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Characteristics of long-term gastric cancer survivors: a population-based SEER analysis

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analysis

By

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The Bachelor of Science in Agriculture
China Agricultural University
2017

Faculty Thesis Advisor: Kevin C. Ward, PhD, MPH

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Abstract

Characteristics of long-term gastric cancer survivors: a population-based SEER analysis

By Jiayi Wu

Background: Gastric cancer (GC) remains the fifth most commonly diagnosed cancer and the third leading cause of cancer death worldwide. Although gastric cancer prognosis remains poor, individual survival time is quite variable. Our aim was to identify demographic, tumor and treatment characteristics associated with long-term overall survival following a gastric cancer diagnosis.

Methods: A population-based retrospective cohort study was conducted using data from patients diagnosed with gastric cancer between 2005 and 2012 registered in the Surveillance, Epidemiology, and End Results (SEER) database (N=43,749). Long-term overall survival was defined as overall survival time ≥ 3 years in our study. Logistic regression analyses was used to estimate the association of each characteristic with long-term survival among all GC patients and patients with advanced stage disease.

Results: A total of 10,715 (24%) patients survived 3 years or longer. Age, race, marital status, urban area, neighborhood poverty, subsite, histological grade, tumor stage and treatment with gastrectomy, radiation and chemotherapy were statistically and independently associated with long-term overall survival following a gastric cancer diagnosis. Age >75 years relative to age <45, married relative to unmarried, urban counties relative to metropolitan areas (OR=0.63, 95% CI=0.45-0.89), overlapping lesion of stomach (OR=0.63, 95% CI=0.45-0.89) relative to cardia, histological grade, and receipt of treatments of gastrectomy, radiation and chemotherapy remained independently and significantly associated with long-term overall survival among GC patients diagnosed with advanced disease.

Conclusion: Our results suggest that long-term gastric cancer survivors have distinct demographic, tumor and treatment characteristics. Age, marital status, urban area, tumor site, histological grade and treatment characteristics were independently and significantly associated with long-term survival among GC patients diagnosed with advanced disease.

Key words: SEER, gastric cancer, long-term survival

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Chapter I: Background

1. Overview of Gastric cancer

Gastric cancer (GC) remains the fifth most commonly diagnosed cancer and the third leading cause of death in the world (1). There were over 1 million new cases and estimated 783,000 deaths in 2018. Incidence is higher in men than women, and higher among other races and ethnicities compared with non-Hispanic Whites. Age, diet, smoking status, gastric disease, tobacco use and Helicobacter pylori (H. pylori) are major risk factors of GC (2, 3). In East Asia, distal or antral gastric cancers are more common and associated with H. pylori infection, alcohol use, high-salt diet and low fruit and vegetable consumption. Proximal stomach (cardia) tumors are more common in western countries and associated with obesity, reflux and Barrett's esophagus (4, 5). In the United States, the estimated numbers of new cases and deaths in 2018 are 26,240 and 10,800, respectively, accounting for 1.5% of all new cancer cases and 1.8% of all cancer deaths. Although GC incidence and mortality are declining, gastric cancer survival remains relatively poor. The five-year survival in the U.S. population from 2008 to 2014 was 31.0% (6). The costs of gastric cancer and gastroesophageal junction cancers (GEJCs) are generally higher than other cancers, even than some of the more common cancers. In the US, the average annual cost per patient was 46,501 USD (1998-2003), compared with 29,609 USD and 35,672 USD for colorectal and lung cancer, respectively (7).

2. Factors associated with gastric cancer survival

Many factors have been investigated in relation to GC survival, including demographics, tumor morphology and treatment.

Demographic factors associated with GC survival

Gastric cancer outcomes vary with age. Overall, elderly patients are associated with worse gastric cancer-specific survival (GCSS). In a SEER population-based study among GC patients with surgery, Peng Song and collegues compared with the middle age group (50-59 years), individuals with younger age (30-39) had the lowest rate of cancer-specific death (HR=0.78, 95% CI=0.62, 0.99) and the eldest group had the highest rate (HR=2.17, 95% CI: 1.91-2.47) (8). A separate study by Xinxing Li and colleagues also suggested that being younger than 60 years was associated with better GCSS among patients with distant metastasis (HR=0.81, 95% CI: 0.77-0.84) (9).

Asian race has been consistently reported to be associated with favorable GC survival compared with other races and ethnicities (10-12). However, a study by Luyimbazi D using SEER dataset suggested that although racial disparities existed in survival from the time of diagnosis, the difference of conditional survival between Asians, White and Blacks diminished after 5 years of survival. Race has less impact the longer patients survived (13).

Socioeconomic status (SES), insurance status and marital status indicate the social support received by gastric cancer patients. High socioeconomic status (SES) was associated with longer gastric and gastroesophageal cancer survival in the California population (14). According to a study of Wu CC, high individual SES was associated with lower probability of death in first five years (OR=0.32, 95% CI: 0.17-0.61) among patients aged less than 65 years in Taiwan, while the significant association was not observed among patients older than 65 (15). Patients with higher individual SES may have more access to earlier detection methods and multimodal treatment related to better survival (16). Differences in survival were not shown to be significant when using neighborhood SES which represents community-income status among Taiwan population in Wu CC's Study (15). However, the association between disadvantaged neighborhoods SES and worse cancer outcome was suggested in other population-based studies (17, 18). The spouse of married patients may provide social support by encouraging patients to have surgery and other

treatments, and may also help to relieve distress and depression following a diagnosis of cancer (19). Married patients were found to be more likely to undergo surgery and have a lower rate of metastasis at diagnosis. Furthermore, according to a SEER study conducted by Jin JJ, compared with patients who were married, patients of other marital status had 20-30 percent higher rate of cancer specific death (20, 21).

Tumor characteristics associated with GC survival

Cancer stage based on the AJCC TNM staging system is an independent predictor for long-term gastric cancer survival (22, 23). The TNM Staging System is based on the extent of the tumor (T), the extent of spread to the regional lymph nodes (N), and the presence of metastasis (M) (24). Several studies have also reported the important role of lymph node involvement and resection on the prognosis of GC survival. In addition to the absolute number of metastatic lymph nodes, the number of lymph nodes removed (25, 26) and the metastatic lymph node ratio (27, 28) are also associated with prognosis.

It is generally recognized that GC of cardia has different clinicopathologic features and is associated with worse survival compared with non-cardia GC (29-31). However, several studies have suggested that the poorer survival observed among patients with cancer of cardia could be explained by the fact that these patients have a greater tendency to be diagnosed at advanced stage. The survival difference between cardia and non-cardia GC was not significant when stratified by stage (32).

Gastric cancer has two typical histological types (33). Diffuse and intestinal types of GC are different in epidemiology, pathogenesis, biological features and clinical performance. It has been widely reported that GC with a poorer differentiated histology or diffuse type is associated with worse prognosis (34). Based on a meta-analysis conducted by Petrelli F, GC patients with a

diffuse histology had a worse prognosis compared with the intestinal type in all subgroups stratified by stage or exposure to adjuvant therapy (overall HR=1.23; 95% CI: 1.17–1.29) (35).

Treatment factors associated with GC survival

The primary curative treatment for GC is radical surgery (36), but treatment depends on the stage. Early-stage GC patients are recommended to undergo radical surgery followed by chemotherapy (37). For GC, surgery is regarded to be high-risk, with morbidity documented as high as 39% (38). Other treatments including neoadjuvant chemotherapy, radiotherapy and molecular-targeted therapies can be performed to improve the prognosis of GC, especially with advanced disease. Previous clinical trials and population-based cohort studies have demonstrated the effect of surgery on the improvement of advanced GC survival (39-41). Patient characteristics associated with favorable outcomes following surgery has also been investigated by some studies (42). Male gender and obesity have been associated with increased rates of complication (43). A study based on the Surveillance Epidemiology of End Results (SEER) database conducted by Seyedin S showed that, treatment with surgery followed by radiotherapy and chemotherapy (SRC) was associated with the best outcome among stage II, III and IV GC patients. It further showed that treatment with surgery alone had the most favorable prognosis among stage I GC patients (44). Another SEER study conducted by Shridhar R reported that surgery and/or radiation were associated with better over survival of metastatic GC (HR of surgery vs none =0.565 95% CI=0.495-0.645; HR of radiation vs none =0.882, 95% CI=0.781-0.995). In the stratified analysis, a significant association between radiation and overall survival was only found among patients with metastatic GC patients undergoing surgery (HR for surgery group=0.733, 95% CI: 0.592-0.907; HR for nonsurgical patients=0.987, 95% CI: 0.847-1.147) (41).

3. Long-term survival of gastric cancer

Although gastric cancer prognosis remains poor, individual survival time is quite variable. Some patients with advanced stage disease could survive well beyond five years. Understanding the characteristics of long-term survivors may provide useful information for both patients and health caregivers (45). Some studies conducted long-term gastric cancer survival analysis using individual survival time as the outcome (46-50). According to a population-based study using dataset of California Cancer Registry (CCR) from 1988 to 2005 , age(HR=1.009), female gender (HR=0.924), race (HR of Asian/Pacific Islander=0.805), highest SES quintile (HR=0.911), anatomic site (HR of non-cardia site compared with cardia=0.900), stage (HR of localized compared with remote=0.201, HR of regional compared with remote=0.528), histology type (HR of intestinal compared with diffuse is 0.742), surgery (HR=0.337) chemotherapy (HR=0.561) and radiation (HR=0.802) were all significantly associated with GC survival (14).

Only a few studies have categorized GC survival time into groups such that the characteristics of long-term gastric survivors could be compared with others. Kadowaki S, et.al, used 514 patients with metastatic gastric cancer after systemic chemotherapy to investigate the clinical characteristics of long-term survivors (survival time beyond 2 years), and found that performance status, previous gastrectomy single metastatic site and normal alkaline phosphatase levels were associated with long-term survival (51). Hochwald SN, et.al, observed that gender, race, tumor stage, nodal status, tumor location, median number of positive nodes and gastrectomy were differently distributed between long-term survivors (cancer specific survival beyond 5 years) and short-term survivors based on 434 gastric cancer patients (52).

To our knowledge, no studies have been conducted to investigate the characteristics of long-term GC survivors by categorizing the survival time into groups based on a national population-based dataset. To address the limitations in the current literature, we used data from the Surveillance, Epidemiology, and End Results (SEER) database to identify the demographic, tumor, and treatment characteristics of long-term gastric cancer survivors.

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Chapter II: Manuscript

Characteristics of long-term gastric cancer survivors: a population-based SEER analysis

By Jiayi Wu

Abstract

Background: Gastric cancer (GC) remains the fifth most commonly diagnosed cancer and the third leading cause of cancer death worldwide. Although gastric cancer prognosis remains poor, individual survival time is quite variable. Our aim was to identify demography, tumor and treatment characteristics associated with long-term overall survival following a gastric cancer diagnosis.

Methods: A population-based retrospective cohort study was conducted using data from patients diagnosed with gastric cancer between 2005 and 2012 registered in the Surveillance, Epidemiology, and End Results (SEER) database (N=43,749). Long-term overall survival was defined as overall survival time ≥ 3 years in our study. Logistic regression analyses was used to estimate the association of each characteristic with long-term survival among all GC patients and patients with advanced stage disease.

Results: A total of 10,715 (24%) patients survived 3 years or longer. Age, race, marital status, urban area, neighborhood poverty, subsite, histological grade, tumor stage and treatment with gastrectomy, radiation and chemotherapy were statistically and independently associated with long-term overall survival following a gastric cancer diagnosis. Age >75 years relative to age <45, married relative to unmarried, urban counties relative to metropolitan areas (OR=0.63, 95% CI=0.45-0.89), overlapping lesion of stomach (OR=0.63, 95% CI=0.45-0.89) relative to cardia, histological grade, and receipt of treatments of gastrectomy, radiation and chemotherapy

remained independently and significantly associated with long-term overall survival among GC patients diagnosed with advanced disease.

Conclusion: Our results suggest that long-term gastric cancer survivors have distinct demographic, tumor and treatment characteristics. Age, marital status, urban area, tumor site, histological grade and treatment characteristics were independently and significantly associated with long-term survival among GC patients diagnosed with advanced disease.

Key words: SEER, gastric cancer, long-term survival

Introduction

Gastric cancer (GC) remains the fifth most commonly diagnosed cancer and the third leading cause of death worldwide (1). Globally, there were over 1 million new cases and estimated 783,000 deaths in 2018. In the United States, the estimated number of new cases and deaths for 2018 were 26,240 and 10,800, respectively, accounting for 1.5% of all new cancer cases and 1.8% of all cancer deaths. Although GC incidence and mortality are declining, gastric cancer survival remains relatively poor. The five-year survival in the U.S. population from 2008 to 2014 was 31.0% (2).

Several factors have been investigated in relation to GC survival, including demographics, tumor morphology and treatment. For demographic characteristics, being younger than 60 years was associated with better cancer specific survival (CSS) among patients with distant metastasis (3). Asian or Pacific Islander race and high socioeconomic status (SES) were associated with longer gastric and gastroesophageal cancer survival in the California population (4). However, other studies have suggested that the association between race and conditional survival diminished after the first few years and longer survival after curative surgery of gastric cancer was found to not differ by race (5). Individual SES has been commonly reported to have an association with GC mortality, but the association of neighborhood SES is arguable (6). Insurance is often used as a proxy measure of SES and is related to access to healthcare. Private insurance but not government insurance has been observed to be associated with overall GC survival in a population-based study (7). Marital status is one commonly used measure of social support for cancer patients, and has been reported to be associated with GC survival (8). For tumor characteristics, cancer stage is an independent factor for long-term gastric cancer survival as it is for most cancers (9). Patients with carcinoma of the cardia and diffuse-type histology were found to be have worse survival (4. 10). Finally, prior clinical trials and population-based cohort studies have demonstrated the effect

of surgery and radiation on the improvement of survival among subjects with gastric cancer (11, 12).

Although gastric cancer prognosis remains poor overall, individual survival time is still quite variable. Some patients with advanced disease survive well beyond five years. Understanding the characteristics of long-term survivors may provide useful information for both patients and health caregivers (13). Many studies conduct long-term gastric cancer survival analysis using individual survival time as the outcome. However, the predictors of individual survival time may differ between long-term survivors and non-long-term survivors. Only a few studies have categorized GC survival time into groups such that the characteristics of long-term gastric survivors could be compared with others. Kadowaki, et.al, used 514 patients with metastatic gastric cancer after systemic chemotherapy to investigate the clinical characteristics of long-term survivors (survival time beyond 2 years). This study found that performance status, previous gastrectomy single metastatic site and normal alkaline phosphatase levels were associated with long-term survival (14). Hochwald SN, et.al, observed that gender, race, tumor stage, nodal status, tumor location, median number of positive nodes and gastrectomy were differently distributed between long-term survivors (cancer specific survival beyond 5 years) and short-term survivors based on 434 gastric cancer patients (15). To our knowledge, no studies have been conducted to investigate the characteristics of long-term GC survivors by categorizing the survival time into groups based on a national population-based dataset. This could only be done properly in the presence of datasets with complete follow-up.

To address the limitations in the current literature, we used data from the Surveillance, Epidemiology, and End Results (SEER) database to identify the demographic, tumor, and treatment characteristics of long-term gastric cancer survivors. SEER collects data on patient demographics, primary tumor sites, tumor morphology, stage at diagnosis, and first course of treatment, and then accurately and completely follow patients for vital status and cause of death.

Methods

Study population

This was a retrospective cohort study of patients from the population-based SEER cancer registries. The data for this analysis were obtained from the SEER 18 registries research database with data through diagnosis year 2015 within the following areas: San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, and Greater Georgia (16). This database had a large geographic coverage, including approximately 27.8% of the U.S. population.

For this study, we identified patients with stomach cancer (ICD-O-3 codes: C16.0- C16.9) diagnosed between 2005 and 2012, and then followed through December 31, 2015. Patients with lymphomas, sarcomas and carcinoid tumors were excluded from the study population, because these tumors used different staging systems. Nine hundred and thirty-seven (2.10%) patients were lost to follow-up within first 3 years after diagnosis and have been excluded. Patients with missing data from any variable except sub-site were excluded from multivariate analysis. (Figure.1)

Patient characteristics

All patient characteristics were collected via SEER and characterized for analysis. Race in the cancer registry is collected from medical records. We defined race using categories of White, Black, American Indian/Alaskan Native, Asian/Pacific Islander and others. Marital status at diagnosis was dichotomized as married and unmarried (including single, separated, divorced, widowed, and unmarried or domestic partner), and insurance status was categorized as uninsured,

any Medicaid, and insured (including private insurance, Medicare and no specifics). We used persons below poverty, which was calculated using the American Community Survey (ACS) 5-year files to indicate neighborhood poverty status and estimate the neighborhood SES linked to the county of the patients. Counties with less than 6 percent of the population below poverty were defined as low neighborhood poverty, and counties with more than 20 percent of the population below poverty were defined as high neighborhood poverty. Geographic area was categorized as metropolitan, urban, and rural using Rural-Urban Continuum Codes (2013) linked to the county of patients. Tumor stage was determined based on a SEER variable that follows the definition from the AJCC (American Joint Committee on Cancer staging system) 6th edition TNM cancer staging system for gastric cancer, but combines clinical and pathological information together. Topography (sub site of tumor) was coded according to specific ICD-O-3 codes. Therapy data, including radiation, chemotherapy, and site-specific surgery status, were also identified from the SEER database.

Outcome

Overall Survival time was obtained from the SEER database. After excluding the small percentage of patients lost to follow-up, patients were categorized into two outcome groups based on overall survival time. Characteristics of the patients who survived for 3 years or longer (long-term survivors) were compared to patients who survived less than 3 years.

Statistical Analysis

Demographic, tumor and treatment characteristics by short-term (overall survival time <3 years) and long-term survival (overall survival time ≥3 years) were summarized using descriptive statistics. The difference in the distributions of these factors between the two groups were compared using chi-square test. Adjusted odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated to estimate the association of each characteristic with long-term overall

survival using multivariate logistic regression model. Analysis were repeated among patients with stage IV cancer. Statistical significance was set at a p-value of 0.05 or a 95% CI that excluded 1.0. All analyses were performed using SAS software, Version 9.4.

Results

A total of 43,749 patients diagnosed with gastric cancer during the period of 2005 to 2012 were included in this study. Twenty-four percent survived 3 years or longer and were defined as long-term survivors. Thirty-five percent of GC patients were diagnosed at age of 60-74. The majority of patients were White (71%) and male (63%). Most patients were from metropolitan areas (90%) and counties with poverty between 6 and 20 percent (85%). The highest proportion of patients had tumors located in the cardia (31%). Forty percent of patients were diagnosed with advanced stage. Less than half of the patients received gastrectomy, radiation or chemotherapy, when examined individually.

Demographic, tumor and treatment characteristics of the two groups are presented in Table 1. A higher proportion of long-term survivors were in the middle age groups (45-74 years old) while a higher proportion of short-term survivors were over age 75. Survival was generally comparable in individuals less than 45 years of age. Compared with short-term survivors, the proportion of Asian or Pacific Islander was higher among long-term survivors. Long-term survivors were also more likely to be married, have Medicare or private insurance and have their tumor located at a distal site. The proportions of lower histological grade were higher among long-term survivors compared with short-term survivors. Stage was of course the strongest predictor of survival with over 53% of long-term survivors presenting with stage I disease compared to only 15% of short-term survivors. Long-term survivors were also more likely to have any type of gastrectomy and/or radiation.

All of the demographic, tumor and treatment characteristics except gender and insurance status remained significantly associated with long-term overall survival after adjusting other variables (Table 2). Insurance status was dropped from the multivariate model. Observations with missing values of race, marital status, urban area, neighborhood poverty and stage were excluded from multivariate analysis.

In multivariate models, younger age was associated with favorable survival. Compared with patients with age of 60-74, patients younger than 45 had 45% higher odds of long-term survival, while patients aged 85 or older had 64% lower odds of being long-term survivors. Asian or Pacific Islander race, compared to Whites, and females were more likely to be long-term survivors. Higher area-based SES, proximity to metropolitan areas and family support were all associated with favorable survival outcome. Married GC patients had 27% higher odds to survive 3 years or longer compared with unmarried patients. The odds ratios of long-term survival among patients living in urban counties and rural counties were 0.87 and 0.70, respectively, compared with those living in metropolitan counties. Finally, patients living in neighborhoods with low poverty had 60 percent higher odds to survive longer than 3 years than those living in neighborhoods with high poverty.

Patients with tumors at body/curvatures (OR=1.28) and gastric antrum/pylorus of stomach (OR=1.16) were more likely to survive 3 years or longer compared with cancers of cardia. Stage suggested the strongest association with long-term survival. The odds of long-term survival among patients with tumor at stage I were approximately three times the odds among patients at stage II, and around 14 times the odds among patients at stage IV. After controlling for stage and other variables, higher histological grade was significantly associated with worse survival. Treatments with gastrectomy, radiation and chemotherapy were all significantly associated with higher probability of surviving 3 years or longer, and partial or subtotal gastrectomy suggested the strongest association with long-term survival among the treatments (OR=7.97).

Forty-three percent of GC patients included in the multivariate analyses were diagnosed with advanced disease (stage IV). The associations of characteristics with long-term survival of these patients are presented in Table 3. For patients with advanced disease, those older than 75 still have lower odds of long-term survival compared with middle age group (60-74). Married patients have 20 percent higher odds of long-term survival among stage IV diagnosed patients. Residents of urban counties at diagnosis remained significantly associated with lower probability to survive 3 years or longer compared with residents of metropolitan counties (OR=0.63). Non-cardia subsites suggested worse long-term survival than cardia among stage IV patients, however, only patients with tumors with an overlapping lesion of the stomach and with unknown subsites were significantly associated with survival. Patients with grade III and grade IV tumors suggested 51 and 64 percent lower odds for surviving long term relative to grade I, respectively. All treatment modalities, including gastrectomy, radiation and chemotherapy, remained significantly associated with long-term survival when restricting the analysis to GC patients with advanced stage.

Discussion

Gastric cancer is known to have poor survival. In this study population, only 24 percent of patients survived 3 years or longer. This study investigated key demographic, tumor and therapy characteristics of these long-term survivors, with the goal of informing gastric cancer prognosis and clinical management.

Younger age, Asian or Pacific Islander, and female gender were associated with a long-term survival, which was consistent with previous population-based studies using survival analysis (3, 4). Several previous studies did not find a significant association of GC survival with age, gender and race (5, 14). One explanation for this inconsistency is that these studies had much smaller sample sizes and may have been underpowered. We also investigated the influence of social

support on survival. Married patients, who are typically more likely to have support from the spouse both physically and psychologically, were more likely to be long-term survivors (8).

Previous studies have found that insurance was associated with the receipt of treatment among GC patients (17). In our study, long-term survivors had a higher proportion of Medicare or private insurance, however, the association was not significant after controlling treatments variables and other covariates. Because detailed information regarding insurance was not available, it is difficult to investigate the specific benefits of insurance for GC survival in this study. In addition, more than 12,000 observations had unknown insurance status, and so, we dropped the insurance variable from our multivariate logistic model.

Individual socioeconomic status (SES) is not available from SEER. Neighborhood poverty and neighborhood area are area-based measures of SES and the accessibility to healthcare resources. A review analysis found that 23 of 25 studies reported significant associations between at least one neighborhood measure of SES and health, controlling for individual SES (18). Neighborhoods with a high proportion of poverty and less urbanization may have a worse environment, higher prevalence of unhealthy behavior and poorer attitudes to health (6). The significant associations found in our study suggest the importance of the neighborhood environment.

Tumor biology also has strong association with survival. After excluding lymphomas, sarcomas and carcinoid tumors which are not staged or treated in the same fashion as other gastric cancers, most GC patients (>70%) had adenocarcinoma. Histological type was not included in this analysis because the small sample size of other types aside from adenocarcinoma. Previous studies reported that cancers of the cardia have different clinicopathologic features from cancers of non-cardia stomach and are associated with poorer survival (19-20). A recent study in China found that the prognosis was not different between cardia and non-cardia for specific stage after

R0 resection (21). In our study, compared with cardia, body/curvatures and antrum/pylorus of stomach were observed to be associated with better survival outcomes. Cancers of the proximal gastric third (cardia and fundus) are related to late presentation, leading to advanced tumor stage at diagnosis. Our study found that proximal gastric cancer had worse prognosis after controlling for stage. This may be explained by the worse prognosis of surgery with proximal gastric cancer, which has been shown to have higher risks of mortality and complications, especially anastomotic leakage (22, 23). We also observed that patients with unknown subsites had a lower probability to survive long term compared with cancers at the cardia. For patients without specific subsites, a high probability of inadequate screening or pathology may cause the lack of appropriate treatments.

Nearly half of the patients in our study were diagnosed at an advanced stage, which is a known major cause of poor survival of gastric cancer. Less than 6 percent of patients with advanced stage GC survived 3 year or longer. After controlling for all other variables, only age, marital status, urban area, tumor site, histological grade and treatment characteristics remained significantly associated with survival among advanced GC patients. Patients living in urban areas were more likely to die within 3 years compared with metropolitan areas after controlling for neighborhood poverty. However, the survival difference between patients living in metro counties and rural counties was no more significant for GC patients diagnosed at advanced disease.

The most surprising result was that for tumor sites. When restricting to stage IV, cardia cancer had the trend of having the best prognosis, although the associations were only significant when compared with tumors at overlapping lesions or unknown subsites. This result also suggests that a major reason for unfavorable prognosis of these cancers is that cardia cancer is more likely to be diagnosed at an advanced stage (22). This study also found that each treatment modality had significant improvement of long-term GC survival even for patients diagnosed at an advanced stage.

Strengths and limitations

We used logistic regression analysis to investigate the characteristics of long-term GC survivors based on a large population with complete follow-up. Because of the poor survival of gastric cancer, this could only be done using a population-based dataset to include sufficient long-term GC survivors, especially for those diagnosed at advanced stage. We used the SEER dataset with the strength of a large sample size, rigorous ascertainment of deaths and extensive quality control of the variables captured by the registries. In addition, we include different demographic variables to investigate the importance of social support on GC survival.

The major limitation was caused by the limited information on individual SES, behavior factors, personal and family health history, detailed treatment and other risk factors of death among GC patients from SEER dataset (13). Potential confounders were possible to exist. Selection bias could also be introduced when excluding a large number of observations with missing data. Unlike survival analysis, we could not censor patients lost to follow-up when using logistic regression analysis. However, there was only 2 percent of the total study population excluded from this study because of the reason above; therefore, the influence should be limited.

Conclusion

The survival of gastric cancer remains poor. Long-term gastric cancer survivors had distinct demographic, tumor and treatment characteristics. Based on a large population from the SEER dataset, measures of social support were significantly associated with survival. Age, marital status, urban area, tumor site, histological grade and treatment characteristics remained significantly associated with long-term survival among advanced GC patients.

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Tables

Table 1. Characteristics of gastric cancer patients by survival time (N=43,749)

Covariate	Level	Total	Short-term N=33034	Long-term[*] N=10715	P-value[**]
Age	<45 years	2467 (5.64)	1850 (5.60)	617 (5.76)	**<.001**
	45-59 years	8812 (20.14)	6305 (19.09)	2507 (23.40)	
	60-74 years	15636 (35.74)	11097 (33.59)	4539 (42.36)	
	75-84 years	11227 (25.66)	8848 (26.78)	2379 (22.20)	
	85+ years	5607 (12.82)	4934 (14.94)	673 (6.28)	
Race	White	31184 (71.28)	23975 (72.58)	7209 (67.28)	**<.001**
	Black	5877 (13.43)	4621 (13.99)	1256 (11.72)	
	American Indian/ Alaska Native	377 (0.86)	305 (0.92)	72 (0.67)	
	Asian/ Pacific Islander	6220 (14.22)	4101 (12.41)	2119 (19.78)	
	Others	46 (0.11)	24 (0.07)	22 (0.21)	
	Unknown	45 (0.10)	8 (0.02)	37 (0.35)	
Sex	Male	27427 (62.69)	20668 (62.57)	6759 (63.08)	0.339
	Female	16322 (37.31)	12366 (37.43)	3956 (36.92)	
Marital	Married	24198 (55.31)	17467 (52.88)	6731 (62.82)	**<.001**
	Unmarried	17330 (39.61)	13870 (41.99)	3460 (32.29)	
	Unknown	2221 (5.08)	1697 (5.14)	524 (4.89)	
Insurance	Uninsured	1143 (2.61)	932 (2.82)	211 (1.97)	**<.001**
	Any Medicaid	5208 (11.90)	4060 (12.29)	1148 (10.71)	
	Insured/No specifics	25336 (57.91)	18785 (56.87)	6551 (61.14)	
	Unknown	12062 (27.57)	9257 (28.02)	2805 (26.18)	
Urban area	Metro counties	39422 (90.11)	29588 (89.57)	9834 (91.78)	**<.001**
	Urban counties	3721 (8.51)	2952 (8.94)	769 (7.18)	
	Rural counties	469 (1.07)	382 (1.16)	87 (0.81)	
	Unknown	137 (0.31)	112 (0.34)	25 (0.23)	

| Covariate | Level | Total | Survival time | | P-value[**] |
			Short-term N=33034	Long-term[*] N=10715	
Neighborhood Poverty	High-poverty	5510 (12.59)	4404 (13.33)	1106 (10.32)	**<.001**
	Middle-poverty	37234 (85.11)	27895 (84.44)	9339 (87.16)	
	Low-poverty	994 (2.27)	726 (2.2)	268 (2.5)	
	Unknown	11 (0.03)	9 (0.03)	2 (0.02)	
Subsite	Cardia	13422 (30.68)	10139 (30.69)	3283 (30.64)	**<.001**
	Fundus	1677 (3.83)	1353 (4.1)	324 (3.02)	
	Body/Lesser and greater curvature	8574 (19.60)	5981 (18.11)	2593 (24.2)	
	Gastric antrum/Pylorus	9717 (22.21)	6742 (20.41)	2975 (27.76)	
	Overlapping lesion of stomach	3173 (7.25)	2667 (8.07)	506 (4.72)	
	Unknown	7186 (16.43)	6152 (18.62)	1034 (9.65)	
Grade	Well differentiated (Grade I)	1528 (3.49)	796 (2.41)	732 (6.83)	**<.001**
	Moderately differentiated (Grade II)	9525 (21.77)	6404 (19.39)	3121 (29.13)	
	Poorly differentiated (Grade III)	23746 (54.28)	18466 (55.90)	5280 (49.28)	
	Undifferentiated/anaplastic (Grade IV)	835 (1.91)	626 (1.90)	209 (1.95)	
	Unknown or others	8115 (18.55)	6742 (20.40)	1373 (12.81)	
Stage	I	10844 (24.79)	5084 (15.39)	5760 (53.76)	**<.001**
	II	4784 (10.94)	2790 (8.45)	1994 (18.61)	
	III	4571 (10.45)	3357 (10.16)	1214 (11.33)	
	IV	17260 (39.45)	16299 (49.34)	961 (8.97)	
	Unknown	6290 (14.38)	5504 (16.66)	786 (7.34)	
Gastrectomy	No gastrectomy	24417 (55.81)	22608 (68.44)	1809 (16.88)	**<.001**
	Partial or subtotal gastrectomy	12787 (29.23)	6424 (19.45)	6363 (59.38)	
	Near total or total gastrectomy	3968 (9.07)	2435 (7.37)	1533 (14.31)	
	Others or unknown	2577 (5.89)	1567 (4.74)	1010 (9.43)	

| | | | Survival time | | |
| | | | ----------------------------------- | | |
Covariate	Level	Total	Short-term N=33034	Long-term[*] N=10715	P-value[**]
Radiation	No or Unknown	33387 (76.31)	26032 (78.8)	7355 (68.64)	**0.002**
	Yes	10362 (23.69)	7002 (21.2)	3360 (31.36)	
Chemotherapy	No or Unknown	24715 (56.49)	18803 (56.92)	5912 (55.17)	**<.001**
	Yes	19034 (43.51)	14231 (43.08)	4803 (44.83)	

* Patients survived 3 years or longer were defined as long-term survivors.

** The p-value is calculated by chi-square test.

Table 2. Multivariate logistic analysis of long-term survival among GC patients (N=30,159)

| Covariate | Level | Survival time ≥ 3 years | |
		Odds Ratio (95% CI)	P-value
Age	<45 years	1.45 (1.26-1.68)	**<.001**
	45-59 years	1.32 (1.21-1.44)	**<.001**
	60-74 years	Ref	Ref
	75-84 years	0.62 (0.57-0.67)	**<.001**
	85+ years	0.36 (0.32-0.41)	**<.001**
Race	White	Ref	Ref
	Black	0.86 (0.78-0.95)	**0.004**
	American Indian/ Alaska Native	0.76 (0.48-1.21)	0.247
	Asian/ Pacific Islander	1.38 (1.26-1.50)	**<.001**
	Others	1.61 (0.61-4.29)	0.339
Sex	Male	0.87 (0.81-0.93)	**0.001**
	Female	Ref	Ref
Marital	Married	1.27 (1.18-1.36)	**<.001**
	Unmarried	Ref	Ref
Urban area	Metro counties	Ref	Ref
	Urban counties	0.87 (0.77-0.98)	**0.021**
	Rural counties	0.70 (0.51-0.96)	**0.026**
Neighborhood Poverty	High-poverty	Ref	Ref
	Middle-poverty	1.30 (1.17-1.44)	**<.001**
	Low-poverty	1.60 (1.27-2.01)	**<.001**
Subite	Cardia	Ref	Ref
	Fundus	0.89 (0.74-1.07)	0.218
	Body/Lesser and greater curvature	1.28 (1.16-1.40)	**<.001**
	Gastric antrum/Pylorus	1.16 (1.06-1.28)	**0.001**
	Overlapping lesion of stomach	0.94 (0.81-1.08)	0.364

Covariate	Level	Survival time ≥ 3 years	
		Odds Ratio (95% CI)	**P-value**
	Unknown	0.91 (0.80-1.03)	0.147
Stage	I	Ref	Ref
	II	0.36 (0.33-0.39)	**<.001**
	III	0.17 (0.15-0.19)	**<.001**
	IV	0.07 (0.07-0.08)	**<.001**
Grade	Well differentiated (Grade I)	Ref	Ref
	Moderately differentiated (Grade II)	0.76 (0.65-0.88)	**<.001**
	Poorly differentiated (Grade III)	0.49 (0.42-0.57)	**<.001**
	Undifferentiated/anaplastic (Grade IV)	0.49 (0.39-0.63)	**<.001**
Gastrectomy	No gastrectomy	Ref	Ref
	Partial or subtotal gastrectomy	7.97 (7.27-8.73)	**<.001**
	Near total or total gastrectomy	6.07 (5.43-6.78)	**<.001**
	Others or unknown	5.24 (4.58-5.98)	**<.001**
Radiation	Yes	1.22 (1.12-1.33)	**<.001**
	No or Unknown	Ref	Ref
Chemotherapy	Yes	1.44 (1.32-1.57)	**<.001**
	No or Unknown	Ref	Ref

Table 3. Multivariate logistic analysis of long-term survival among advanced GC patients
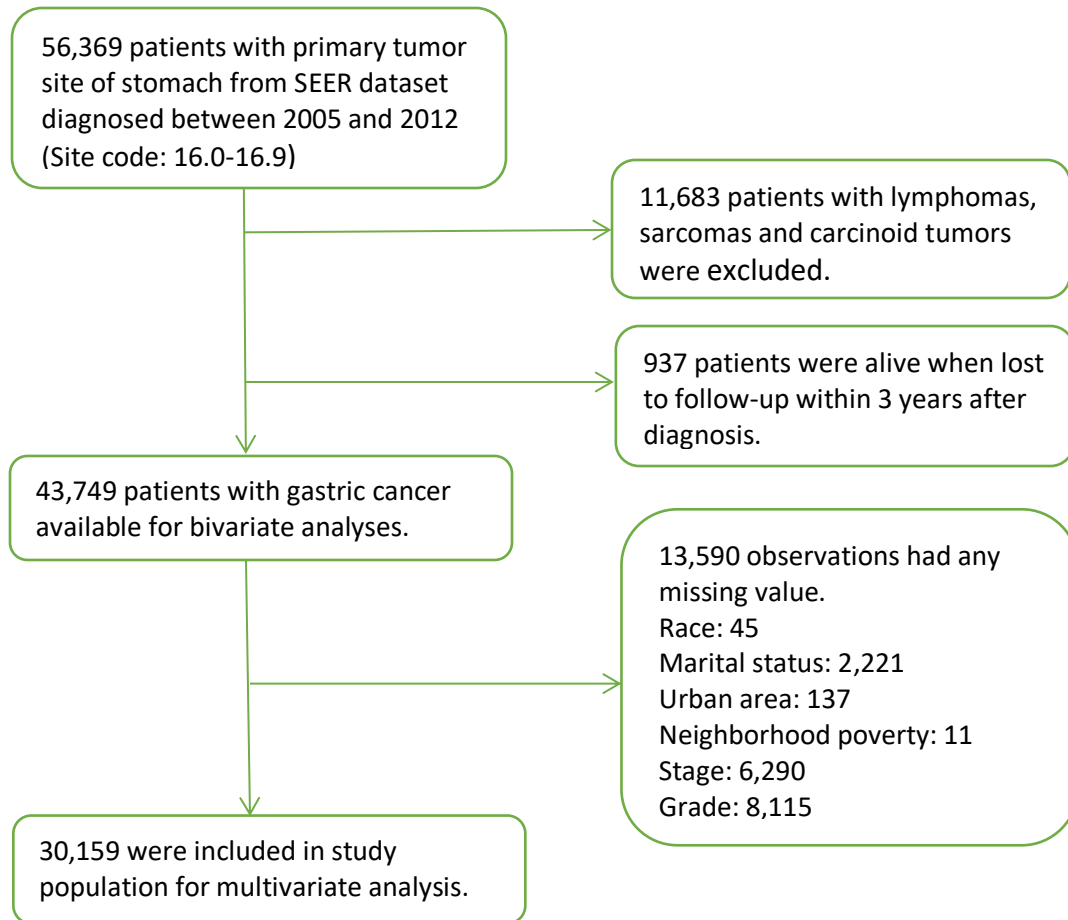
(N=12,988)

| Covariate | Level | Survival time ≥ 3 years | |
		Odds Ratio (95% CI)	OR P-value
Age	<45 years	1.07 (0.82-1.39)	0.881
	45-59 years	1.12 (0.94-1.35)	0.098
	60-74 years	Ref	Ref
	75-84 years	0.78 (0.62-0.98)	**0.030**
	85+ years	0.58 (0.36-0.95)	**0.031**
Race	White	Ref	Ref
	Black	1.00 (0.79-1.27)	0.999
	American Indian/ Alaska Native	0.91 (0.27-3.04)	0.881
	Asian/ Pacific Islander	1.14 (0.93-1.41)	0.212
Sex	Male	0.89 (0.75-1.05)	0.170
	Female	Ref	Ref
Marital	Married	1.20 (1.02-1.42)	**0.032**
	Unmarried	Ref	Ref
Urban area	Metro counties	Ref	Ref
	Urban counties	0.63 (0.45-0.89)	**0.009**
	Rural counties	1.13 (0.57-2.26)	0.729
Neighborhood Poverty	High-poverty	Ref	Ref
	Middle-poverty	1.11 (0.85-1.45)	0.435
	Low-poverty	1.43 (0.85-2.39)	0.175
Subsite	Cardia	Ref	Ref
	Fundus	0.69 (0.44-1.10)	0.120
	Body/Lesser and greater curvature	0.95 (0.76-1.20)	0.674
	Gastric antrum/Pylorus	0.93 (0.74-1.17)	0.512
	Overlapping lesion of stomach	0.63 (0.47-0.86)	**0.003**

Covariate	Level	Survival time ≥ 3 years	
		Odds Ratio (95% CI)	OR P-value
	Unknown	0.75 (0.57-0.99)	**0.041**
Grade	Well differentiated (Grade I)	Ref	Ref
	Moderately differentiated (Grade II)	0.81 (0.49-1.34)	0.406
	Poorly differentiated (Grade III)	0.49 (0.30-0.80)	**0.004**
	Undifferentiated/anaplastic (Grade IV)	0.36 (0.18-0.71)	**0.004**
Gastrectomy	No gastrectomy	Ref	Ref
	Partial or subtotal gastrectomy	5.27 (4.38-6.34)	**<.001**
	Near total or total gastrectomy	4.28 (3.39-5.41)	**<.001**
	Others or unknown	3.63 (2.58-5.11)	**<.001**
Radiation	Yes	1.52 (1.29-1.80)	**<.001**
	No or Unknown	Ref	Ref
Chemotherapy	Yes	3.42 (2.79-4.19)	**<.001**
	No or Unknown	Ref	Ref

Figures

Figure 1. Flow diagram of selection and inclusion/exclusion process

56,369 patients with primary tumor site of stomach from SEER dataset diagnosed between 2005 and 2012 (Site code: 16.0-16.9)

11,683 patients with lymphomas, sarcomas and carcinoid tumors were excluded.

937 patients were alive when lost to follow-up within 3 years after diagnosis.

43,749 patients with gastric cancer available for bivariate analyses.

13,590 observations had any missing value.
Race: 45
Marital status: 2,221
Urban area: 137
Neighborhood poverty: 11
Stage: 6,290
Grade: 8,115

30,159 were included in study population for multivariate analysis.

Chapter III: Summary and possible future directions

The present study observed that age, race, marital status, urban area, neighborhood poverty, subsite, histological grade, tumor stage and treatment with gastrectomy, radiation and chemotherapy were independently and significantly associated with long-term gastric cancer survival based on a population-based dataset.

In the future, more characteristics of long-term gastric cancer survivors are expected to be investigated. Those variables would include individual SES, BMI, healthy behaviors, diet, medical histories, detailed insurance information and detailed treatments. Several genes and biomarkers have suggested significant associations with GC survival in clinical trials and small cohort studies. Population-based data are expected to be available to investigate these associations in the general population.

The association between neighborhood area and long-term survival could also be further investigated. We observed that patients with advanced GC living in urban areas were more likely to die within 3 years compared with metropolitan areas after controlling for neighborhood poverty. However, the survival difference between patients living in metro counties and rural counties was no more significant for GC patients diagnosed at advanced disease. The explanations of these associations are unclear. Because the sample size of GC patients diagnosed with advanced disease was not very large in our study, a study for advanced GC with detailed information about neighborhood area and larger sample size is expected.

Our study used a US national dataset to investigate the characteristics of long-term survivors of GC. A comparison study between America and other countries may be expected in future, especially for East Asia countries, which have higher incidence but better survival of gastric cancer. This study will aim to investigate whether the characteristics of long-term survivors of GC vary in different countries.