

Development and Validation a Nomogram and Prognosis of Chemotherapy for Evaluation in Giant-cell Lung Carcinoma With Metastases: A Propensity Score Matching Analysis

Zhihao Yang (✉ 3478033787@qq.com)

Wenzhou Medical University <https://orcid.org/0000-0002-1924-9987>

Kun Chen

Wenzhou Medical University

Xinbo Zhang

Wenzhou Medical University

Tianhao Zhao

Wenzhou Medical University

Deyao Xie

Wenzhou Medical University

Xiaofang Deng

Wenzhou Medical University

Jiandong Zhang

Wenzhou Medical University

Dezhi Cheng

Wenzhou Medical University

Research

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Abstract

Background and Objectives: Whether chemotherapy could improve prognosis for giant-cell lung carcinoma with metastases remains controversial. The present study aimed to determine the significance of chemotherapy in patients with metastases giant-cell Lung carcinoma, and to develop a nomogram to predict its outcomes.

Methods: Data of 566 patients from the Surveillance, Epidemiology, and End Results (SEER) database were analyzed; 346 matched patients were divided into a chemotherapy group and non-chemotherapy group, respectively, using the propensity score matching method. Univariate and multivariate analyses were performed to determine the prognostic factors of giant-cell lung carcinoma, and subgroup analysis was performed according to the site of metastases. While a visual nomogram was established to judge the prognosis.

Results: With the median follow-up of 20.5 months, The 3-year survival rates were 20.2% in the chemotherapy set and 16.7% in the non-chemotherapy set ($P=0.006$). Chemotherapy did improve the Giant-cell Lung Carcinoma survival rates in patients with metastases ($HR = 0.490$, $95\% CI = 0.358-0.669$, $P<0.001$). In subgroup analysis, radiotherapy did not improve the Giant-cell Lung Carcinoma survival rates in patients with metastases ($HR = 0.951$, $95\% CI = 0.690-1.311$, $P = 0.758$, Table 2). Chemotherapy improved the CSS in patients with lung metastases ($HR = 0.090$, $95\% CI = 0.017-0.470$, $P = 0.004$). In addition, chemotherapy improved the CSS in patients with brain metastases ($HR = 0.117$, $95\% CI = 0.014-0.955$, $P = 0.045$). Compared with bone metastasis, liver metastasis and metastasis of more than 2 sites, the effect of chemotherapy is not obvious. Furthermore, our nomogram could predict the probability of surviving to the median survival time of the population with a c-index of 0.768.

Conclusion: The benefit of chemotherapy in giant-cell lung carcinoma with metastases patients was obviously different, and the recommendation of chemotherapy for this population should be individualized. Chemotherapy should be considered for patients with only lung metastasis or brain metastasis, but chemotherapy could be avoided in those with other site metastases or multiple metastases. We developed the first competing risk nomogram to predict the risk of GCLC patients, which performed well in the evaluation and might be helpful for individualized screening.

Introduction

Lung cancer accounts for a relatively large proportion of human tumors around the world and bring about approximately 30% of tumor-related deaths. Most lung cancers are non-small cell tumors. This type accounts for nearly 80% of all carcinoma of the lungs, and only 4-6 percent of patients were alive more than five years[1]. GCLC is a poorly differentiated carcinoma consists of highly polymorphic mononuclear or multinuclear giant cells and is identified as one of the non-small cell lung carcinoma (NSCLC)[2]. A study described that GCLC accounted for nearly 0.3–0.4 percent of primary lung cancers, with a growth rate of approximately three new cases per million persons per year among the 60,000 patients in the

US[3]. GCLC appears as a large necrotic block with no obvious structural form. Microscopic observation shows that GCLC comprises giant, multinucleated, and weirdly shaped cells. Its background contains a large number of neutrophils and lymphocytes, and there is no specific pattern of adenocarcinoma, squamous cell carcinoma, or large squamous cell carcinoma[4]. Five subsets were identified by World Health Organization (WHO) in 2004: spindle cell carcinoma, pleomorphic carcinoma, giant cell carcinoma, pulmonary blastoma and carcinosarcoma[2]. Currently, we can determine that a tumor is GCLC by using CT, which shows a large and central low-attenuation area or cavity. This imaging is consistent with the tumor necrosis area found in pathological specimens[5]. There are data showing that the palliative chemotherapy response in advanced lung sarcomatoid carcinoma is poor[6]. Patients who do not undergo surgery after receiving appropriate chemotherapy, radiotherapy or combined adjuvant therapy can also have a prolonged survival time[7]. Because the poor prognosis and shortened survival time associated with tumour heterogeneity is worse than that for ordinary NSCLC, Maneenil et al recommend early consideration of surgical resection and perioperative chemotherapy[8].

A nomogram is an intuitive diagram to quantify and provide the survival probability of a GCLC patients undergoing the progress of clinical events[9, 10]. The thoracic surgeon can refer to such a probability to make a decision on the next treatment plan. In addition, we not only assessed the accuracy of the nomogram, but also calibrated it.

Methods

Patient selection

This retrospective study was conducted by acquiring data from the Surveillance Epidemiology and End Results (SEER) database. Data were obtained by SEER*Stat 8.3.6 in October 2019. Using this software, we screened GCLC patients between 2004 and 2016. We limited this study population based on the following criteria: age at diagnosis: ≥ 18 years old, primary site: lung and bronchus, primary site and morphology ICD-O-3: GCLC (8030, 8031, 8032, 8033, 8034, and 8035). Patients were excluded if their age, race, survival time, pathological diagnosis, or presence/absence of metastasis were unknown or if their pathological results were from an autopsy or a death certificate.

For the SEER database, cancer-specific survival (CSS) was defined as death due to GCLC, and overall survival (OS) was defined as death regardless of cause. The primary outcome was CSS, with OS and CSS considering other non-GCLC-related deaths as the secondary outcome. Survival time was defined as the time from diagnosis to the date of death.

Ethics statement

Data from the SEER database are free to use and do not require informed patient consent. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. It was not

appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of research

Statistical analysis

Clinical characteristics were compared among the chemotherapy set and nonchemotherapy set, using Pearson's chi-square test. To remove confounding factors between baseline characteristics among each set as much as possible, we set the proportion for propensity score matching (PSM) analysis at 0.2. CSS analysis was conducted after PSM, and survival curves were created for age, race, T stage, N stage, M stage, chemotherapy, surgery and radiotherapy by using the Kaplan-Meier method. The CSS values between the different sets were compared by performing the log-rank test. Univariate and multivariate Cox regression models were used to evaluate the CSS hazard ratios (HRs) and 95% confidence intervals (CIs) of patients in the chemotherapy set compared to those in the nonchemotherapy set. In the univariate analysis, we added meaningful or clinical variables to the multivariate Cox regression analyses. HRs and 95% CIs were calculated by using multivariate Cox proportion hazard models, with adjustments for age, race, sex, T stage, N stage, M stage, grade, chemotherapy, surgery and radiotherapy. Multivariate Cox models were conducted for subset analyses to determine whether there was a significant interaction between different characteristics. A novel visible nomogram of the model was developed to evaluate the discriminatory performances, which was measured by the concordance index (C-index), and the C-index was adjusted for the predictive accuracy, which was equaled to the area under curve of receiver operating characteristic curves. The calibration curve of nomogram was setting to reflect the relationships of the predicted out versus observed results. All statistical analyses for predicting CSS were performed using R software (version 3.6.3). All P values lower than 0.05 with two-sided comparisons were deemed to indicate statistical significance.

Results

Tumour information and patient characteristics

A total of 566 patients with GCLC who met the research criteria were eventually selected. The median age of patients was 71 years (interquartile range (IQR): 63–78). Tumour information and patient characteristics stratified by chemotherapy are summarized in Table 1. There were significant differences in age at diagnosis, T stage, N stage, M stage and surgery between the chemotherapy set and the nonchemotherapy set ($P < 0.001$). The PSM method was used to balance baseline characteristics between each set, and there were 173 patients in each set after PSM. Between the two sets, we found that T stage, N stage, M stage and surgery showed statistically significant differences ($P < 0.05$); for other baseline characteristics, no significant differences were observed ($P > 0.05$, Table 1).

Cancer-specific survival analysis

The median survival was 20.5 months (IQR: 17.8–22.5), and 188 people died of GCLC. There were 93 (26.88%) GCLC-related death events observed in the chemotherapy set and 95 (27.46%) in the

nonchemotherapy set. The 3-year CSS were 20.2% in the chemotherapy set and 16.7% in the nonchemotherapy set ($P = 0.006$). Kaplan-Meier analysis showed that patients treated with chemotherapy had a better CSS than patients who did not receive chemotherapy; the log-rank test P value was 0.037 (Figure 1A). In the univariate analyses, age, race, T stage, N stage, M stage, chemotherapy, surgery and radiotherapy were significantly associated with CSS. Except for the radiotherapy results, the results from the multivariate analyses were consistent of univariate analyses; the details are shown in Table 2. In the multivariate Cox regression analyses, radiotherapy did not significantly improve the CSS for GCLC patients (HR = 0.951, 95% CI = 0.690-1.311, $P = 0.758$, Table 2). Cox proportional hazard regression analyses revealed that T stage, N stage, metastatic sites and surgery were independent prognostic factors. Age, grade, race, sex and radiotherapy were not significant factors. As shown in Table 3, chemotherapy improved the CSS in patients with lung metastases (HR = 0.090, 95% CI = 0.017-0.470, $P = 0.004$, Figure 1B, Table 3). In addition, chemotherapy improved the CSS in patients with brain metastases (HR = 0.117, 95% CI = 0.014-0.955, $P = 0.045$, Figure 1E, Table 3). Surprisingly, we found that there were no differences in the CSSs in patients with no metastases or with multiple metastases (Figure 1C, Figure 1D, Figure 1F). The results are shown in a forest plot to make them more intuitive (Figure 2).

Nomogram

Eventually, in order to better estimate the multiple independent risk factors, which were according to univariate and multivariate COX regression analyses, of CCS in GCLC patients for prognostic capability (Figure 3). To interpret the meaning of graph, we set a patient's value is located on each variable axis, then depict a red line to identify the number of points for which we choose the variable. The integrated all points is positioned to the total points axis, which would determine the likelihood of median survival time for 1 or 3 years by a red line was drawn downward. The gray color area under the curve of total points and the green box represent the sample size, which shows the patients statistics of the GCLC and the population distribution of the prognosis. We found that the prediction of C-index was 0.768 [95% confidence interval (CI), 0.746-0.789]. The Receiver Operating Characteristic (ROC) was used to evaluate the accuracy of the model (Figure 4), The Area Under Curve (AUC) is 0.877 (95% confidence interval (CI), 0.835-0.919). The calibration plot of the nomogram had reached a good concordance between the CSS prediction risk and the actual observed incidence (Figure 5).

Discussion

With the improvement of diagnostic techniques and treatment options, the OS and CSS rates of patients with non-metastatic NSCLC continue to increase. However, in terms of metastasis, the time from the occurrence of the primary tumor to the determination of metastasis is not certain. It is generally believed that this process requires a certain amount of time for the appropriate conditions to develop and interactions within the tumor microenvironment. Altorki et al's research shows that before metastasis, immune cells [11], organ-specific inducing substances, growth factors, inflammatory factors and extracellular matrix-modified proteins create a more favourable microenvironment for metastatic tumour cells. The method by which metastatic tumour cells interact with the host organ microenvironment is

complex. Different types of interactions may lead to unique patterns of transfer events. The Vieira et al study found that most patients with lung sarcomatoid carcinoma have a high vascular invasion rate and a high recurrence rate after surgical resection, which indicates that this type of tumour has a high metastasis rate and poor prognosis characteristics[12, 13]. In previous research, we found that approximately 71.9% of patients with lung sarcomatoid carcinoma are smokers. Such a high smoking rate is related to the occurrence of tumours, but smoking status has no significant effect on the prognosis and survival of patients with lung cancer[12, 14]. At the same time, the formulation of chemotherapy programmes has been reported for different lung cancer subtypes and stages, and the effects of single and combined targeted therapy applications have also been reported[15-17]. We studied the effect of chemotherapy on the CSS rate of GCLC through PSM. Some of the clinicopathological parameters showed significant differences between the chemotherapy set and the nonchemotherapy set. It was found that patients younger than 71 years old had a good prognosis after chemotherapy, and patients older than 71 years old had no difference in prognosis, regardless of whether they received chemotherapy or not; this may be related to the body's cardiopulmonary functional reserve, the tolerance to toxicity and the side effects of chemotherapy drugs. It is reported that the proportion of patients aged 80 and above who undergo systemic chemotherapy has decreased significantly, which is consistent with our previous PSM data. There were 184 people who were 71 years old or older and did not receive chemotherapy. The possible reason is that elderly patients and their families may be unwilling to undergo this treatment. Therefore, due to the side effects, we prefer to suggest a milder treatment for advanced cancer in elderly patients[18]. There are also studies showed that few elder patients receive further treatment after relapse or metastasis[19]. Our data from the PSM analysis show that T stage, N stage, metastatic factors, surgery and chemotherapy are statistically significant factors, but the differences in outcomes related to chemotherapy, race and sex are not obvious. Interestingly, there was no significant difference in the effect of radiotherapy in our study, either within or between sets. Martin et al's study showed that the benefits of postoperative radiotherapy have not been shown to improve the survival rate of patients with typical lung sarcomatoid carcinoma[20]. According to previous research, platinum-based palliative chemotherapy strategies are less effective for the treatment of lung cancer, and the results for GCLC as a subtype in our study are slightly different from those in this previous report. We found that patients receiving chemotherapy had improved CSS compared with that of patients not receiving chemotherapy. An analysis within the chemotherapy set showed that patients with lung, brain, and bone metastases had a significantly better CSS than those in the nonchemotherapy set. The analysis between sets showed that chemotherapy had no significant effect on the prognosis of patients with or without metastasis. A possible reason is that the systemic chemotherapy does not convey additional benefits in patients without metastasis. Local treatments, including stereotactic body radiation therapy (SBRT), and other treatments, can also be utilized. A multicentre, randomized, controlled phase 2 study showed that local consolidation therapy in oligometastatic NSCLC can significantly prolong the survival duration while delaying the appearance of new metastatic foci[21]. Patients with single-site metastases with only brain or intra-pulmonary metastases have better CSS with chemotherapy. Previous studies have many controversial aspects, and one study showed that palliative chemotherapy used in NSCLC is not effective for advanced lung sarcomatoid carcinoma. No patients achieved an effective response after

chemotherapy, and the median OS was only 5 months. Lung sarcomatoid carcinoma has a higher rate of local recurrence after surgery and a higher incidence of metastases at diagnosis[6]. The Vieira et al study showed that patients receiving platinum chemotherapy had a prolonged OS while with no difference in PFS[22]. Chaft et al's research suggests that not all lung sarcomatoid carcinomas are refractory to chemotherapy. Due to the poor prognosis after recurrence of sarcomatoid carcinoma, relapse should be prevented and delayed as much as possible. Neoadjuvant or adjuvant chemotherapy could be used in patients with resectable lung cancer. In addition, according to Wang et al's research, when NSCLC has a high degree of vascular invasion, the relative risk of recurrence and death is 4 and 2 times higher. Therefore, it is recommended that NSCLC patients receive systemic chemotherapy rather than palliative chemotherapy[23, 24]. However, the analysis within the set showed that the prognosis of patients with liver metastases was worse than that of the other metastatic sets[25], and the effect of chemotherapy was poor. The results of the Wu et al study identified that patients with liver metastases had significantly lower PFS and OS. Rong et al showed that the effect of chemotherapy in early bone metastasis was significant; however, in this retrospective analysis, the effect of chemotherapy on bone metastasis was not beneficial as expected. The analysis between sets showed that chemotherapy had no significant effect on patients with 2 or more metastases. The possible reason is that an increased tumor burden leads to chemotherapy being ineffective. The Joss study found that patients with two or more metastases in distant organs had a lower chemotherapy response rate than patients with less tumor burden (patients with local disease or a metastatic disease in an extrathoracic organ); the reason may be that a larger tumor burden results in more cell populations that are resistant to multiple drugs[26].

Overall, the prognosis of GCLC patients is unsatisfactory. At present, an array of clinical prediction models are showing a hot trend, but most of the clinical prediction models are general studies of NSCLC, and do not involve the prognosis prediction of GCLC[27-29]. In order to express this screening and integration data more concretely, we constructed this nomogram for clinical practice conveniently, which predicted its 1 and 3 year survival probability. Contemporarily, with the sustainable basic study and the development of cure strategies[30, 31], and the novel detection techniques appeared[32], The new prediction model we have established opens up a novel way for the prognosis prediction of GCLC patients through the independent prognostic factors screened. The evaluation of this model has a well accuracy and calibration. The C-index value for predicting the survival probability was 0.768, The Area Under Curve of ROC was 0.877, which was statistically higher than that TNM 8th Edition[33].

The strange thing is that radiotherapy is not included in the nomogram model. We suspect that this may be related to the dose and location of radiotherapy. According to Johnson's point of view, the increase in dose compared with the standard dose of radiotherapy can improve the survival rate. A high dose of cardiac radiotherapy is an important independent prognostic factor to reduce survival rate[34].

Our research still has many shortcomings. For example, the relationship between chemotherapy and the time of surgery in the SEER database is not clear; second, the description of the type of surgery is slightly unclear, and it is not clear whether the surgery performed was a lobectomy or lung segment resection. In addition, data on complications and costs of treatment are minimal, the sample size for tumor data is

small, and the tracking time is short. The abovementioned limitations may introduce a degree of uncertainty in our results. The data in the SEER database are common, and it lacks the unique data contained in databases in other regions, but the SEER database does provide many types of valid and reliable data for retrospective analysis. Our data compilation is expected to provide a better treatment results for patients with GCLC.

Conclusion

In summary, we found that T stage, N stage, metastatic site, chemotherapy and surgery were associated with the CSS of GCLC. Patient characteristics has little effect on prognosis. In future research we propose exploring the effect of tumour heterogeneity on prognosis. The effect of radiotherapy for treating GCLC was not a significant factor before and after matching; therefore, it is recommended that this treatment should not be considered as the primary method. The benefit of chemotherapy in patients with GCLC varies greatly, and the most rational proposal of chemotherapy for this population should be individualized. Patients with only brain or lung metastases may undergo chemotherapy, but chemotherapy could be avoided in those with no metastases or multiple metastases. This study development an ideal model of nomogram, which predict the survival outcomes for GCLC patients consultation and thoracic surgeon making a reasonable decision. These results enhance our understanding of GCLC and highlight how cancer treatment strategies can be improved.

Declarations

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Authors' contributions

Kun Chen and Zhihao Yang collected the data and drafted the manuscript. Dezhi Cheng conceived and designed the study and reviewed and finalized the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the Surveillance, Epidemiology, and End Results (SEER) database.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.²The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.³The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.⁴The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.⁵The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.⁶The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.⁷The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.⁸The First Affiliated Hospital of Wenzhou Medical University,Zhejiang,325000,China.

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Tables

Table1 Comparison of demographic and tumor characteristics between CHEMO group and no-CHEMO group.

| Variables | Before PSM | | P-value | After PSM | | P-value |
|-----------|----------------|-------------------|---------|----------------|-------------------|---------|
| | CHEMO N=261 | No-CHEMO N=305 | | CHEMO N=173 | No-CHEMO N=173 | |
| AGE | ≤71 | 177 | 0.035 | 97 | 89 | 0.101 |
| | >71 | 84 | | 76 | 84 | |
| GRADE | 1 | 3 | 0.340 | 3 | 2 | 0.584 |
| | 2 | 1 | | 0 | 1 | |
| | 3 | 195 | | 126 | 129 | |
| | 4 | 62 | | 44 | 41 | |
| RACE | White | 221 | 0.338 | 148 | 141 | 0.103 |
| | Black | 22 | | 14 | 26 | |
| | Other | 18 | | 11 | 6 | |
| SEX | Male | 157 | 0.807 | 100 | 105 | 0.581 |
| | Female | 104 | | 73 | 68 | |
| T | 1 | 13 | <0.001 | 11 | 14 | 0.001 |
| | 2 | 84 | | 60 | 53 | |
| | 3 | 89 | | 57 | 72 | |
| | 4 | 74 | | 45 | 34 | |
| N | 0 | 113 | <0.001 | 89 | 95 | <0.001 |
| | 1 | 38 | | 26 | 19 | |
| | 2 | 84 | | 44 | 42 | |
| | 3 | 26 | | 14 | 17 | |
| M | None | 176 | <0.001 | 114 | 115 | 0.001 |
| | Bone | 19 | | 16 | 13 | |
| | Brain | 16 | | 5 | 11 | |
| | Liver | 2 | | 2 | 3 | |
| | Lung | 13 | | 12 | 9 | |
| | Multiple | 35 | | 24 | 22 | |
| SURG | No | 163 | <0.001 | 101 | 102 | <0.001 |
| | Yes | 98 | | 72 | 71 | |
| RADIO | No | 122 | 0.340 | 117 | 109 | 0.849 |
| | Yes | 139 | | 56 | 64 | |

Table2 Univariate and multivariate analysis for CSS in patients with metastases.

| Variables | | Univariate analysis | | Multivariate analysis | |
|-----------|----------|-------------------------|-----------|-------------------------|-------|
| | | HR (95% CI) | P | HR (95% CI) | P |
| AGE | ≤71 | Reference | - | Reference | - |
| | >71 | 1.309 (1.034-1.659) | 0.026 | 0.766 (0.556-1.056) | 0.104 |
| GRADE | I+II | Reference | - | Reference | - |
| | III+IV | 1.364 (0.563-3.306) | 0.491 | 0.1219 (0.297-5.002) | 0.784 |
| RACE | White | Reference | - | Reference | - |
| | Black | 1.475 (1.046-2.081) | 0.027 | 1.408 (0.917-2.160) | 0.118 |
| | Other | 0.859 (0.491-1.502) | 0.594 | 1.755 (0.885-3.480) | 0.107 |
| SEX | Male | Reference | - | Reference | - |
| | Female | 0.951 (0.748-1.208) | 0.679 | 1.133 (0.831-1.546) | 0.430 |
| T | 1 | Reference | - | Reference | - |
| | 2 | 2.739 (1.420-5.283) | 0.003 | 5.084 (1.822-14.183) | 0.002 |
| | 3 | 4.415 (2.304-8.459) | <0.001 | 7.556 (2.731-20.909) | <0001 |
| | 4 | 6.229 (3.196-12.141) | <0.001 | 6.545 (2.301-18.614) | <0001 |
| | N | 0 | Reference | Reference | - |
| N | 1 | 1.939 (1.356-2.781) | <0.001 | 1.924 (1.209-3.062) | 0.006 |
| | 2 | 2.691 (2.025-3.577) | <0.001 | 1.846 (1.251-2.724) | 0.002 |
| | 3 | 3.563 (2.380-5.336) | <0.001 | 2.233 (1.339-3.722) | 0.002 |
| | M | None | Reference | Reference | - |
| M | Single | 2.717 (2.033-3.630) | <0.001 | 1.863 (1.250-2.777) | 0.002 |
| | Multiple | 4.582 (3.222-6.517) | <0.001 | 2.736 (1.730-4.327) | <0001 |
| SURG | No | Reference | - | Reference | - |
| | Yes | 0.273 (0.209-0.356) | <0.001 | 0.380 (0.249-0.582) | <0001 |
| RADIO | No | Reference | - | Reference | - |
| | Yes | 1.443 (1.133-1.838) | 0.003 | 0.951 (0.690-1.311) | 0.758 |
| CHEMO | No | Reference | - | Reference | - |
| | Yes | 0.744 (0.559-0.991) | 0.043 | 0.490 (0.358-0.669) | <0001 |

| TABLE 3 Subgroup analyses of radiotherapy effect on BCSS in patients with different features. | | | | |
|---|------------------------|---------------------------|---------------------|--------|
| Subgroup | Chemo(patients/events) | No Chemo(patients/events) | Hazard Ratio(95%CI) | P |
| Age | | | | |
| Less than 71 yr | 186/53 | 186/54 | 0.655(0.447-0.958) | 0.029 |
| More than 71 yr | 160/40 | 160/41 | 0.891(0.576-1.378) | 0.604 |
| Race | | | | |
| White | 289/77 | 289/71 | 0.796(0.576-1.100) | 0.166 |
| Black | 40/11 | 40/19 | 0.835(0.397-1.757) | 0.634 |
| Other | 17/5 | 17/5 | 0.410(0.116-1.448) | 0.166 |
| Sex | | | | |
| Male | 205/57 | 205/59 | 0.785(0.545-1.130) | 0.193 |
| Female | 141/36 | 141/36 | 0.681(0.428-1.082) | 0.104 |
| Grade | | | | |
| I+II | 6/2 | 6/0 | 0.744(0.559-0.991) | 0.043 |
| III+IV | 340/91 | 340/95 | 0.726(0.544-0.969) | 0.029 |
| T | | | | |
| T1 | 25/2 | 25/2 | 1.741(0.243-12.445) | 0.581 |
| T2 | 113/30 | 113/23 | 0.983(0.577-1.713) | 0.983 |
| T3 | 129/35 | 129/46 | 0.631(0.405-0.982) | 0.041 |
| T4 | 79/26 | 79/24 | 0.310(0.170-0.566) | <0.001 |
| N | | | | |
| N0 | 184/36 | 184/37 | 0.929(0.587-1.471) | 0.753 |
| N1 | 45/18 | 45/10 | 0.827(0.379-1.807) | 0.635 |
| N2 | 86/29 | 86/34 | 0.350(0.207-0.592) | <0.001 |
| N3 | 31/10 | 31/14 | 0.305(0.123-0.759) | 0.011 |
| Surge | | | | |
| Yes | 143/27 | 143/27 | 0.853(0.500-1.455) | 0.56 |
| No | 203/66 | 203/68 | 0.599(0.426-0.843) | 0.003 |
| Radio | | | | |
| Yes | 120/39 | 120/39 | 0.836(0.536-1.305) | 0.431 |
| No | 226/54 | 226/56 | 0.699(0.480-1.017) | 0.061 |
| M | | | | |
| None | 229/50 | 229/51 | 0.839(0.569-1.240) | 0.378 |
| Bone | 29/13 | 29/11 | 0.449(0.195-1.034) | 0.06 |
| Brain | 16/3 | 16/10 | 0.117(0.014-0.955) | 0.045 |
| Liver | 5/1 | 5/1 | 1.000(0.063-15.988) | 1 |
| Lung | 21/5 | 21/6 | 0.090(0.017-0.470) | 0.004 |
| Multiple | 46/21 | 46/16 | 0.574(0.292-1.126) | 0.106 |

Figures

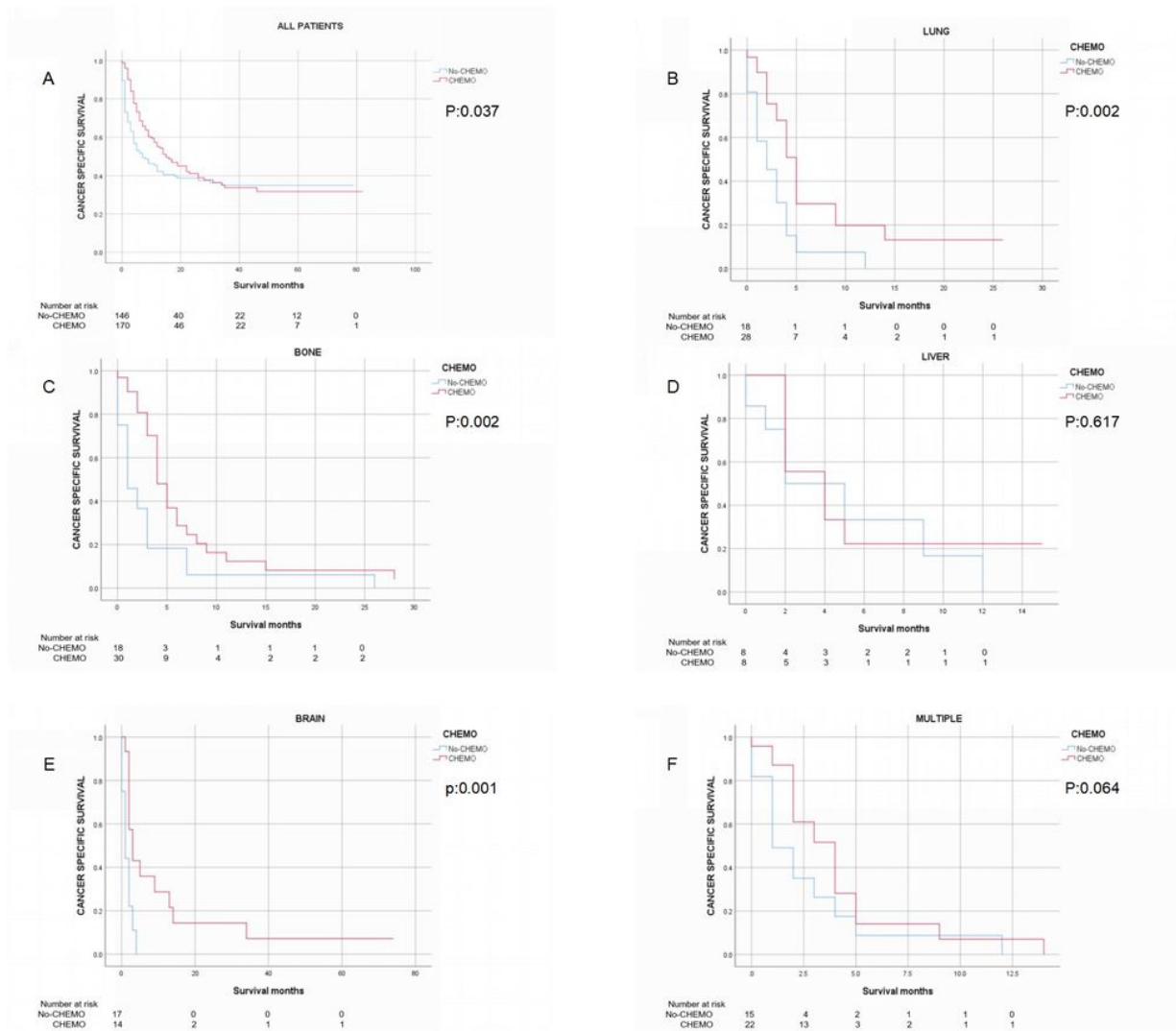


Figure 1

(A) Survival of GCLC Patients stratified by chemotherapy; (B) Survival of GCLC Patients with lung metastasis stratified by chemotherapy; (C) Survival of GCLC Patients with bone metastasis stratified by chemotherapy; (D) Survival of GCLC Patients with liver metastasis stratified by chemotherapy; (E) Survival of GCLC Patients with brain metastasis stratified by chemotherapy; (F) Survival of GCLC Patients with multiple metastasis stratified by chemotherapy

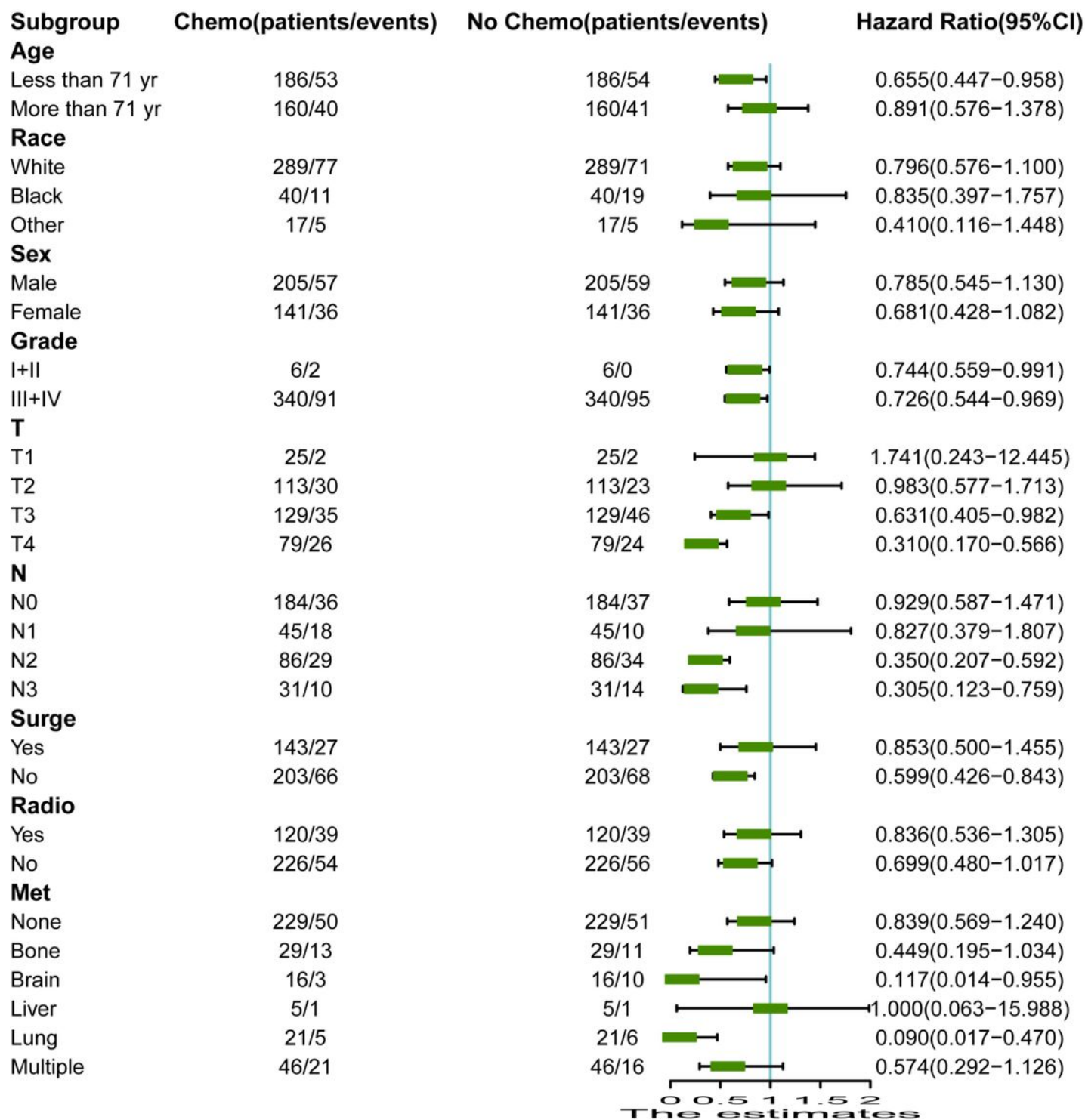


Figure 2

The forest plot for GCLC patients comparing CSS between the CHEMO group and no-CHEMO group according to different variable

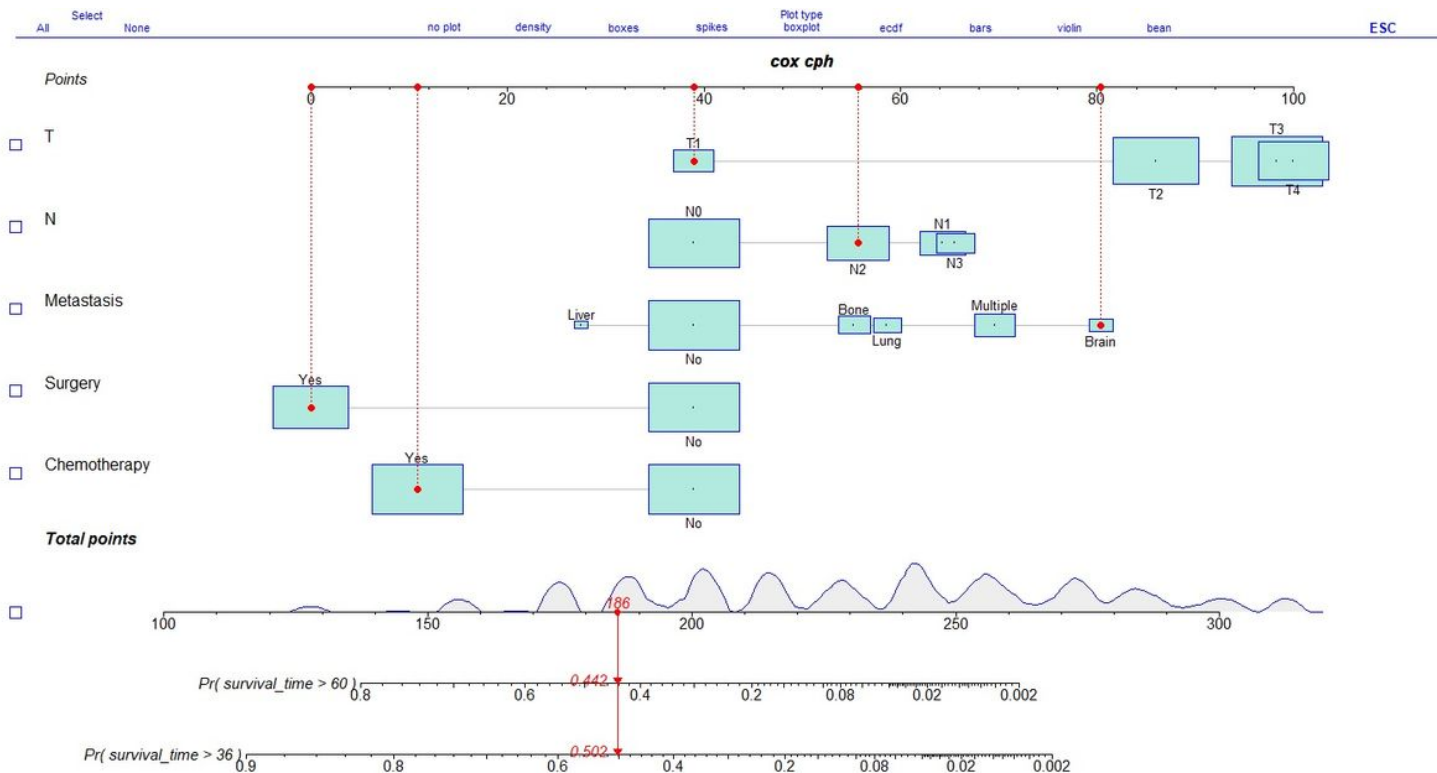


Figure 3

Cancer specific survival nomogram for GCLC patients.

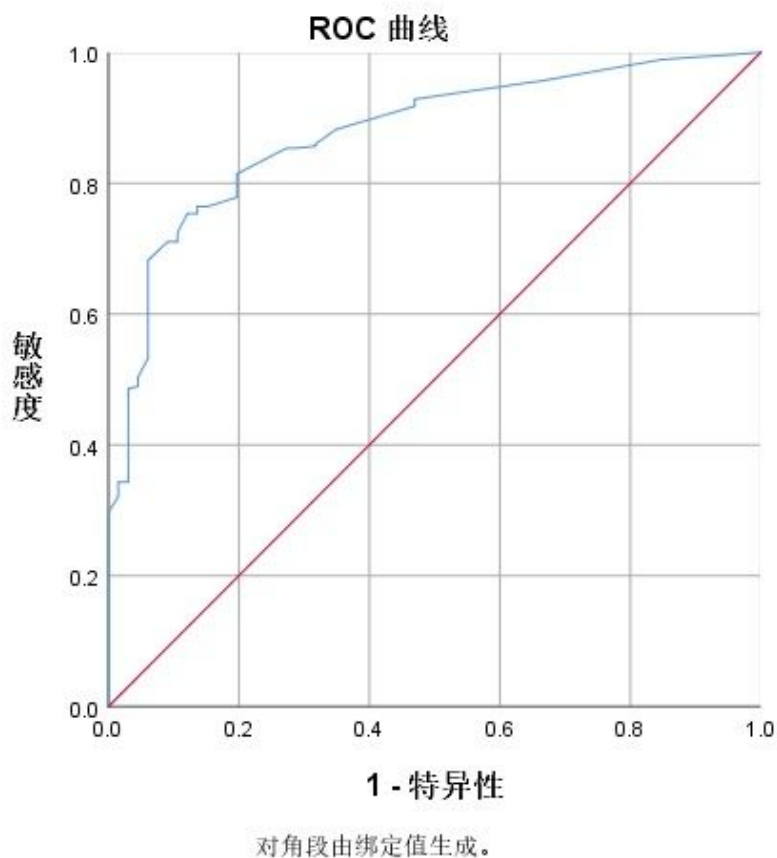


Figure 4

Receiver operating characteristic (ROC) curves of clinical events in GCLC patients.

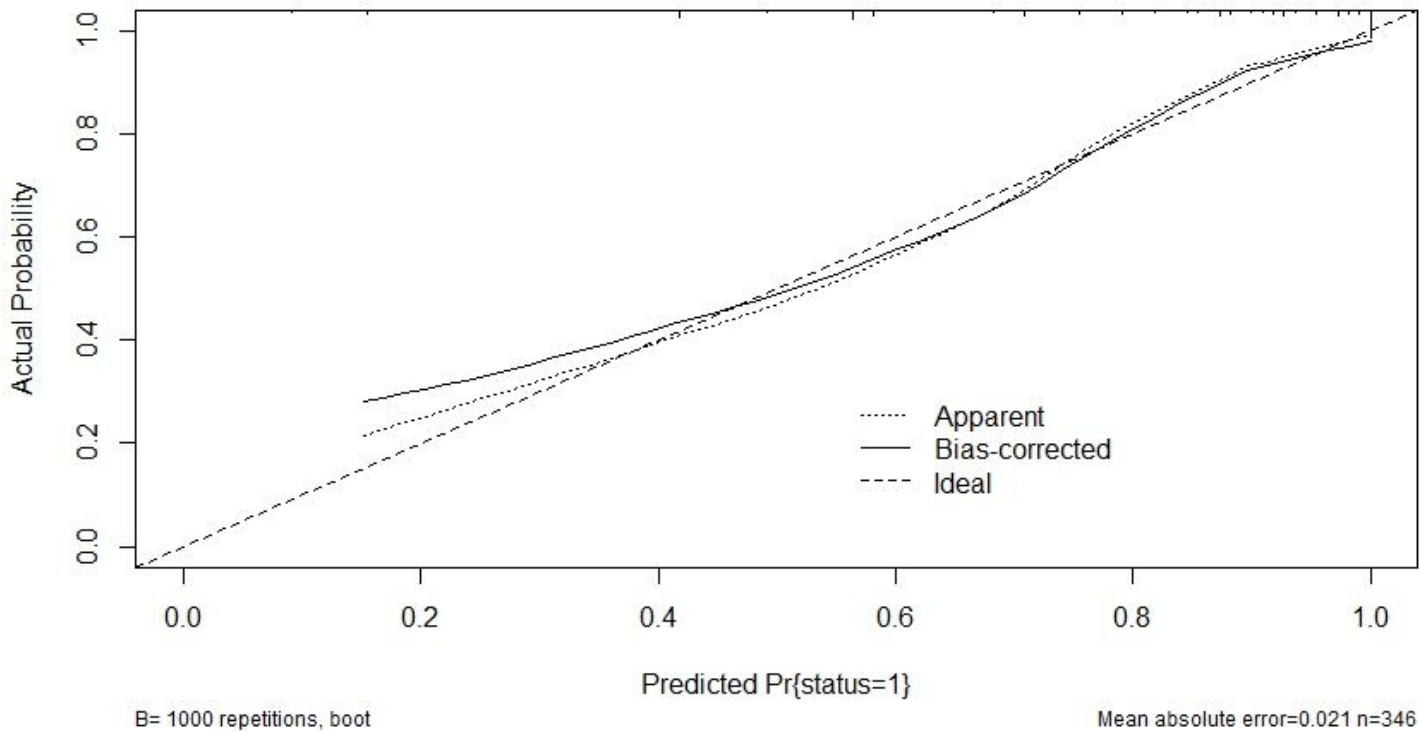


Figure 5

Calibration plot for the cancer specific survival nomogram.