Operable gastric adenocarcinoma with different histological subtypes: Cancer-specific survival in the United States

Chun-Lin Lin, Guang-Wei Zhu, Yong-Jian Huang, Wei Zheng, Shu-Gang Yang, Jian-Xin Ye
The First Affiliated Hospital of Fujian Medical University, Department of Gastrointestinal Surgery 2 Section, 20th, Chazhong Road, Fuzhou, Fujian, China

INTRODUCTION

Gastric cancer is one of the most common malignant tumors in the world. According to statistics from the International Agency for Research on Cancer, in 2012, there were approximately 952,000 new cases of gastric cancer and 723,000 deaths worldwide, ranking fifth in the incidence of malignant tumors and third in mortality rate. Although the incidence and mortality of gastric cancer are steadily declining and have been associated with a comparative decrease in Helicobacter pylori infection, differential trends such as an increase in gastric adenocarcinoma (GA), particularly gastric signet ring cell carcinoma (GSRC), have been observed.
been observed. As Henson\cite{7} reported, from 1937 to 2000, the incidence of SRC grew by more than 6.5% annually in the United States. Therefore, it is necessary for us to evaluate the prognosis of GSRC and generate a predictive model to aid in clinical decisions.

SRC is a subtype of adenocarcinoma that has a large vacuole and contains many mucins, pushing the nucleus to one side and resembling a signet ring. It can originate from any tissue, including the colon, breast, prostate, and gallbladder, but it is mostly associated with gastric cancer. For decades, GSRC has been reported as a type of histology with poor survival\cite{8,9,10} that seriously threatens human health. A retrospective study of 198 patients performed by Aguiar\cite{8} demonstrated that the GSRC type had the worst prognosis of all gastric cancer histology types, and Liu\cite{9} reported that the survival rate of 1464 GSRC patients was lower than that of patients with other types of gastric cancer. A study of 59 patients who underwent resection described by Guillaume\cite{10} indicated that GSRC patients had a worse prognosis than NGSRC patients. However, an increasing number of studies have confirmed that GSRC patients do not have a worse prognosis than patients with other histological types of gastric cancer. A study of 128 patients with GSRC enrolled to analyze prognosis, performed by Fang et al.\cite{11} indicated a better result for patients with the GSRC type during the early stage, than patients with other types of gastric cancer histology. Although the survival and histological type of gastric cancer have been assessed, most of the studies have been based in single centers and examined small samples, and their results are conflicting. In this study, we compared the prognostic outcomes of GA between GSRC patients and NGSRC patients based on sufficient and complete data. Furthermore, a nomogram was generated in our study to predict the survival of GA patients. The present study was conducted to compare survival between patients with different histological types and to develop a predictive model for GA.

**PATIENTS AND METHODS**

**Data selection**

The surveillance, epidemiology, and end results (SEER) database was launched by President Richard Nixon\cite{12} in 1973 and provides cancer data (e.g., treatment, primary site, tumor size, tumor stage, treatment regimen, pathological type, time of death, and cause of death) from the population-based registries of 18 sites that cover approximately 30% of the USA population. We used SEER*Stat software (version 8.3.5, http://seer.cancer.gov/seerstat/) to identify patients who were diagnosed with GA. To obtain enough data from the SEER database, the selection process was as follows [Figure 1]. Data regarding the histological type, sex, age, race, American Joint Committee on Cancer (AJCC, 7th Edition) stage, T stage, N stage, M stage, differentiation grade, tumor size, gastric cancer-specific death, vital status, and survival time were extracted from the SEER database (2004–2013) for further analysis. Gastric cancer-specific survival (GCSS) was defined as the time from diagnosis to death related to gastric carcinoma.

**Inclusion and exclusion criteria**

Inclusion criteria were as follows: the primary tumor site was limited to the stomach (C16.0–C16.9); the histology type was limited to adenocarcinoma, which was further categorized as SRC (ICD-03, 8490/3) or adenocarcinoma (ICD-03, 8140/3); the diagnosis was made between 2004 and 2013; and the diagnostic method was limited to surgery. The exclusion criterion was as follows: if the information of patient was incomplete (e.g., sex, age, race, AJCC T stage; N stage; M stage, differentiation grade, tumor size, or survival time). The time frame from 2004 to 2013 was selected because information on the AJCC TNM stage became available in 2004; meanwhile, patients diagnosed after 2013 were excluded to ensure a sufficient follow-up time. All the cases were staged based on the criteria in the 7th edition of the AJCC staging manual.
Statistical analysis
Statistical analysis was performed with IBM SPSS 24.0. GCSS was calculated with Kaplan–Meier and log-rank methods. To reduce the differences in variables between GSRC and NGSRC, propensity score matching (PSM)\(^{[12]}\) was conducted. Nine variables that could affect the selection of histology types were used to perform PSM through logistic regression. These variables were sex, age, race, AJCC T stage, N stage, differentiation grade, tumor size, and year of diagnosis. In the two groups, the patients were matched 1:1. After PSM, the clinical characteristics were verified by Chi-square test for significance. Univariate and multivariate analyses were performed with Cox regression to identify independent prognostic risk factors. All results are reported as the hazard ratios (HRs) and 95% confidence intervals (CIs). A \( P \) value <0.05 was considered statistically significant. The nomogram, concordance index (C-index), receiver operating characteristic (ROC) curve and calibration plot were generated using the RMS package\(^{[13]}\) in R version 3.5.3 (http://www.r-project.org/).

RESULTS

Demographics
A total of 10,031 patients with GA were included: 2934 had GSRC and 7097 had NGSRC. The median follow-up periods of GSRC and NGSRC patients were 67 months and 69 months, respectively. Patient clinical characteristics and tumor-related variables before PSM are summarized in Table 1. The two histological type groups differed significantly in nearly all clinical variables.

Propensity score matching
PSM generated 2152 patient pairs whose clinical characteristics and tumor-related variables after propensity score matching are shown in Table 1. All variables were perfectly balanced between the two groups. As shown in Tables 2 and 3, the 5-year GCSS rate of GA patients with GSRC was 46.1%, and that of patients with NGSRC was 46.7%; the difference was not significant by univariate \( (X^2 = 0.050, P = 0.824) \) and multivariate (GSRC group as a ref., HR = 0.988, 95% CI 0.912–1.070; \( P = 0.759) \) analyses. The 1-, 2-, 3-, 4-, and 5-year GCSS rates are given in Table 2. Sex, differentiation grade, age, race, AJCC T stage, N stage, M stage, and tumor size were identified as significant risk factors for poor survival by the univariate analysis and therefore included in the multivariate Cox regression analysis. Ultimately, the multivariate Cox regression analysis revealed that tumor size, age, race, AJCC T stage and N stage (all \( P < 0.001) \) were independent prognostic factors (Table 3, all \( P < 0.05) \).

Subgroup analysis
We further analyzed the effect of histological type on the long-term (more than 5 years) GCSS rate at each TNM stage, including stage I, II, III, and IV. We found that GSRC patients had a similar long-term GCSS rate to NGSRC patients in each TNM stage \( (P > 0.05) \). Histological...
type was further validated as not an independent prognostic factor in patients with stage I (GSRC as a reference, HR = 0.996, 95% CI 0.790–1.256, X² = 0.001, P = 0.975), stage II (GSRC as a reference, HR = 0.998, 95% CI 0.848–1.176, X² < 0.001, P = 0.985), stage III (GSRC as a reference, HR = 1.013, 95% CI 0.904–1.134, X² = 0.051, P = 0.822), and stage IV (GSRC as a reference, HR = 0.839, 95% CI 0.682–1.034, X² = 2.892, P = 0.089) [Figure 2].

Nomogram of GCSS for GA patients
The survival nomogram that incorporated all significant independent risk factors for GCSS in the training cohort is shown in Figure 3. The nomogram identified the TNM stage as the largest contributor to GCSS, followed by T stage, N stage, age, differentiation grade, race, tumor size, and histological type. Each variable was assigned a score on a point scale. The 3- and 5-year GCSS probability could be predicted by calculating the total score, locating it on the total point scale, and then drawing a line down on the GCSS scale. The C-index for GCSS prediction was 0.720 in the training cohort. The ROC curve analysis and calibration plot for the probability of 3- and 5-year GCSS showed an optimal model between the actual observation and prediction by the nomogram [Figure 4a-d].

Validation of predictive accuracy of the nomogram plot for GCSS
In the validation cohort, the C-index of the nomogram for predicting GCSS was 0.724, and the ROC curve analysis and calibration plot also showed an optimal model of probability between the observation and prediction in 3- and 5-year GCSS [Figure 4e and f].

DISCUSSION
We conducted this study to compare the prognosis of GSRC patients to that of NGSRC patients and constructed a nomogram to predict survival for patients with GA. Moreover, PSM was performed to reduce bias and to make a more reasonable comparison between the two groups.

The 1-, 3-, and 5-year GSRC-specific survival rates were 74.5%, 51.9%, and 46.1%, respectively, which were not worse than those of non-signet ring cell cancer (NSRC) (P > 0.05). Furthermore, we studied different prognoses between GSRC and NGSRC in each tumor stage. The results suggested that GSRC did not confer significantly worse survival. Compared with NGSRC patients, GSRC patients in different tumor stages (stages I, II, III, and IV) experienced a similar 5-year cancer-specific survival rate (all P < 0.05).

Table 3: Univariate and multivariate Cox analyses of the determinants of gastric cancer-specific survival of patients with gastric adenocarcinoma

| Variable         | No. of patients | 5-year GCSS (%) | Univariate Log-rank text X² | P | Multivariate HR | 95% CI | P |
|------------------|-----------------|-----------------|-----------------------------|---|-----------------|--------|---|
| Histology type   |                 |                 |                             |   |                 |        |   |
| SRC              | 2152            | 46.1            | 0.050                       | 0.824 | 1               |        |   |
| NSRC             | 2152            | 46.7            |                            |     | 0.980           | Reference |   |
| Age              |                 |                 |                             |   |                 |        |   |
| <60              | 1522            | 50.1            | 40.447                      | <0.001 | 1               |        |   |
| >=60             | 2782            | 44.5            |                            |     | 1.509           | 1.382-1.647 | <0.001 |
| Race             |                 |                 |                             |   |                 |        |   |
| White            | 3034            | 43.6            | 33.836                      | <0.001 | 1               |        |   |
| Black            | 424             | 49.8            |                            |     | 0.983           | 0.852-1.35 | 0.815  |
| Other            | 846             | 54.8            |                            |     | 0.769           | 0.687-0.860 | <0.001 |
| TNM stage        |                 |                 |                             |   |                 |        |   |
| Stage I          | 1182            | 79.1            | 1161.471                    | <0.001 | 1               |        |   |
| Stage II         | 1041            | 49.8            |                            |     | 1.428           | 1.121-1.820 | 0.004  |
| Stage III        | 1670            | 29.3            |                            |     | 1.660           | 1.228-2.243 | 0.001  |
| Stage IV         | 411             | 13.9            |                            |     | 3.137           | 2.312-4.256 | <0.001 |
| T stage          |                 |                 |                             |   |                 |        |   |
| Stage T1         | 746             | 32.5            | 680.632                     | <0.001 | 1               |        |   |
| Stage T2         | 1500            | 48.5            |                            |     | 1.971           | 1.549-2.507 | <0.001 |
| Stage T3         | 1340            | 34.9            |                            |     | 2.511           | 1.922-3.279 | <0.001 |
| Stage T4         | 718             | 25.2            |                            |     | 3.198           | 2.418-4.228 | <0.001 |
| N Stage          |                 |                 |                             |   |                 |        |   |
| Stage N0         | 1418            | 73.6            | 887.227                     | <0.001 | 1               |        |   |
| Stage N1         | 657             | 46.3            |                            |     | 1.472           | 1.223-1.771 | <0.001 |
| Stage N2         | 780             | 38.7            |                            |     | 1.531           | 1.252-1.873 | <0.001 |
| Stage N3         | 1449            | 24.2            |                            |     | 2.179           | 1.754-2.708 | <0.001 |
| M stage          |                 |                 |                             |   |                 |        |   |
| Stage M0         | 3893            | 49.9            | 454.157                     | <0.001 | 1               |        |   |
| Stage M1         | 411             | 13.9            |                            |     | 1.106           | 1.012-1.209 | 0.026  |
| Tumor size       |                 |                 |                             |   |                 |        |   |
| <=5 cm           | 2578            | 56.2            | 314.964                     | <0.001 | 1               |        |   |
| >5 cm            | 1726            | 31.9            |                            |     | 1.066           | 1.002-1.109 | 0.026  |

GCSS: Gastric cancer-specific survival, SRC: Signet ring cell, NSRC: Non-signet ring cell, HR: Hazard ratio

Table 2: Comparison of GCSS (%) between GSRC and NGSRC patients post surgery

| Year      | GCSS (%) GSRC (n=2152) | GCSS (%) NGSRC (n=2152) | X² | P |
|-----------|-------------------------|--------------------------|----|---|
| 1-year    | 74.5                    | 74.0                     | 0.207 | 0.649 |
| 2-year    | 59.3                    | 59.8                     | 0.016 | 0.899 |
| 3-year    | 51.9                    | 51.7                     | 0.036 | 0.850 |
| 4-year    | 48.2                    | 48.8                     | 0.037 | 0.847 |
| 5-year    | 46.1                    | 46.7                     | 0.050 | 0.824 |

GCSS: Gastric cancer-specific survival, GSRC: Gastric signet ring cell carcinoma, NGSRC: Gastric non-signet ring cell carcinoma
In terms of the prognosis of GSRC, Jiang reported that GSRC is associated with a better prognosis than NGSRC in the early stage of GA, but the two showed similar survival outcomes in the advanced stage. Ha reported that in the early stage, GSRC had a better prognosis than NSRC. However, some studies have demonstrated that in the early stage, the survival outcomes are similar between GSRC and NGSRC. Concerning GSRC in the advanced stage, some studies have shown similar survival outcomes to those of NGSRC. Li showed that GSRC had more lymph node metastasis, deeper tumor invasion, and intraperitoneal dissemination than NGSRC, leading to a worse prognosis. The same study concluded that the prognosis was comparable in the early and advanced stages and that GSRC patients had no worse survival outcomes than NGSRC patients.

In our study, before PSM, 1527 (52%) patients with GSRC were in stage III or IV, while only 2599 (37%) patients with NGSRC were in stage III or IV. This shows that GSRC patients usually present at a later stage overall, leading, in general, to a worse prognosis. If the prognosis was compared between the two groups directly without matching, the results were insignificant. In contrast to previous studies, our study showed that GSRC patients had a similar prognosis to NGSRC patients, and the major reason for this difference was maybe due to selection bias. Most of the previous studies were retrospective and vast differences existed between patients. For these reasons, PSM was used to maintain the balance in variables related to survival between the two groups in our study. Therefore, we confidently believe that patients with GSRC have a similar prognosis to those with other kinds of adenocarcinoma if the patients have the same characteristics.
Currently, the AJCC TNM stage is commonly used to predict the prognosis of cancer patients. However, whether additional variables are important risk factors for individual patients is unknown. Thus, we constructed a nomogram to comprehensively consider the prognosis. Nomograms have been proven to be more accurate than the conventional AJCC TNM stage for the prediction of survival in many cancers.\textsuperscript{20,21} Hence, a nomogram for GA patients after gastrectomy was constructed by combining the TNM stage and other important risk factors. The nomogram showed a good predictive ability for prognosis. This finding was supported by the calibration curves, ROC curve analyses, and C-index values (0.720 and 0.724 for the training cohort and validation cohort, respectively).

Nevertheless, this study has some limitations. First, information on the specific surgical procedures performed on the patients enrolled was lacking, which may have affected the prognosis. Patients with gastric cancer can undergo noncurative surgeries, including diagnostic
laparoscopy and feeding jejunostomy. To exclude these patients, this study enrolled only patients who underwent surgery and whose number of lymph nodes swept was clearly documented. On the premise of a guarantee for patients to undergo curative surgery, laparoscopic surgery or open surgery has little effect on patients.\(^{[22,23]}\) Second, all the data were derived from the SEER database, which lacks information on chemotherapy and radiation therapy. Data obtained from the SEER registry and Medicare insurance claim documents should be combined to analyze chemotherapy and radiation therapy related information. While the Medicare program provides health insurance only for the population aged more than 65 years in the United States, these patients do not represent all American patients with gastric cancer. Therefore, in terms of GCSS, an analysis of all patients may be more accurate.

**CONCLUSION**

In conclusion, patients with GSRC had a similar prognosis to those with NGSRC. These findings suggest that GSRC should not be regarded as a distinct type of GA. Moreover, the nomogram constructed in our study can be used to predict the prognosis of GA patients after gastrectomy.

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**Conflicts of interest**

There are no conflicts of interest.

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