Identifying Benefit Factors Associated With Primary Tumor Resection in Patients With Stage IV Gastric Cancer: a Propensity Score-matched Analysis

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Research Article

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Abstract

Background: At present, the beneficial factors related to surgery at the primary tumor site in patients with stage IV gastric cancer (GC) are unclear. We developed a new selection process to determine the beneficial factors associated with primary tumor surgery.

Methods: Patients with stage IV GC were screened from the Surveillance, Epidemiology, and End Results (SEER) database and were divided into surgery and non-surgery groups. The Kaplan-Meier method was used to estimate the survival curve before and after the propensity score-matched analysis (PSM). We believe that patients in the surgery group who have a longer median cancer-specific survival (CSS) time than those in the non-surgery group can benefit from surgery. Use Multivariate Logistic regression analysis to determine the benefit factors related to surgery.

Results: A total of 7259 patients with stage IV GC were included, of which 29.95% (2174) underwent primary tumor surgery. After PSM, the median CSS of the surgery group and the non-surgery group was 12 months and 7 months, respectively ($p < 0.001$). Multivariate COX regression analysis showed that age, T stage, primary tumor site, histological classification, histological grade, and chemotherapy were independently correlated with CSS. We included the independent related factors affecting CSS in COX analysis in the multivariate Logistics regression model. The results showed that T stage, histological grade, and chemotherapy were related to surgical benefit.

Conclusion: The surgery to the primary tumor site can prolong the survival time of patients with stage IV GC, and surgeons should screen patients before surgery. Our results show that patients with T stage T4b and histological grade GIII/GIV do not benefit from surgery, while patients receiving chemotherapy can benefit from surgery.

Introduction

Gastric cancer (GC) remains significant cancer worldwide and is responsible for an estimated 769,000 deaths in 2020, ranking fourth for mortality globally [1]. More than one-third of all GC patients have distant metastasis (stage IV) at diagnosis. The survival time of these patients is short, rarely more than one year, and the treatment options are limited, including palliative chemotherapy, immunotherapy, and targeted therapy [2–4].

Generally speaking, for patients with stage IV GC, clinicians will not actively choose to operate on the primary tumor site unless there is bleeding, perforation, or obstruction that may require emergency surgery. Because the main focus and goal of such patients are disease control, not radical cure [5]. However, for patients at high risk of related GC complications, the role of primary site surgery has recently become an important topic of debate. Many studies have shown that primary tumor resection is associated with improved survival [6–8]. On the contrary, a recent randomized trial (Regatta) showed that removal of primary tumors did not bring survival benefits to patients with stage IV GC [9]. From these

studies, we recognize that not all primary tumor surgery can prolong the survival time of patients, and clinicians are not sure about the factors associated with surgical benefits.

Based on this, we propose a hypothesis that the degree of benefit of surgery will vary depending on the inherent characteristics of the primary tumor and treatment options; that is, specific patients are related to surgical benefits. The purpose of this study is to use an extensive national database to test such a hypothesis.

Method

Database

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database collects cancer diagnosis, treatment, and survival data from approximately 30% of the American population. It is an essential population-based resource with the advantages of a large sample size and solid statistical efficiency. We have access to the database (SEER-Stat user name: 19379-Nov2019). We obtained the status of chemotherapy and radiotherapy by applying for additional authorization and knew the potential biases associated with these data.

Patient selection

According to the International Classification of Oncology Diseases (ICD-O-3), the SEER*Stat software version 8.3.9 was used to extract the records of metastatic gastric cancer from the SEER database (Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying). Since the TMN staging information of the sixth edition of the American Joint Commission on Cancer (AJCC) was available since 2004, to obtain a sufficient sample size, we finally selected patients from 2004 to 2015 and reclassified the TNM staging to the eighth edition of AJCC. The exclusion criteria are as follows: unknown surgical information, unknown TNM stage, unknown histological grade, unknown survival months, unknown mode of treatment, not the only tumor and not the first tumor. After screening, we collected a total of 7259 samples in this study.

Statistical analysis

The study samples were divided into surgery and non-surgery groups according to primary site treatment. Considering the rationality of classification, we use X-Tile software (Yale University in New Haven, Connecticut, USA) to evaluate the appropriate cut-off value of age (*Supplementary Figure 1*)[10]. The results show that the appropriate age is 66 and 76 years old. Since there must be data biases and confounding variables in the retrospective study, we use the propensity score matching method (PSM) to reduce the influence of these deviations and to confounding variables to make a reasonable comparison between groups [11]. The patients in the surgery group and the non-surgery group were matched at 1:1 in age group, gender, race, primary site, histological classification, histological grade, T stage, N stage, treatment (radiotherapy and chemotherapy). The caliper value is set to 0.02. The differences in clinical

characteristics of continuous variables or classified variables before and after PSM were tested by student t-test or chi-square test. OS and CSS are the results of our main concern. We define OS as the interval between diagnosis and death or the last follow-up. CSS is defined as the time from diagnosis to cancer-specific death or the date of the last follow-up. Kaplan-Meier analysis and log-rank test were used to describe the survival differences between patient groups, and the median OS and CSS were calculated. Use Multivariate Cox proportional hazard regression for analyzing the factors related to survival in the cohort before and after PSM. All statistical tests were bilateral; $P < 0.05$ was considered to be statistically significant.

Identify relevant benefit factors

We hypothesized that the median CSS of survival in the surgery group was longer than in the non-surgery group. The patients in the surgery group were re-grouped according to the median CSS time of survival in the non-surgery group. The survival time was longer than the median CSS in the non-surgery group; otherwise, we included it in the non-beneficial group. The patients whose survival time was longer than the median CSS of the non-surgery group were included in the benefit group; otherwise, they were included in the non-benefit group. We incorporated the independent factors affecting CSS in multivariate Cox analysis into the multivariate Logistic regression model to determine the relevant benefit factors.

Result

Characteristics of patients before and after PSM treatment

We screened 24140 patients with stage IV GC from the SEER database, of whom 7259 met the criteria. Figure 1 shows the screening process. Of these eligible patients, 2174 (29.95%) received surgery at the primary tumor site. As shown in Table 1, the average age in the surgery group was 61.86 ± 14.29 years old and that in the non-surgery group was 62.28 ± 13.99 years old. The ages of the two groups are similar ($p = 0.104$). Before PSM, there were significant differences in baseline characteristics between the two groups except for age groups. After 1:1PSM, the distribution of almost all variables in 2848 patients (1424 pairs) became more balanced (Table 2).

Table 1
Demographic information for patients with stage IV GC before PSM

	No. of Patients (%)			
	All patients (n = 7259)	**Non-surgery to primary site (n = 5085)**	**Surgery to primary site (n = 2174)**	**P-value**
Age				0.104
Mean(SD)	62.88 (14.20)	62.28 (13.99)	61.86 (14.29)	
Age group				0.795
< 66	4165	2905(57.1)	1260(58.0)	
66–76	1849	1305(25.7)	544(25.0)	
> 76	1245	875(17.2)	370(17.0)	
Gender				< 0.001
Male	4661	3353(65.9)	1308(60.2)	
Female	2598	1732(34.1)	866(39.8)	
Race				< 0.001
White	5141	3683(72.4)	1458(67.1)	
Black	996	710(14.0)	286(13.2)	
Other	1122	692(13.6)	430(19.8)	
T stage				< 0.001
T1/ T2	2314	2114(41.6)	200(9.2)	
T3	1629	967(19.0)	662(30.5)	
T4a	1248	455(8.9)	793(36.5)	
T4b	2068	1549(30.5)	519(23.9)	
N stage				< 0.001
N0	2535	2210(43.5)	325(14.9)	
N1/N2	3390	2514(49.4)	876(40.3)	
N3a	881	248(4.9)	633(29.1)	

GC, gastric cancer; PSM, propensity score matching; SD, Standard deviation.

		No. of Patients (%)		
N3b	453	113(2.2)	340(15.6)	
Primary site				< 0.001
Cardia	2283	1947(38.3)	336(15.5)	
Fundus/ Body	1033	757(14.9)	276(12.7)	
Antrum/ Pylorus	1434	744(14.6)	690(31.7)	
Greater/ Lesser curvature	793	454(8.9)	339(15.6)	
Overlapping lesion	803	509(10.0)	294(13.5)	
Other	913	674(13.3)	239(11.0)	
Histology				< 0.001
Adenocarcinoma	4747	3445(67.7)	1302(59.9)	
Signet ring cell carcinoma	1637	1066(21.0)	571(26.3)	
Other	875	574(11.3)	301(13.8)	
Grade				< 0.001
I/ II	1676	1251(24.6)	425(19.5)	
III/ IV	5583	3834(75.4)	1749(80.5)	
Radiation				< 0.001
No	5770	3978(78.2)	1792(82.4)	
Yes	1489	1107(21.8)	382(17.6)	
Chemotherapy				< 0.001
No	2468	1579(31.1)	889(40.9)	
Yes	4791	3506(68.9)	1285(59.1)	

GC, gastric cancer; PSM, propensity score matching; SD, Standard deviation.

Table 2
Demographic information for patients with stage IV GC after PSM

	No. of Patients (%)		
	Non-surgery to primary site (n = 1424)	**Surgery to primary site (n = 1424)**	**P-value**
Age			0.856
Mean(SD)	61.85 (14.14)	61.87 (14.15)	
Age group			0.837
< 66	840(59.0)	826(58.0)	
66–76	351(24.6)	364(25.6)	
> 76	233(16.4)	234(16.4)	
Gender			0.670
Male	899(63.1)	888(62.4)	
Female	525(36.9)	536(37.6)	
Race			0.426
White	1013(71.1)	983(69.0)	
Black	188(13.2)	195(13.7)	
Other	223(15.7)	246(17.3)	
T stage			0.243
T1/T2	223(15.7)	197(13.8)	
T3	477(33.5)	467(32.8)	
T4a	336(23.6)	328(23.0)	
T4b	388(27.2)	432(30.3)	
N stage			0.942
N0	319(22.4)	321(22.5)	
N1/N2	785(55.1)	795(55.8)	
N3a	230(16.2)	218(15.3)	
N3b	91(6.3)	90(6.3)	

GC, gastric cancer; PSM, propensity score matching; SD, Standard deviation.

	No. of Patients (%)		
Primary site			< 0.001
Cardia	425(29.8)	274(19.2)	
Fundus/ Body	173(12.1)	198(13.9)	
Antrum/ Pylorus	272(19.1)	446(31.3)	
Greater/ Lesser curvature	151(10.6)	202(14.2)	
Overlapping lesion	171(12.0)	157(11.0)	
Other	232(16.3)	147(10.3)	
Histology			0.443
Adenocarcinoma	926(65.0)	902(63.3)	
Signet ring cell carcinoma	339(23.8)	342(24.0)	
Other	159(11.2)	180(12.6)	
Grade			0.928
I/ II	317(22.3)	319(22.4)	
III/ IV	1107(77.7)	1105(77.6)	
Radiation			0.426
No	1112(78.1)	1122(78.8)	
Yes	312(21.9)	302(21.2)	
Chemotherapy			0.636
No	487(34.2)	499(35.0)	
Yes	937(65.8)	925(65.0)	
GC, gastric cancer; PSM, propensity score matching; SD, Standard deviation.			

Survival outcome of surgery group and non-surgery group

Kaplan-Meier analysis and log-rank test were performed on the population before and after PSM based on OS/CSS. The results showed that (Fig. 2), the median OS of matched surgery group and the non-surgery group was 11 months and 6 months respectively(HR = 0.599, 95CI: 0.552–0.650, $p < 0.001$). The median CSS is 12 months and 7 months respectively (HR = 0.577, 95CI:0.531–0.628, $p < 0.001$). We can see that whether before or after matching, patients in the surgery group have longer OS and CSS than

patients in the non-surgery group, indicating that surgery on the primary site of stage IV gastric cancer patients can gain a significant survival advantage. *Supplementary Table 1* shows the specific OS/CSS differences between groups.

Primary tumor resection as an independent prognostic factor affecting the survival of patients with stage IV GC

Figure 3 and Fig. 4 show the forest plots of HR for the multivariate COX analysis of CSS in the cohort before and after PSM, respectively. The cohort before matching showed that age, T stage, N stage, primary tumor site, histological classification, and histological grade were risk factors for CSS in patients with stage IV GC. In contrast, surgery to primary site and chemotherapy were protective factors related to CSS. After PSM, the N stage was no longer an independent risk factor for CSS in patients with stage IV GC. In addition, both forest plots showed that gender, race, and radiation had no significant effect on the CSS of the cohort.

Determine the related benefit factors of primary site surgery

We believe that patients in the surgery group who survive longer than the median CSS of the non-surgery group (7 months) can gain a survival advantage from surgery. According to statistics, 897 patients (62.99%) survived for more than 7 months in the surgery group. These patients were classified as a beneficial group, and the remaining 527 patients were classified as a non-beneficial group.

The independent factors affecting CSS in multivariate Cox analysis (age, T stage, primary tumor site, histological classification, histological grade, chemotherapy) were included in the Multivariate Logistics regression model (Table 3). The results showed that patients with T stage T4b and histological grade GIII/GIV had difficulty benefiting from surgery, while patients receiving chemotherapy were more likely to benefit from surgery.

Table 3
Logistics regression model for predicting surgery-related beneficial factors

	Adjust OR (95% CI)	P value
Age group		
< 66	Reference	
66–76	0.903 (0.681–1.199)	0.482
> 76	0.853 (0.609–1.195)	0.356
T stage		
T1/T2	Reference	
T3	1.134 (0.774–1.661)	0.520
T4a	0.927 (0.620–1.388)	0.714
T4b	0.639 (0.435–0.939)	0.023*
Primary site		
Cardia	Reference	
Fundus/Body	1.200 (0.778–1.850)	0.410
Antrum/Pylorus	0.763 (0.537–1.084)	0.131
Greater/ Lesser curvature	0.937 (0.616–1.425)	0.760
Overlapping lesion	0.654 (0.417–1.027)	0.065
Other	0.784 (0.496–1.238)	0.286
Histology		
Adenocarcinoma	Reference	
Signet ring cell carcinoma	0.847 (0.630–1.137)	0.269
Other	0.913 (0.638–1.306)	0.619
Grade		
I/II	Reference	
III/IV	0.583 (0.429–0.791)	0.001*
Chemotherapy		
No	Reference	

GC, gastric cancer; OR, odds ratio; CI, confidence interval; OR > 1 indicates higher odds of benefit from surgery.

Yes	3.978 (3.084–5.131)	<0.001*

GC, gastric cancer; OR, odds ratio; CI, confidence interval; OR > 1 indicates higher odds of benefit from surgery.

Discussion

This study analyzed the data of 24140 patients with stage IV GC from the SEER database and made two critical findings. First, survival analysis showed that patients who underwent surgery at the primary tumor site had an advantage in OS/CSS compared with patients who did not undergo surgery. Surgery was a protective factor affecting patients' CSS. Second, through the re-grouping of patients who underwent surgery at the primary tumor site, we preliminarily identified and described the factors related to the benefits of surgery at the primary tumor site.

Our conclusions are consistent with a previous study that evaluated patients in the SEER database who were diagnosed with stage IV GC between 2010 and 2015 [7]. However, unlike our study, this study did not include the T stage and N stage, which are closely related to prognosis, because the SEER database lacks stage information in the eighth edition of AJCC. Our study chose to include larger sample size, eligible patients between 2004 and 2015, and reclassified TNM stages according to AJCC 8th, making our results more convincing.

At present, the primary treatment for stage IV GC is systematic. Surgeries are often performed in emergencies such as bleeding, perforation, or obstruction [12]. Moreover, the surgery of the primary tumor can also reduce the tumor burden, reverse the tumor-induced immunosuppression, and eliminate the source of further metastasis [13]. Many studies have shown that resection of the primary tumor can prolong the survival time of patients with stage IV GC. A retrospective study of 288 patients in Turkey showed that surgery at the primary tumor site in patients with stage IV GC might improve survival regardless of the occurrence of life-threatening tumor-related complications (12vs.7.8 months, $p < 0.001$) [6]. Another study, based on the GIRGC database, focused on factors that affect the risk of survival and recurrence. The results show that patients with stage IV GC can benefit from radical gastrectomy after chemotherapy. Further analysis showed that the only independent prognostic factor affecting OS was the presence of more than one type of metastasis (HR4.41,95%CI1.72 ~ 11.3, $p = 0.002$) [14].

However, an open, randomized phase 3 trial (REGATTA) denied the benefits of surgery at the primary tumor site (16.6vs.14.3 months, $P = 0.70$) [9]. Although this study represents the highest level of such research at present, there are still some limitations. First, the study focused only on the prognosis of patients, such as post-chemotherapy surgery, which hindered the broad clinical application of the results. Secondly, the chemotherapy regimen used in this study was S-1 plus cisplatin. A phase III study showed that SOX (S-1 plus oxaliplatin) chemotherapy regimen for patients with stage IV GC was safer than S1 plus cisplatin [15]. Not only that, we found that in this study, the chemotherapy cycle of patients in the

surgical group was shorter than that in the chemotherapy group alone, which may have an impact on survival outcomes.

The differences in the results of the above different studies also reveal that not all patients who undergo surgery for primary tumors can benefit from the surgery, which also shows that there are still limitations in the choice of patients undergoing surgery. Therefore, we propose a new selection process to determine the benefit factors associated with surgery to primary tumor site: First, Patients with stage IV GC who meet the criteria were included. PSM was used to eliminate the selection bias according to the baseline characteristics. Second, According to the median CSS time (7 months) of the non-surgery group, the patients in the surgery group were subdivided into benefit group (survival time more than 7 months) and non-benefit group (survival time less than 7 months). Third, A multivariate logistic regression model was established according to the pre-surgery baseline characteristics of beneficial and non-beneficial groups. The model determined the related factors of surgical benefit.

The results showed that the patients with T stage T4b and histological grade GIII/GIV could not benefit from the surgery. When the tumor is in the T4b stage, it shows that the tumor has invaded the adjacent structures and organs, which means that a broader range of surgery and more surgery-related complications occur. Similarly, higher-grade tumors usually lead to the rapid development of the disease. They are less sensitive to radiotherapy and chemotherapy, and surgery can bring limited survival benefits to such patients, which can explain our results to some extent. Our analysis shows that receiving chemotherapy is more beneficial to patients from surgery. Therefore, active surgery should be recommended for lower T-stage patients, lower histological grade, and chemotherapy. However, the SEER database does not provide information on the sequence of chemotherapy and surgery. In the real world, most clinicians will choose pre-surgery chemotherapy to reduce the size of the tumor and eliminate micro-metastasis to improve the effectiveness of surgical treatment [16,17]. This result also confirms our view that only specific patients will benefit from the surgery. The potential benefits will vary depending on the characteristics and treatment of the primary tumor.

There are limitations to this study. First of all, the SEER database lacks the number of metastatic sites and surgical data. It has been proved that the number of distant metastases has a significant impact on the prognosis [14]. It is a limitation of the database itself. Secondly, the SEER database lacks information on targeted therapy and immunotherapy. We cannot answer whether resection of the primary tumor will bring more survival benefits before or after targeted therapy and immunotherapy. Finally, despite the use of the retrospective study of PSM, there may still be research biases. And this is only a preliminary study, and the results need to be verified by future prospective trials. Finally, despite the use of PSM to reduce selective bias, this retrospective study may still be biased. And this is only a preliminary study, and the results need to be verified by future prospective trials.

Generally, surgery at the primary tumor site can bring survival benefits to patients with stage □ GC. In addition, we propose a new selection process to screen patients with stage IV GC who can benefit from surgery. The analysis results showed that patients with T stage T4b and histological grade GIII/GIV could

not benefit from the operation, and such patients should consider comprehensive treatment. Patients who receive chemotherapy can benefit from surgery, and such patients should be recommended to undergo surgery actively.

Declarations

Data Availability Statement

Publicly available datasets were analyzed in this study. This data can be found here: (https://seer.cancer.gov/).

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Not applicable.

Author Contributions

HY and ZL: conceive this study. HY: collect/analyze data and consult the relevant literature and write manuscripts. All the authors contributed to this article and approved the submitted version.

Competing Interests

The authors have declared that no competing interest exists.

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Figures

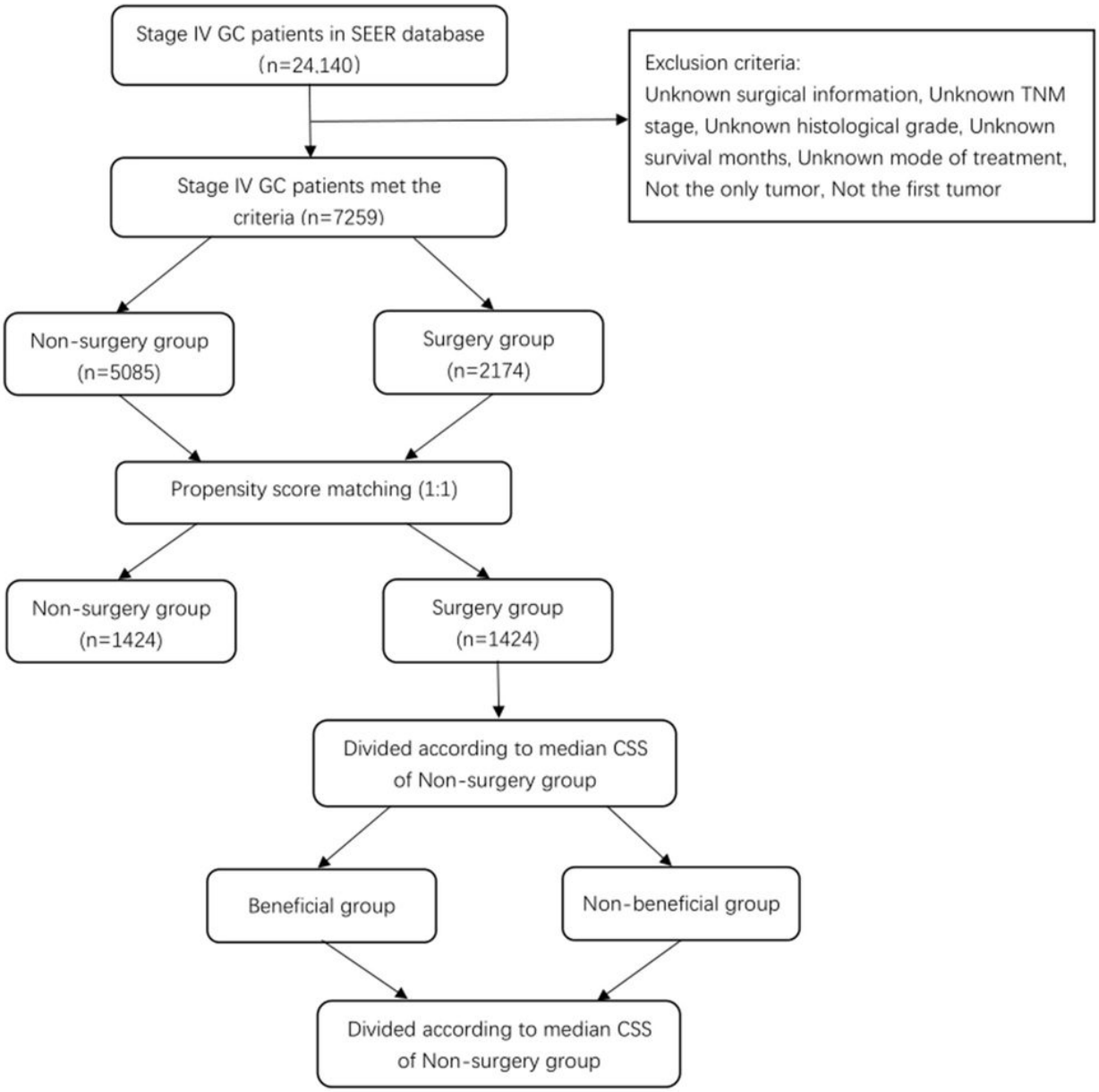

Figure 1

Flowchart of the screening process. SEER, Surveillance, Epidemiology and End Results; PSM, propensity score-matched; GC, gastric cancer; CSS, cancer specific survival

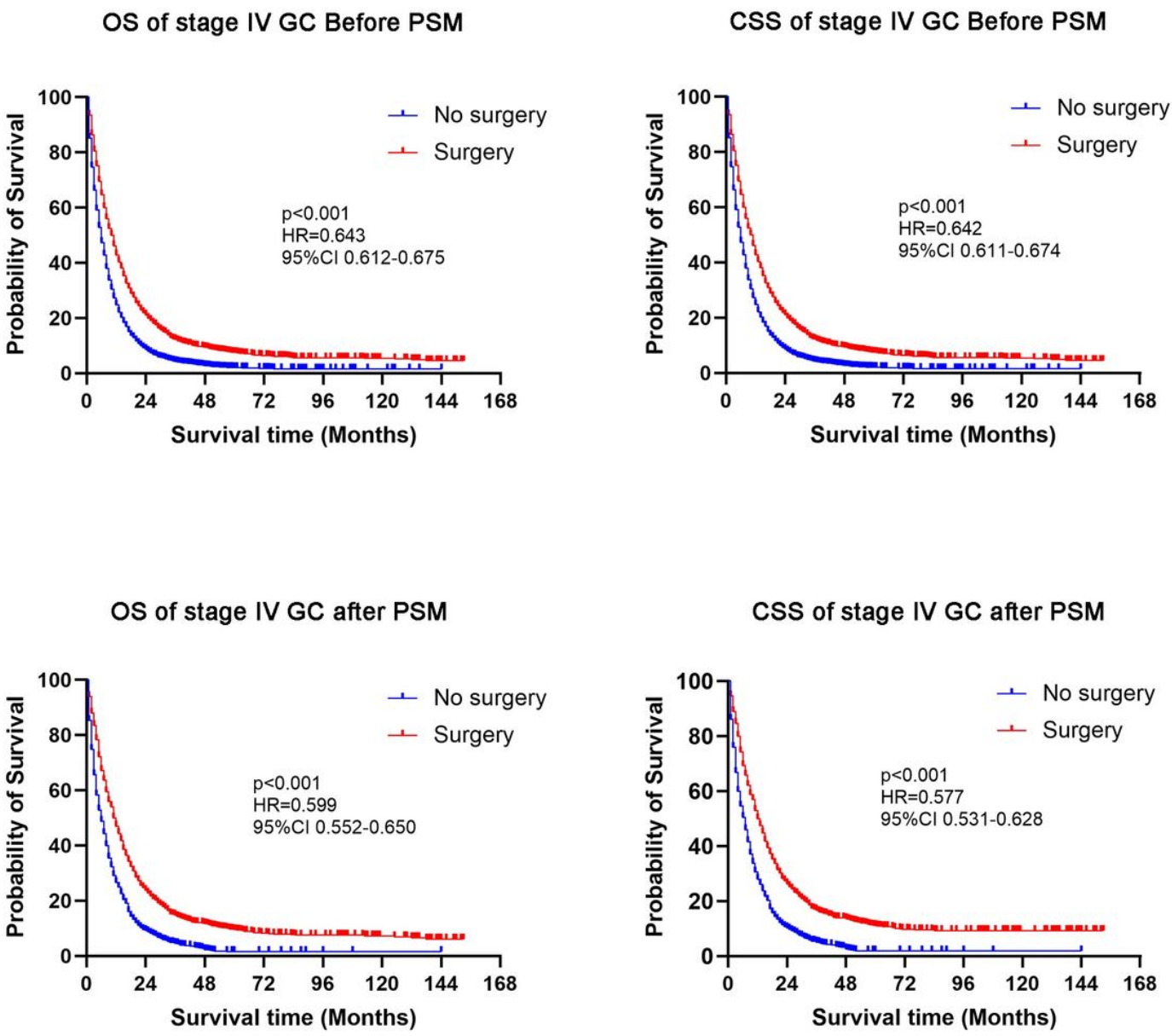

Figure 2

Kaplan-Meier analysis of stage IV GC patients according to treatment. GC, gastric cancer; SEER, Surveillance, Epidemiology and End Results; PSM, propensity score matching; OS, overall survival; CSS, cancer specific survival; HR, hazard ratio.

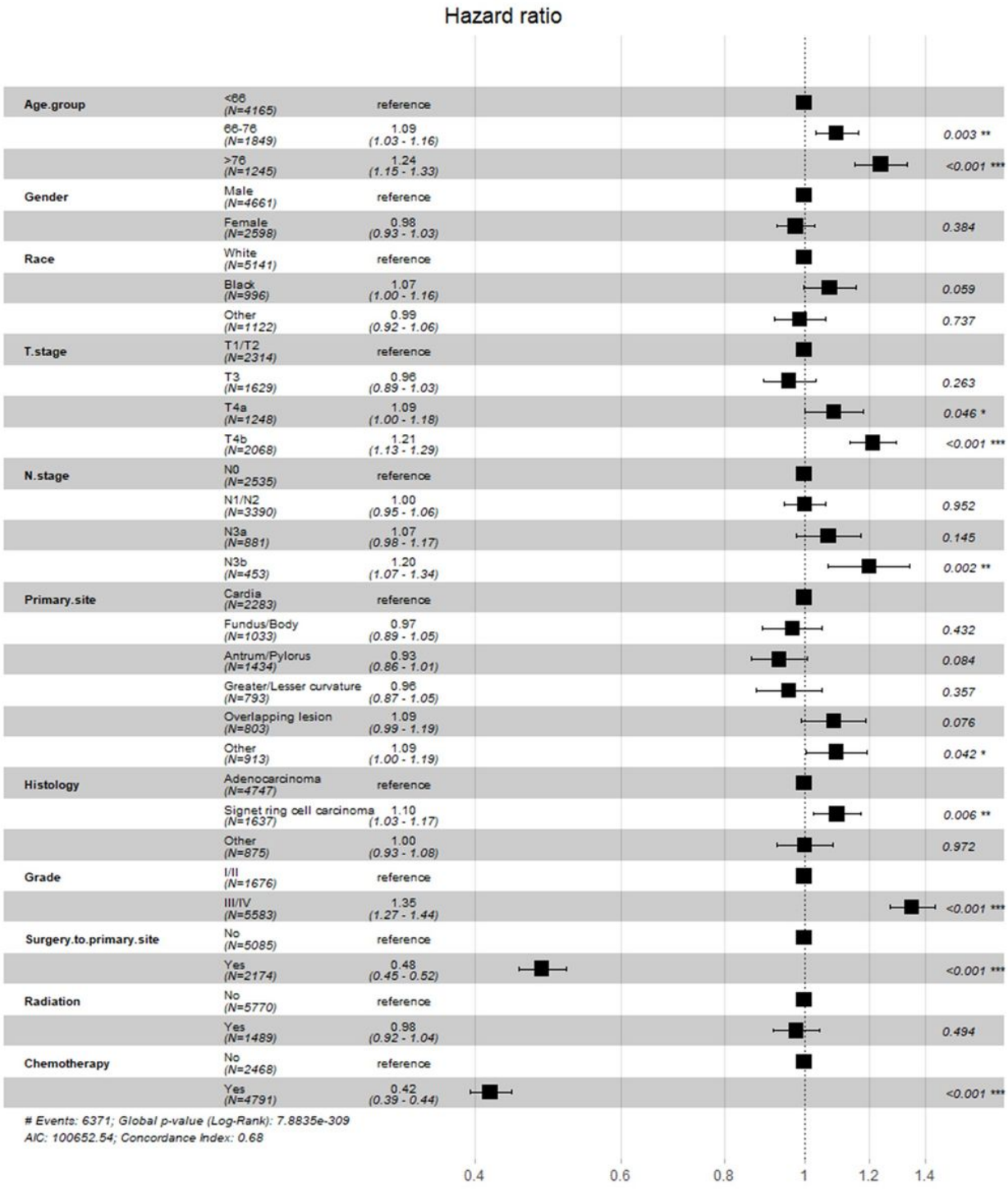

Figure 3

Forest plot of the factors that influence CSS in patients before PSM. CSS, cancer specific survival; PSM, propensity score matching.

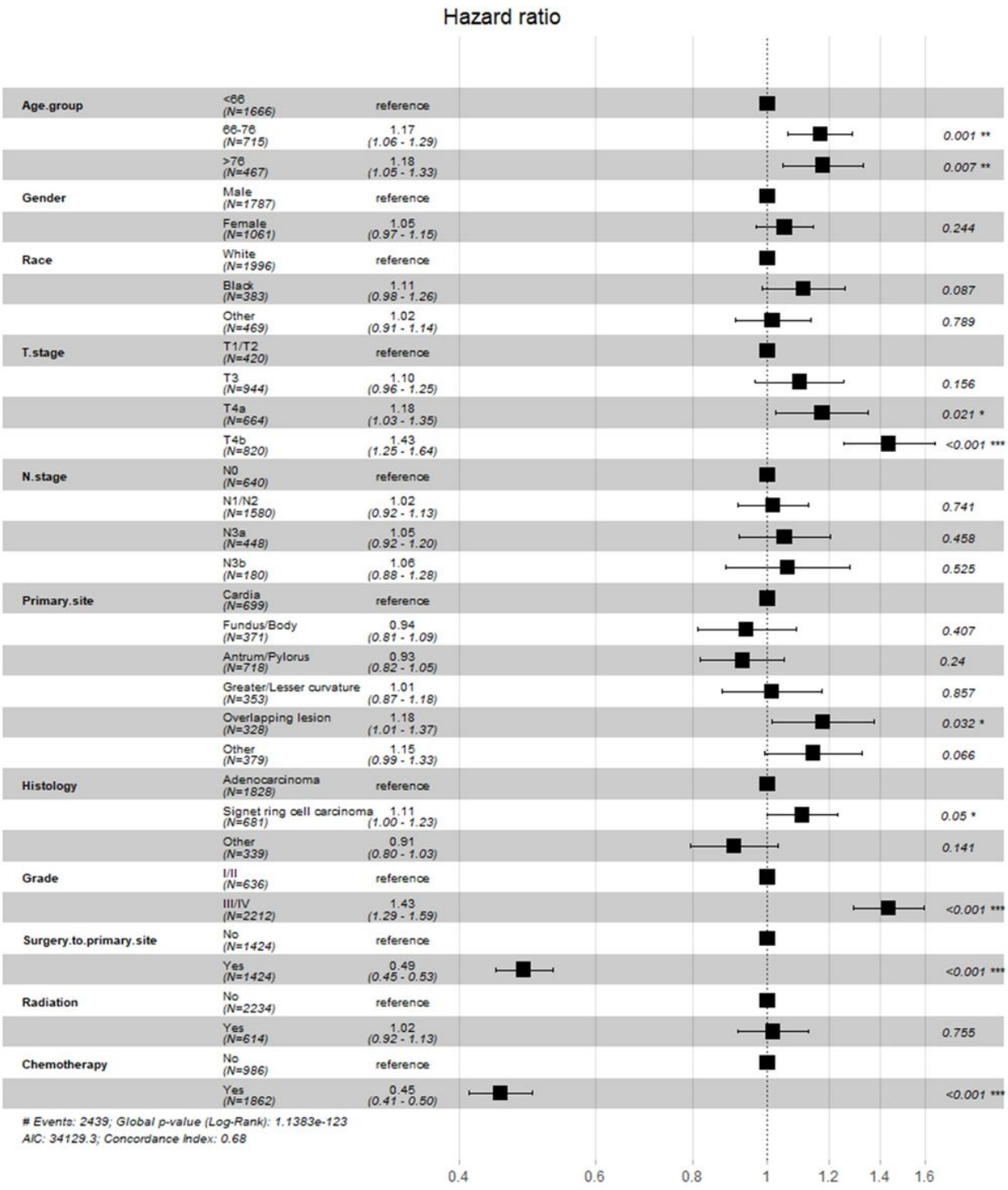

Figure 4

Forest plot of the factors that influence CSS in patients after PSM. CSS, cancer specific survival; PSM, propensity score matching.

Supplementary Files

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- TableS1.docx