

# Proportion and Prognosis of Bone Metastases from Gastric Cancer in SEER database

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## Research article

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# Abstract

**Purpose** The purpose of this study was to analyze the proportion and prognosis of bone metastases at diagnosis of gastric cancer using population-based data from SEER. **Patients and methods** Patients with gastric cancer and bone metastases (GCBM) at the time of diagnosis in advanced gastric cancer were identified using the Surveillance, Epidemiology and End Result (SEER) database of the National Cancer Institute. Multivariable logistic and Cox regression were performed to identify predictors of the presence of GCBM at diagnosis and factors associated with all-cause mortality and gastric cancer-specific mortality. Survival curves were obtained according to the Kaplan-Meier method and compared using the log-rank test. **Results** We identified 975 patients with gastric cancer and bone metastases at the time of diagnosis, representing 5.31% of the entire cohort and 13.35% of the subset with metastatic disease to any distant site. Among entire cohort, multivariable logistic regression identified five factors (lower age, diffused-type, adverse pathology grade, N1 staging and presence of more extraosseous metastases to liver, lung and brain.) as positive predictors of the presence of bone metastases at diagnosis. Median survival among the entire cohort with GCBM was 4.0 months (interquartile range: 1.0-8.0mo). Multivariable Cox model in SEER cohort confirmed two factors (non-cardia stomach and absence of chemotherapy) as negative predictors for overall survival. We also found poor survival in non-surgical patients using Fine and Gray's competing risk regression model. **Conclusion** The findings of this study provided population-based estimates of the proportion and prognosis for GCBM at time of diagnosis. These findings provided guidance for screening and treatment of GCBM patients. Chemotherapy may make benefit for overall survival, but the role of surgery remained to be determined by further research.

## Introduction

Gastric Cancer (GC) was the fourth malignant tumor in the world, and the second common cause of cancer-related death, representing 8% of all malignant tumors and 10% of total deaths.[ 1] Although the reported morbidity and mortality rates had steadily decreased over the last decade in the world [ 1], the estimated new GC patients and deaths in United States in 2018 were still 26240 and 10800.[ 2] Furthermore, about 40% of patients presented with evidence of distant metastases.[ 3-5] The most common site of distant metastases was the peritoneum, followed by the liver, lung and bone.[ 5] Bone metastases (BM) were a relatively uncommon **discovery**, which had been reported in only 0.9% to 10% of the GC patients in clinical practice.[ 6-10] While at postmortem examination, 13.4-15.9% of patients were found to have evidence of bone metastases [ 11], and the proportion increased up to 45.3% in bone screening studies.[ 12, 13] However, all these patients were unselected, including synchronous and metachronous metastatic patients. BM was associated with poor survival in patients with advanced gastric cancer. It was believed that the prognosis of gastric cancer patients with bone metastases (GCBM) was poorer than those with liver metastases.[ 14] The median survival time was 3-4 months after diagnosis of GCBM.[ 8, 14] And the overall survival of synchronous group was significantly shorter than metachronous group in a Korean research.[ 15]

Bone metastases was usually accompanied with serious complications during the patients' disease course, and the kind most well known was called skeletal-related events (SREs), including pathological fractures, severe bone pain, bone marrow infiltration, spinal cord compression, and hypercalcemia, which would result in a negative impact on the patients' quality of life and survival.[ 10] The frequency of SREs among GCBM was 37% to 84% in previous literature reported.[ 7, 8, 10, 16] And the median time to the first SRE was 2 months and the median survival after SRE occurrence was 3 months in an observational study.[ 10] Therefore, an early detection of BM would be useful for its treatment.

A Korean research [ 15] based on analysis of 141 patients suggested that a lower age, signet ring cell histology, primary tumor involving  $\geq$  two-thirds of the stomach, pleural metastasis, thrombocytopenia and elevated alkaline phosphatase were factors significantly associated with presence of GCBM, and initial BM, poor performance status, peritoneal metastasis, hypercalcemia and high carcinoembryonic antigen (CEA) were identified as poor prognostic factors. But most studies published before [ 6-16] were small sample with unselected patients, a population-based estimate relating to the frequency and prognosis of bone metastases at diagnosis of gastric cancer was lacking. Since there had not clear guideline for treatment of GCBM, some researches thought that chemotherapy and bisphosphonate therapy will improve overall survival and prolong time to the first SRE.[ 7, 8, 10, 17-19] Besides, radiotherapy may be quite effective to relieve severe pain and to prevent fractures in GCBM but with no improvement in survival.[ 8, 10, 20] However, the role of surgery in GCBM had not been identified yet. Only a few case reports [ 21] hypothesized that gastrectomy plus metastasectomy may be an effective therapeutic choice for improving quality of life and survival in selected patients with bone metastases.

Current guidelines did not recommend routine screening of bone metastases in patients with both localized and metastatic gastric cancer only if detection of symptoms. However, most patients were asymptomatic during illness.[ 7] Only 32.4% of patients complained about symptoms.[ 19] Bone screening could detect bone metastasis at the time approximately 3 months earlier than that using plain X-rays.[ 22] An early diagnosis of bone metastases will significantly improve time to first SRE and prolong the median survival time.[ 10] Therefore, a study based on population level with outcome of patient characteristics and the clinical and sociodemographic predictors about GCBM was particularly important to determine which patients need further examination.

The purpose of this study was to use data from the Surveillance, Epidemiology and End Results (SEER) database between 2010 and 2014 to survey the incidence proportion and **predictive factors** of bone metastases at the time of cancer diagnosis among patients with gastric cancer on a population-based level. We also wanted to characterize prognostic factors on the survival of patients at diagnosis of gastric cancer with bone metastases.

## Material And Methods

### Study population

Data was obtained from SEER database, which was the largest publicly available cancer dataset and collected cancer data from 18 population-based cancer registries covering about 28 percent of the United States population.[ 23] This database included information about cancer incidence as well as demographic information: age, gender, race, year at diagnosis, tumor staging, tumor size, treatment, marital status, insurance, education, family income and so on. We used the SEERStat published by SEER to identify eligible patients in this study, which we could get from the official network (<https://seer.cancer.gov/>). The SEER database provided patients information up to 2014 based on the November 2016 submission, and it started to release metastatic information related to bone metastases from 2010. Thus, we can get data about GCBM between 1 January 2010 and 31 December 2014. Besides, bone metastases included only the bone, but not bone marrow in the SEER database.

Within the SEER database, we identified 36982 patients with gastric cancer from 2010 to 2014. Patients with other cancer, less than 18 or more than 85 years old, with other pathological type were excluded from the analysis, leaving 18364 patients in the final cohort for proportions analysis. Of these, 7305 patients were diagnosed with metastases to any distant site and 975 patients were diagnosed as GCBM. We subsequently removed patients with an unknown follow-up, leaving 973 patients eligible for survival analyses. The percentage of distant metastases to any site was 39.78% and bone metastases were 5.31%. Data extraction flowchart was showed in Figure 1. The inclusion criteria were as follows: age more than 18 years old and less than 85 years old at time of diagnosis; gastric cancer as the only one primary cancer; with identified pulmonary metastases; confirmation of diagnosis based on pathology of a specimen, rather than based on radiography or laboratory; with active follow-up. And we excluded those patients conformed to one of the following standards: age less than 18 years old or more than 85 years old at the time of diagnosis; with more than one primary cancer; unknown bone metastases; cancer diagnosed by radiography or laboratory; pathological type confirmed to be NET stomach, sarcoma, GIST or lymphoma; without active follow-up.

## Statistical analysis

Descriptive statistics was used to calculate the absolute number and frequency among patients with BM at the time of cancer diagnosis. Proportion was defined as the percentage of gastric cancer patients diagnosed with BM among the entire study cohort and the patients with metastatic disease to any distant site. All data were stratified by year at diagnosis, age, gender, race, original, primary site, pathology grade, Lauren classification, T staging, N staging, tumor size, treatment, number of extraosseous metastatic sites and other sociodemographic information, such as: marital status, residence type, insurance situation, bachelor education, median household income and smoking status. Residence type, education level, median household income and smoking status were defined by the county attributes from the US Census 2010-2014 American Community Survey 5-year data files, which we could get from the SEER\*Stat software.

Multivariable logistic regression was used to determine predictors of the presence of bone metastases at diagnosis. Survival estimates were obtained according to the Kaplan-Meier method and compared using the log-rank test. Variables that reached significance with  $P < 0.05$  were entered into the multivariable analyses using the Cox regression model to identify covariates associated with increased all-cause mortality. Besides, we used Fine and Gray's competing risk regression to assess gastric cancer-specific mortality.[ 24]

All statistical analyses were performed using SPSS statistical software (version 18.0). The competing risks analysis was performed in R (version 3.4.4; R Foundation) using the cmprsk package (version 2.2-7). Statistical significance was set at two-sided ( $P < 0.05$ ).

## Results

### Frequency analysis

A total of 18364 patients in the U.S. were diagnosed with gastric cancer between 2010 and 2014, including 975 patients diagnosed with GCBM whose median age was 66 years old, consisted of 662 men (67.90%) and 313 women (32.10%). Their demographic and clinical characteristics were shown in Table 1.

On univariable logistic regression (Table S2) among the entire cohort, there were seven factors that showed significance ( $P$  value  $< 0.05$ ). They were age, pathology grade, Lauren classification, T staging, N staging, number of extraosseous metastatic sites to liver, lung, and brain and insurance situation. We put them on multivariable logistic regression which showed that age, pathology grade, Lauren classification, T staging, N staging and number of extraosseous metastatic sites to liver, lung and brain had significance among the entire cohort and age, pathology grade, Lauren classification, T staging, N staging, tumor size and number of extraosseous metastatic sites to liver, lung and brain had significance among the subset with metastatic disease to any distant site.

On the multivariable logistic regression (Table 2) among the entire cohort, grade III-IV (vs grade I-II; OR, 2.00; 95% CI, 1.62-2.47;  $P < 0.001$ ), diffused-type (vs intestinal-type; OR, 1.44; 95% CI, 1.23-1.68;  $P < 0.001$ ), N1 (vs N0; OR, 1.63; 95% CI, 1.39-1.93;  $P < 0.001$ ), 1 extraosseous metastatic site (vs 0 extraosseous metastatic site; OR, 2.07; 95% CI, 1.75-2.45;  $P < 0.001$ ), 2 extraosseous metastatic sites (vs 0 extraosseous metastatic site; OR, 5.51; 95% CI, 4.05-6.56;  $P < 0.001$ ), 3 extraosseous metastatic sites (vs 0 extraosseous metastatic site; OR, 10.80; 95% CI, 4.61-25.13;  $P < 0.001$ ) were associated with significantly greater odds of having bone metastases at diagnosis. And, insurance status was not associated with a risk of bone metastases at diagnosis in the multivariable model. While, age 61-80 years (vs age 18-40 years; OR, 0.61; 95% CI, 0.47-0.80;  $P < 0.001$ ) and age 80+ years (vs age 18-40 years; OR, 0.35; 95% CI, 0.24-0.52;  $P < 0.001$ ), T2 (vs T1; OR, 0.60; 95% CI, 0.46-0.77;  $P < 0.001$ ), T3 (vs T1; OR, 0.60; 95% CI, 0.46-0.77;  $P < 0.001$ ) and T4 (vs T1; OR, 0.69; 95% CI, 0.54-0.89;  $P = 0.003$ ) were associated with marginally lower odds of bone

metastases at diagnosis. The multivariable logistic regression of subset with metastatic disease was also showed in Table 2.

## Survival analysis

On univariate analysis among the subset with bone metastases, there were four factors that were significantly associated with all-cause mortality, while five factors were significantly associated with for gastric cancer-specific mortality. Table S3 showed univariate analysis for all-cause mortality and gastric cancer-specific mortality among GCBM. On multivariable Cox regression (Table 3) for all-cause mortality among patients with GCBM at diagnosis, absence of chemotherapy (vs chemotherapy; HR, 3.50; 95%CI, 3.01-4.07;  $P < 0.001$ ), middle of stomach (vs upper of stomach; HR, 1.58; 95% CI, 1.24-2.01;  $P < 0.001$ ), lower of stomach (vs upper of stomach; HR, 1.39; 95% CI, 1.11-1.75;  $P = 0.004$ ) were significantly associated with an increased all-cause mortality. And absence of surgery (vs surgery; HR, 1.63; 95%CI, 1.10-2.40;  $P = 0.01$ ) were significantly associated with an increased gastric cancer-specific mortality only. Gastric cancer-specific mortality among patients with GCBM was also presented in Table 3. Survival estimates of overall (Figure 2A) and as stratified by primary site (Figure 2B) chemotherapy (Figure 2C), surgery (Figure 2D) were graphically displayed in the Figure 2.

## Discussion

This study analyzed the frequency and survival of gastric cancer patients with bone metastases at their initial diagnosis using data from the SEER database. Previously published data had evaluated the proportion and prognosis of GCBM roughly, but most of patients in these studies were diagnosed early gastric cancer first, and then developed BM in their disease course.[ 6-16] Besides, previous studies that described the frequency of bone metastases from gastric cancer had yielded varying results, rang from 0.9% to 10% in current clinical practice.[ 6-10] A Korean research estimated that the cumulative percentage over time of bone metastases among patients with gastric cancer was 2.4% among the entire cohort.[ 7] At the same time, a multicenter study from Italy including more than 2000 GC patients identified 208 patients (10%) with bone metastases.[ 10] However, the frequency of bone metastases was found to be 13.4-15.9% at postmortem examination [ 11], and increased up to 45.3% in bone screening studies [ 12, 13]. Most studies above [ 3-9, 11-13, 15, 16] were small sample from single institution, which were unpersuasive. So a study based on population level to describe the frequency and prognosis of patients who presented with de novo bone metastases was urgently needed. In this large retrospective study, we found that 5.31% of patients with gastric cancer had bone metastases at diagnosis, and 13.35% of those with any metastases at diagnosis had bone metastases. This result was a little different from that of previous published studies [ 6-13], but was similar to that of a previous study using SEER database, which showed 5.09% of BM in all patients and 12.40% in metastatic disease.[ 14] Most asymptomatic patients could not be assessed at initial diagnosis due to lack of bone scan supporting. On another hand, patients may develop BM later after diagnosis of early-stage GC in SEER. And our work

only focused on patients with metastatic gastric cancer at initial diagnosis, so the frequency of BM may be underestimated.

An early detection of BM showed great significance. 37% to 84% of GC patients presented with SREs that pain is the most frequent form.[ 7, 8, 10, 16] These patients might benefit from adjuvant therapy with an agent like bisphosphonate if an early detection of GCBM. Nicola et al [ 10] analyzed 208 GCBM patients which showed that early detection of BM can prolong the first SREs time from 4 months to 7 months. However, routine screening of bone metastases was not recommended in present guideline, and many scholars thought it is required to assess bone metastases at the time of the initial diagnosis and during the follow-up observations.[ 8-10] Imaging examinations like bone scan, MRI, or PET-CT were more appropriate compared to [laboratory](#) indexes like ALP, LDH, and tumor markers in some researches.[ 19, 22] Thus, method and frequency of bone scan need to be estimated in further study.

Risk factors for the presence of BM at GC diagnosis were determined using multivariate logistic regression. We found that patients had significantly greater odds of having bone metastases at diagnosis when they showed the five factors as follow: lower age, diffused-type, adverse pathology grade, N1 staging and presence of more extraosseous metastases to liver, lung and brain. The presence of diffused-type seemed to be associated with bone metastases in our study, which was reported in the previous studies.[ 15, 25, 26] Takahashi et al [ 27] found a rule that intestinal-type and diffuse-type GC were associated with liver metastases and bone metastases, separately, attribute to different expressions of extracellular matrix metalloproteinase inducer. Younger patients had a significantly greater likelihood to be bone metastases, which was more distinct among the cohort with metastatic disease. The phenomenon was same to the study published before [ 15, 25, 26], due to the biological characteristic of younger GC patients was always related to signet ring cell type. Patients with N1 staging, adverse pathology grade and presence of more extraosseous metastases to liver, lung and brain were easier to be bone metastases, too. The finding was only seen in N1 staging because of lack of patients with N2 staging (N=38) and N3 staging (N=45) and most N staging of our study was based on [clinical](#) staging which was not accurate enough. Moreover, we guessed that the same problem existed in the variable of T staging. Furthermore, these results should be confirmed with more studies carefully. To say the least, our study indicated that GC patients with high risk factors above need further examination.

Prognostic factors of BM at GC diagnosis were analyzed using multivariate Cox model. We found that patients had a significantly higher risk of mortality when they showed the two factors as follow: non-cardia stomach and absence of chemotherapy. We also found poor survival in non-surgical patients using Fine and Gray's competing risk regression model. Tumor located at non-cardia stomach had a worse median survival time in this study, which was different from the study before. Kim's research [ 28] found that cardia stomach showed poor survival in GC, but this study included I-IV staging patients, which may not be specific. There was no definite guideline of therapeutic regimens in gastric cancer patients with bone metastases. Kwon et al found that the median survival time prolong about 4 months in the palliative chemotherapy group compared with the supportive care group, but this study only included 26 patients.[ 29] Besides, there was a lack of evidence to assess the effect of surgery. The

median OS was 4.0 months from initial diagnosis of GCBM in the SEER, which was in accordance with the result reported by previous studies.[ 8, 14] The median OS of patients with and without chemotherapy was 6 and 1 months, separately, in this study. We can find a significant increase in the hazard ratio (3.10 to 4.21;  $P < 0.001$ ) for all-cause mortality among absence of chemotherapy vs chemotherapy. And the median OS of patients with and without surgery was 7 and 3 months, separately. The hazard ratio (1.10 to 2.40;  $P = 0.01$ ) had a significant increase from absence of surgery to surgery on competitive risk model, while showed no significance in all-cause mortality analysis. Because the number of GCBM patients who received surgery was only 33 in SEER, accurate analysis was difficult to obtain, which need further investigation including more patients. Besides, radical cure was attempted in only one case whose median OS was 9 months. The result was unsatisfactory. Although Young's case report [ 21] described a patient with synchronous GCBM survived for 60 months after gastrectomy and metastasectomy, Young did not recommend routine surgery for GCBM patients. In general, chemotherapy may be treated as a baseline treatment for patients with GCBM, while surgery may be available for those highly selected patients with caution. We did not recommend routine surgery at [the present stage](#).

Although our study was based on population-level, containing large of case, we should not ignore its limitations.

Firstly, we could known those patients with metastatic disease to bone, liver, lung and brain, but the SEER database did not provide information about other metastatic sites, like peritoneal metastases. Moreover, we only had information on synchronous metastasis to bone, lack of a relative minority compared to those patients who may develop metachronous metastasis; Secondly, information relating to comorbidities, performance status was not available in the SEER database; Thirdly, residence type, education level, and median household income were defined at a county level, not a patient level, possibly affecting the results of the logistic and Cox regressions; Fourth, the SEER did not record the extent of bone lesions, information about SREs, bisphosphonate therapy and [laboratory](#) indexes.

To the best of our knowledge, this study was the first population-based analysis of patients with bone metastases at initial diagnosis of gastric cancer. It provided important suggestions for clinicians to consider designing studies that evaluate the utility of screening among patients with higher risk of bone metastases. The prognostic factors on GCBM were analyzed in this study too. Besides, we described the significance of different treatment on GCBM, which might provided some help to clinical practice.

## Conclusion

In conclusion, the findings of this study based on a population level provided estimates of the frequency for GCBM at time of diagnosis. Patients present with lower age, diffused-type, adverse pathology grade, N1 staging and presence of more extraosseous metastases to liver, lung and brain had significantly greater odds of having bone metastases at diagnosis. A series of risk factors for BM in GC patients were identified, which can indicate routine screening in such patients. Furthermore, the study identified that non-cardia gastric cancer with bone metastases had a significantly higher risk of mortality.

Chemotherapy may be the basic treatment for GCBM at present, while surgery may be available for those highly selected patients with caution. And we did not recommend routine surgery at present.

## Declarations

## Acknowledgements

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## Ethics approval and consent to participate

The SEER was public-use data: informed consent was waived (data sources: <https://seer.cancer.gov/>). And our study was deemed exempt from institutional review board approval by Nanfang Hospital, Southern Medical University.

## Author contributions

All authors listed had made a substantial contribution to the work. YMJ and GXL put forward the conception and designed the study. WCH, TL and MLZ collected and collated the data. ZPS, HC and ZH analyzed data and wrote the manuscript together. HL, JY and YFH made contribution to proofread the article. Finally, all the authors take responsible to the final manuscript and approved it for publication.

## Disclosure

The authors declare no conflict of interest.

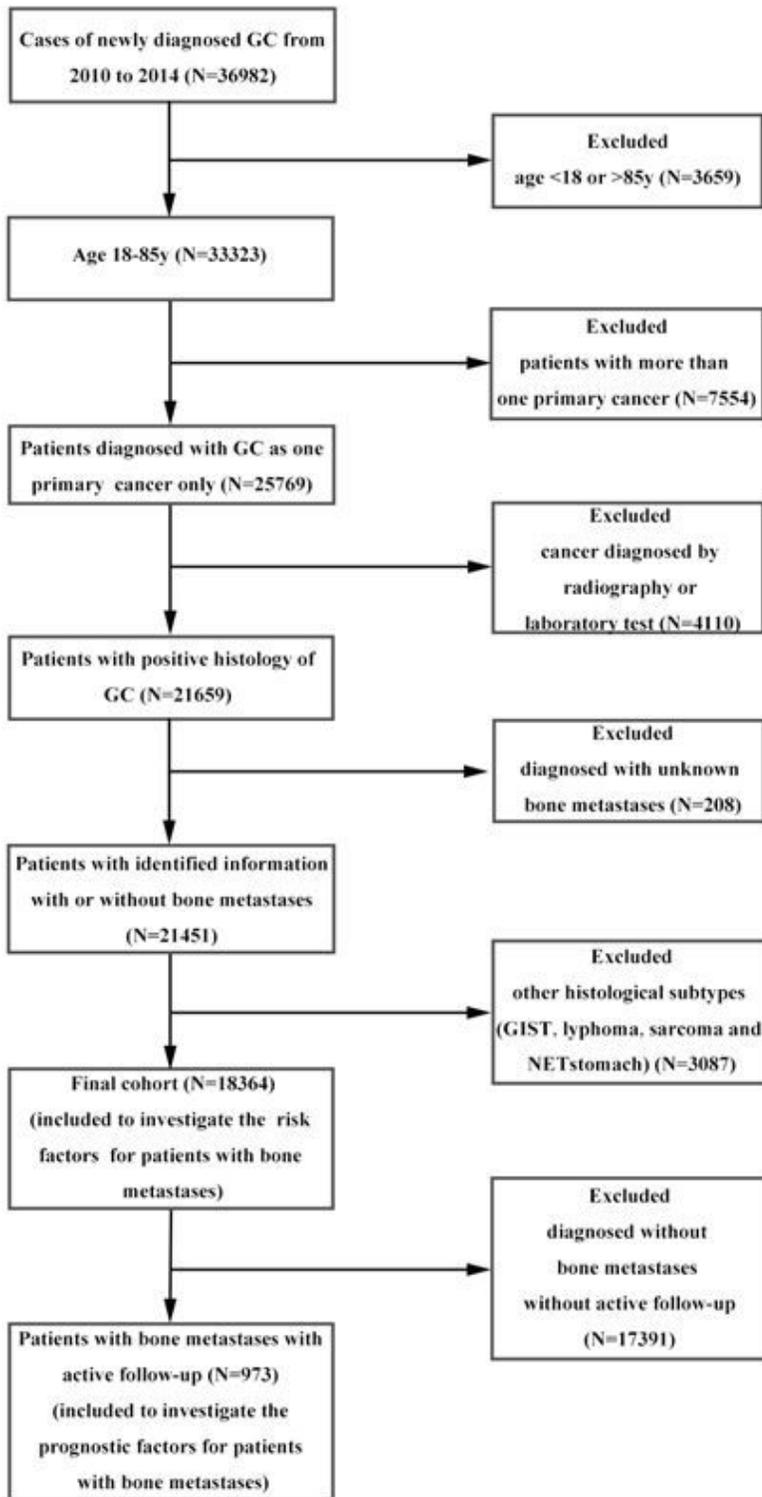
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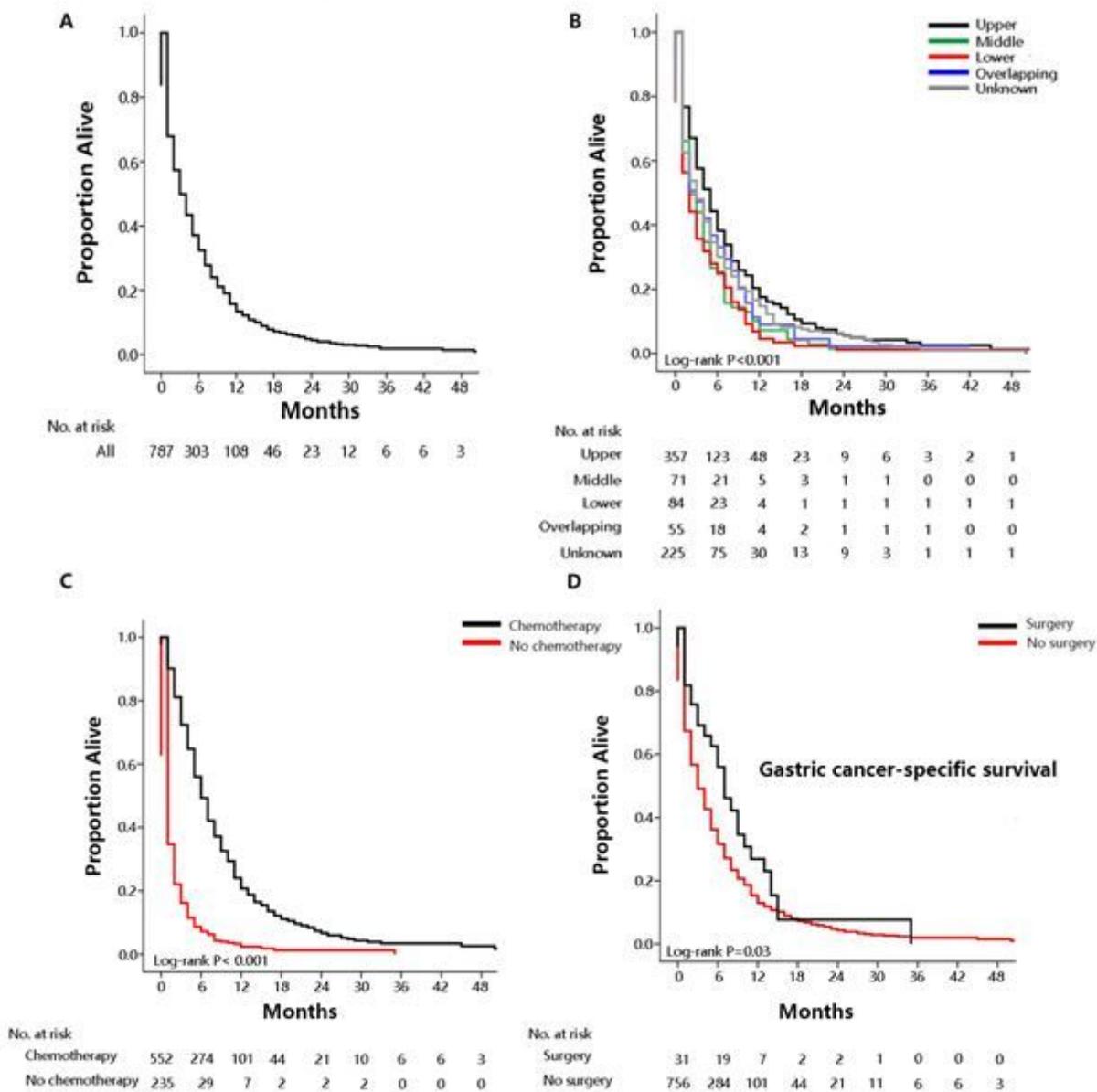
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## Figures



**Figure 1**

Data extraction flowchart from the SEER database



**Figure 2**

Overall survival among patients with GCBM at diagnosis (A. overall), stratified by primary site (B) chemotherapy (C), surgery (D)

## Supplementary Files

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