potential to become cancer biomarkers and cancer treatment targets in the future. Chemotherapy, target immunotherapy, or neoadjuvant chemotherapy are used to down-stage tumors and achieve resectability.

In this paper, the clinical prediction model of metastatic GBC patients is established through SEER database, which provides a preliminary personalized treatment strategy for such patients. It not only predicts the survival and disease progression risk of patients, but also provides basic basis for medical team in clinical treatment selection, surgical decision-making and follow-up.

This study has many limitations. The SEER database is concentrated in parts of the United States, covering about 30% of the U.S. population. Thus, its population representation may be limited. When studying specific populations or socioeconomic groups, there is a possibility of bias that can arise. As a result, it may not fully reflect the cancer situation in the entire United States or even other countries. The database mainly collects epidemiological information related to cancer, but the detailed information on clinical characteristics and treatment is relatively limited. In addition, the limited sample size of GBC patients with distant target organ metastasis included in the database may limit the study of these types of cancer.

Conclusions

This study shows that different target organ metastasis may affect the OS of patients with distant metastatic GBC. Patients receiving palliative surgery, primary site resection, radical surgery, and chemotherapy have significant survival benefits in OS and CSS. In terms of research methods, this paper analyzes the OS and CSS of GBC patients with different target organ metastasis and explores the different effects of these metastasis patterns on the two survival endpoints. Due to data limitations, in the future, another independent data set is expected to verify this result. Therefore, more options are sought for GBC patients with distant metastasis clinically.

Ethics Approval

Since the SEER database only contains disease-related information for patients and it does not contain any identifying patient information, no ethical approval is required for this article.

Funding

No financial support was received for this study.

Authors' Contributions

Xu completed data collection and document writing. Xu and Li jointly completed the data analysis. Junhua Gong completed drawing and table making. Jianping Gong proposed some modification suggestions. Li determines the theme and research direction of the article. All authors reviewed the manuscript.

Conflict of Interest

There is no interest dispute in this paper and related research.

Acknowledgments

The author expresses gratitude to Professor Guangkuo Li (Chengdu Second People's Hospital) for assisting with statistical analysis.

Availability of Data and Materials

Information regarding the accessibility and provision of data and materials utilized in this study can be made available upon request.

Informed Consent

All the data in this study are derived from open free databases, and these data do not contain any information related to the privacy of patients.

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