ORIGINAL ARTICLE

Primary tumor resection benefited the survival of patients with distant metastatic gastric cancer

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Background: The role of surgery in the treatment of patients with distant metastatic (M1) gastric cancer (GC) remains controversial currently. This study aimed to clarify the impact of primary tumor resection (PTR) on the survival of such patients. **Materials and Methods:** The surveillance, epidemiology, and end results database was adopted to extract eligible patients. We designed a retrospective case–control study. The patients were divided into two groups according to whether they received PTR. The 1:1 propensity score matching (PSM) analysis was performed to balance the confounding factors between no-surgery and surgery groups. The categorical variables were described with Chi-square tests. Cancer-specific survival (CSS) and overall survival (OS) were evaluated by Kaplan–Meier method with log-rank test. Cox proportional hazard models were utilized to identify prognostic factors of CSS. **Results:** A total of 1716 patients were included, including 1108 (64.6%) patients without surgery and 608 (35.4%) patients with surgery. After PSM, most confounders were well balanced between the two comparison groups. Survival analysis in matched cohorts indicated that surgery exerted significant survival advantages in both CSS and OS curves. The median CSS was 11.0 (9.8–12.2) months in the surgery group versus 9.0 (8.0–10.0) months in the no-surgery group ($P < 0.001$). Multivariable Cox regression analysis identified surgery as an independent prognostic factor for favorable prognosis (hazard ratio: 0.689, 95% confidence interval: 0.538–0.881, $P = 0.003$). **Conclusion:** Surgery showed significant survival benefits for the patients with M1 stage GC. Our study has provided additional evidence to support PTR for these patients.

Key words: Metastatic, stomach neoplasms, surgery, survival

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INTRODUCTION

Gastric cancer (GC) is the third cause of cancer-related death.[1] An estimation of over 950,000 new cases of GC has been diagnosed every year, leading to 720,000 deaths in 2012.[2] Adenocarcinoma represents the majority of GCs.[3] Some metabolic abnormalities, such as abnormal glucose homeostasis, may lead to imbalanced energy generation, impair the immune system, and progressively engender GC.[4] Most patients with GC are diagnosed at locally advanced stages.[5] Approximately 35% of GC patients have the evidence of distant metastases (M1) at initial diagnosis.[6] Some predictors, such as weight, age, sex, and type 2 diabetes mellitus, have been reported to affect the prognosis of the patients.[7] The clinical outcomes of these patients largely depend on the high percentage of both local recurrence and distant metastases rates.[8] The treatment for these patients is rather tough, the median survival time of GC patients with distant metastases is <12 months, and the 5-year survival is <10% without surgical treatment.[9]

This poses a challenging health problem in urgent need of individualized management.

With respect to the treatment of metastatic GC, surgery represents the cornerstone of curative treatment for locally advanced GC,[10] but its role in the management of GC patients with distant metastases has not been sufficiently clarified. The Dutch GC Trial provided the first evidence to prove the survival benefits of palliative gastrectomy

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for patients with metastatic GC.[11] On the other hand, in REGATTA trial, gastrectomy followed by chemotherapy failed to show any survival benefit when compared with chemotherapy alone for advanced GC.[12] Currently, primary tumor resection (PTR) has not been recommended by clinical guidelines for GC patients with distant metastases.[13] The survival benefits of PTR for these patients still remain vague. The eligible criteria for PTR have not been established for these patients. Hence, the effect of PTR for GC patients with distant metastases is still necessary to be evaluated in detail.

In this article, we retrospectively analyzed the survival impact of PTR for GC patients with distant metastases. We also identified the prognostic factors for these patients, in order to determine the candidates who may benefit from PTR. Our study hopefully provides some evidence to facilitate the decision-making for optimal surgery of M1 stage GC.

MATERIALS AND METHODS

Patient selection

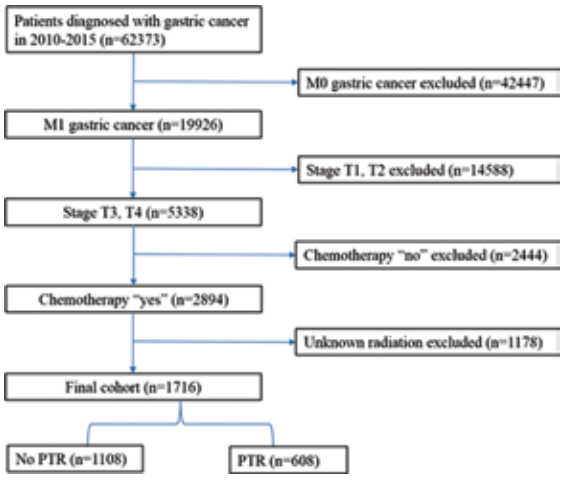
All data in this study were extracted from the surveillance, epidemiology, and end results (SEER) 18 registries custom database (with additional treatment fields). The patients were recruited using SEER * Stat version 8.3.6 software directly (https://seer.cancer.gov/seerstat/). We have signed the data use agreement for the SEER 1975–2016 research database file and acquired the permission to extract the research data. The identity information on individual patients has been excluded from the computer files. The SEER database is an openly accessible database, so our study was exempt from institutional ethical review board. The GC patients were selected from the SEER database, which comprises 18 cancer registries and covers approximately 30% of the US population.[14] We adopted the following inclusion criteria: (1) the patients were diagnosed from 2004 to 2015; (2) primary site was stomach; (3) behavior recode for analysis was malignant; (4) primary GC was the first or only cancer diagnosis; (5) chemotherapy recode was "yes;" and (6) the M stage was M1. The diagnosis was pathologically confirmed GC. Those patients were excluded if any table variable was unknown or missing data. We designed a retrospective case–control study. The process of patient selection is shown in Figure 1.

Data collection

The following table variables were extracted: year of diagnosis, age at diagnosis, sex, race recode, primary site, histologic type, grade, tumor size, stage T, stage N, regional nodes examined, radiation sequence with surgery, surgery of primary site, survival months, cause-specific death classification, and vital status recode. As for cancer-specific survival (CSS), only death due to GC was considered as an event occurrence, while for overall survival (OS), it was death due to any cause.[15] In this study, CSS was the primary endpoint, and OS was the secondary endpoint. The patients were divided into two groups according to whether they received PTR. They were grouped as chemotherapy only (no surgery) versus palliative PTR with chemotherapy (surgery). We evaluated the effect of PTR on the prognosis of patients with distant metastatic GC. The CSS and OS were calculated in the two comparison groups. Moreover, we also identified the prognostic factors for these patients, highlighting the impact of surgery on their survival.

Statistical analysis

The selected patients were divided into those not received PTR (no surgery) versus those received PTR (surgery). Differences between categorical variables were evaluated by Pearson Chi-square or Fisher's exact test. A propensity score matching (PSM) process was performed to minimize the possibility of selection bias between the two groups of patients. The significant variables in descriptive statistics before PSM were used as the matching confounders to estimate the propensity scores of receiving surgery. The PSM used a 1:1 nearest neighbor algorithm without replacement.[16] The caliper width was set at 0.01. The survival probability was estimated by Kaplan–Meier (KM) method and compared by log–rank test. Univariate and multivariable Cox proportional hazards (PH) regression models were fitted to identify independent prognostic factors of CSS in the postmatching cohort. Using Schoenfeld residuals, assumption of PH was tested. If the PH assumption was not met, accelerated failure time models were utilized.[17] The variables in univariate models were further included in the multivariable model. The PSM was implemented by R version 3.5.3 (http://www.R-project.org). The statistical analyses were conducted by SPSS software version 25.0 (SPSS, Chicago, IL, USA). A two-tailed $P < 0.05$ was considered statistically significant.



Figure

RESULTS

Patient characteristics

A total of 1716 patients who met inclusion criteria were included. In the cohort before PSM, 1108 (64.6%) patients did not receive surgery, while 608 (35.4%) patients received surgery. There were significant differences in all variables between the two groups ($P < 0.05$). As for demographic factors, compared to the no-surgery group, patients in the surgery group were more likely to have age ≤50 (31.7% vs. 24.0%), more female (42.3% vs. 33.1%), and more other race (22.7% vs. 12.4%). With respect to tumor features, the surgery group displayed more antrum cancer, more subtype 8144, 8145, 8490, more Grade III/IV, tumor size ≤50 mm, more stage T3, N2/N3, more LN examined >10. In addition, the surgery group showed significantly higher proportions of receiving radiotherapy. The PSM was initiated to adjust potential confounders, including diagnosis year, age, gender, race, primary site, subtype, grade, tumor size, T stage, N stage, LN examined, and radiation status. The 1:1 PSM developed matched cohorts of 186 patients without surgery and 186 patients with surgery. After PSM, the cohorts were well matched with no significant differences in most variables except primary site, subtype, and tumor size. The patient clinicopathological characteristics before and after PSM are summarized in Table 1.

Survival analysis in unmatched cohort

As for the cohort before PSM, the KM plots indicated that the surgery group had significantly superior survival to the no-surgery group in both CSS and OS curves [Figure 2]. The median CSS of surgery group was 13.0 (11.9–14.1) months, while that of the no-surgery group was only 8.0 (7.5–8.5) months [Table 2, $P < 0.001$]. In parallel, the median OS of surgery group was also better than that of the no-surgery group. The results before PSM showed that surgery exerted significant survival advantages for the unmatched patients.

Survival analysis in matched cohort

After PSM, there were no significant differences in most confounders between the two groups. The KM plots exhibited that survivals of surgery group were notably better than no-surgery group in both CSS and OS curves [Figure 3]. Concretely, the median CSS was 11.0 (9.8–12.2) months in the surgery group versus 9.0 (8.0–10.0) months in no-surgery group [Table 3, $P < 0.05$]. Likewise, the median OS of surgery group was also remarkably superior to that of no-surgery group. The results after PSM confirmed that PTR had significant survival benefits for the patients with stage.

Identify prognostic factors

We developed the Cox PH models to identify prognostic factors of CSS in the matched cohort. In univariate analysis, the significant variables were LN examined >10, received post-Radiation therapy (RT), and received surgery ($P < 0.05$). All the variables were subsequently included in the multivariable Cox regression model. After adjusting the confounders, surgery was proved to be an independent protective factor for favorable prognosis (hazard ratio) (HR < 1, $P < 0.05$). To verify if the PH

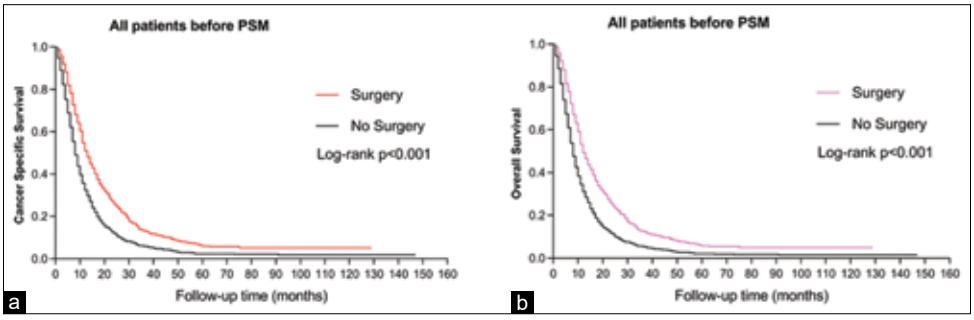


Figure 2: Kaplan-Meier survival curves before propensity score matching. (a) Cancer-specific survival ($P < 0.001$). (b) Overall survival ($P < 0.001$)

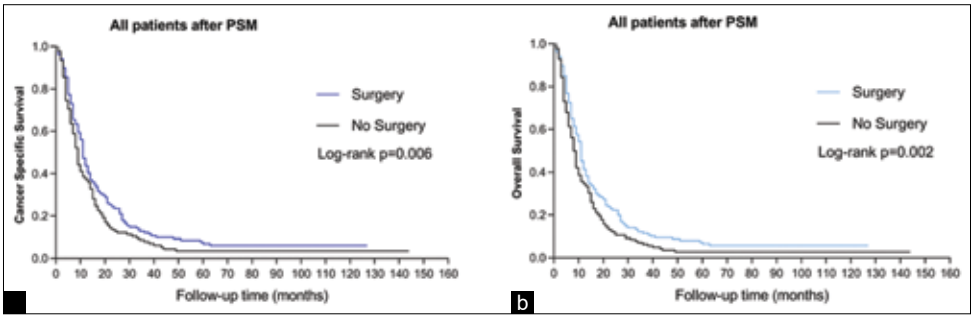


Figure 3: Kaplan-Meier survival curves after propensity score matching. (a) Cancer-specific survival ($P < 0.05$). (b) Overall survival ($P < 0.05$)

Table 1: Baseline characteristics of patients with stage M1 gastric cancer

Characteristics	Before PSM			After PSM		
	No surgery (*n*=1108; 64.6%), *n* (%)	Surgery (*n*=608; 35.4%), *n* (%)	*P*	No surgery (*n*=186; 50%), *n* (%)	Surgery (*n*=186; 50%), *n* (%)	*P*
Diagnosis year						
2004-2009	558 (50.4)	352 (57.9)	0.003	105 (56.5)	99 (53.2)	0.532
2010-2015	550 (49.6)	256 (42.1)		81 (43.5)	87 (46.8)	
Age (years)						
≤50	266 (24.0)	193 (31.7)	0.002	47 (25.3)	51 (27.4)	0.443
50-70	614 (55.4)	313 (51.5)		95 (51.1)	101 (54.3)	
>70	228 (20.6)	102 (16.8)		44 (23.7)	34 (18.3)	
Gender						
Male	741 (66.9)	351 (57.7)	<0.001	116 (62.4)	113 (60.8)	0.749
Female	367 (33.1)	257 (42.3)		70 (37.6)	73 (39.2)	
Race						
White	835 (75.4)	392 (64.5)	<0.001	123 (66.1)	134 (72.0)	0.467
Black	136 (12.3)	78 (12.8)		23 (12.4)	19 (10.2)	
Others	137 (12.4)	138 (22.7)		40 (21.5)	33 (17.7)	
Primary site						
Cardia	454 (41.0)	92 (15.1)	<0.001	58 (31.2)	26 (14.0)	<0.001
Antrum	174 (15.7)	191 (31.4)		32 (17.2)	68 (36.6)	
Overlapping	147 (13.3)	114 (18.8)		21 (11.3)	32 (17.2)	
Stomach NOS	149 (13.4)	67 (11.0)		36 (19.4)	28 (15.1)	
Body	117 (10.6)	76 (12.5)		24 (12.9)	20 (10.8)	
Lesser curvature	67 (6.0)	68 (11.2)		15 (8.1)	12 (6.5)	
Subtype						
8140	714 (64.4)	245 (40.3)	<0.001	107 (57.5)	83 (44.6)	<0.001
8144	54 (4.9)	77 (12.7)		6 (3.2)	27 (14.5)	
8145	44 (4.0)	67 (11.0)		12 (6.5)	19 (10.2)	
8490	296 (26.7)	219 (36.0)		61 (32.8)	57 (30.6)	
Grade						
I	18 (1.6)	6 (1.0)	<0.001	3 (1.6)	4 (2.2)	0.835
II	228 (20.6)	77 (12.7)		30 (16.1)	25 (13.4)	
III	844 (76.2)	497 (81.7)		146 (78.5)	148 (79.6)	
IV	18 (1.6)	28 (4.6)		7 (3.8)	9 (4.8)	
Tumor size (mm)						
≤30	78 (7.0)	44 (7.2)	<0.001	20 (10.8)	8 (4.3)	0.010
30-50	127 (11.5)	140 (23.0)		24 (12.9)	40 (21.5)	
>50	903 (81.5)	424 (69.7)		142 (76.3)	138 (74.2)	
T stage						
T3	288 (26.0)	357 (58.7)	<0.001	78 (41.9)	85 (45.7)	0.464
T4	820 (74.0)	251 (41.3)		108 (58.1)	101 (54.3)	
N stage						
N0	381 (34.4)	65 (10.7)	<0.001	38 (20.4)	51 (27.4)	0.063
N1	634 (57.2)	233 (38.3)		118 (63.4)	95 (51.1)	
N2	62 (5.6)	191 (31.4)		21 (11.3)	33 (17.7)	
N3	31 (2.8)	119 (19.6)		9 (4.8)	7 (3.8)	
LN examined						
≤10	1059 (95.6)	206 (33.9)	<0.001	146 (78.5)	143 (76.9)	0.709
>10	49 (4.4)	402 (66.1)		40 (21.5)	43 (23.1)	
RT						
No	1090 (98.4)	459 (75.5)	<0.001	170 (91.4)	170 (91.4)	0.344
Post-RT	16 (1.4)	120 (19.7)		14 (7.5)	16 (8.6)	
Pre-RT	2 (0.2)	29 (4.8)		2 (1.1)	0 (0.0)	

8140=Adenocarcinoma; 8144=Adenocarcinoma, intestinal type; 8145=Adenocarcinoma, diffuse type; 8490=Signet ring cell adenocarcinoma. PSM=Propensity score matching; LN=Lymph node; RT=Radiotherapy

Table 2: Comparison of median survival for the patients before propensity score matching (*n*=1716)

Before PSM	Patients, *n*	95% CI, months	
		Median CSS	Median OS
No surgery	1108	8.0 (7.5-8.5)	8.0 (7.5-8.5)
Surgery	608	13.0 (11.9-14.1)	12.0 (11.0-13.0)
P		<0.001	<0.001

PSM=Propensity score matching; CSS=Cancer-specific survival; OS=Overall survival

Table 3: Comparison of median survival of the patients after PSM (*n*=372)

After PSM	Patients, *n*	95% CI, months	
		Median CSS	Median OS
No surgery	186	9.0 (8.0-10.0)	8.0 (6.8-9.2)
Surgery	186	11.0 (9.8-12.2)	11.0 (9.7-12.3)
P		0.006	0.002

PSM=Propensity score matching; CSS=Cancer-specific survival; OS=Overall survival

assumption was valid, Schoenfeld residuals were evaluated in terms of ranked survival time for selected predictors. All fitted lines originated from individual scatter plots appeared horizontal. These results confirmed that the PH assumption was satisfied. Concretely, the HR of surgery was 0.689, with 95% confidence interval = 0.538–0.881, P = 0.003. Hence, surgery was identified as a beneficial prognostic factor for the patients with M1 stage GC. The detailed results are listed in Table 4.

DISCUSSION

At present, radical surgery for patients with metastatic GC still remains controversial.[18] Few studies have adequately clarified the role of surgical resection in the treatment of such patients.[19] Based on a large cohort from the SEER database, we used PSM analysis to investigate the clinicopathological and treatment features of patients with M1 stage GC, highlighting the impact of surgery on the prognosis of these patients. The PSM has well-balanced most confounding factors between the no-surgery group and the surgery group. The overall results indicated that PTR was associated with significant survival benefits for these patients.

The role of surgery in treating patients with metastatic GC has been evaluated by several previous publications. A retrospective SEER study was conducted to investigate whether GC patients with distant metastases might benefit from surgery.[20] Although their results revealed that resection of either primary tumor or distant metastatic tumors improved the survival of the patients, the baseline characteristics among treatment groups were not well matched. The selection bias and potential confounders may well undermine their power of analysis. Comparatively, our study adopted the PSM method to balance the confounders between surgery group and no-surgery group. The results based on PSM analysis become more convincing. In parallel, another study has compared the outcomes of metastatic GC patients stratified by surgery and RT.[21] It was reported that surgery and radiation were associated with improved survival only in a subset of patients with metastatic GC. The tumor histology in this study comprised many subtypes. Moreover, the survival benefits of surgery were also confounded with radiotherapy. The survival advantage of surgery was not adequately highlighted in this report. By contrast, our study specifically focused on the survival impact of surgery on the patients with M1 stage GC. Our results have highlighted the role of surgery in improving the patients' survival. Anyway, either previous literature or our study has consistently found that PTR improved the survival of distant metastatic GC. In our matched cohorts, the median CSS was 11.0 (9.8–12.2) months in the surgery group versus 9.0 (8.0–10.0) months in the no-surgery group. The median OS of surgery group was also significantly superior to that of the no-surgery group. Hence, the survival benefits of surgery for such patients were further confirmed from our study.

In terms of the prognostic factors for patients with M1 stage GC, a recent study indicated that surgery and age ≤60 years old were independent protective factors for these patients, while radiotherapy was not associated with CSS of the patients.[22] Another study also analyzed the proportion and prognosis of liver metastases at diagnosis of GC from the SEER database. It identified age, tumor location, Lauren classification, T stage, surgery, chemotherapy, and marital status as independent predictors for the patients' OS.[23] By comparison, the multivariable Cox analysis in our study also showed that surgery was an independent protective factor for those patients. Thus, surgery was identified as an independent beneficial prognostic factor for improving the patients' survival.

There are several limitations of our study. First, our study is a retrospective analysis of the patients from the SEER database, some unmeasured confounders may well engender potential bias. For instance, the exclusion of the missing data may become a source of bias. The patient status, surgical pattern, and different chemotherapy regime may also have contributed to the study bias.[24] Second, the number of metastases, whether the patients received synchronous or metachronous surgery, and comorbidities were not available in the SEER database.[25] Third, the findings of this study only represent the American population, which is hard to be generalized to the global population such as Chinese, Japanese, and Korean.[26] In spite of the limitations above, the SEER registry data are highly complete and represent the real-world population, thus reducing the potential bias.

Table 4: Cox proportional hazards regression model for cancer-specific survival (*n*=372)

Characteristics	Univariate Cox		Multivariable Cox	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Diagnosis year				
2004-2009	Reference		Reference	
2010-2015	0.945 (0.758-1.177)	0.613	1.027 (0.809-1.303)	0.827
Age (years)				
≤50	Reference		Reference	
50-70	0.966 (0.743-1.256)	0.797	0.914 (0.695-1.201)	0.517
>70	1.079 (0.783-1.486)	0.643	1.036 (0.733-1.464)	0.843
Gender				
Male	Reference		Reference	
Female	1.188 (0.950-1.485)	0.130	1.085 (0.844-1.395)	0.524
Race				
White	Reference		Reference	
Black	0.859 (0.599-1.232)	0.407	0.877 (0.600-1.283)	0.500
Others	0.890 (0.676-1.171)	0.404	0.797 (0.594-1.070)	0.131
Primary site				
Cardia	Reference		Reference	
Antrum	1.085 (0.794-1.482)	0.608	1.226 (0.844-1.781)	0.286
Overlapping	1.401 (0.973-2.017)	0.070	1.315 (0.855-2.023)	0.213
Stomach NOS	1.097 (0.777-1.549)	0.597	1.095 (0.741-1.618)	0.649
Body	1.177 (0.788-1.758)	0.426	1.261 (0.809-1.966)	0.306
Lesser curvature	0.967 (0.594-1.572)	0.891	0.941 (0.557-1.589)	0.820
Subtype				
8140	Reference		Reference	
8144	1.048 (0.709-1.548)	0.814	1.108 (0.720-1.705)	0.640
8145	0.764 (0.489-1.192)	0.236	0.802 (0.501-1.284)	0.358
8490	1.339 (1.048-1.710)	0.019	1.248 (0.938-1.660)	0.129
Grade				
I	Reference		Reference	
II	0.934 (0.399-2.187)	0.875	0.647 (0.257-1.627)	0.354
III	1.085 (0.482-2.441)	0.843	0.775 (0.319-1.882)	0.574
IV	1.041 (0.403-2.686)	0.934	0.726 (0.259-2.037)	0.543
Tumor size (mm)				
≤30	Reference		Reference	
30-50	1.244 (0.773-2.002)	0.369	1.604 (0.954-2.699)	0.075
>50	1.177 (0.773-1.791)	0.447	1.356 (0.857-2.145)	0.193
T stage				
T3	Reference		Reference	
T4	0.892 (0.717-1.111)	0.307	0.932 (0.730-1.189)	0.571
N stage				
N0	Reference		Reference	
N1	1.151 (0.881-1.504)	0.301	1.158 (0.869-1.544)	0.316
N2	0.873 (0.608-1.254)	0.462	0.913 (0.613-1.359)	0.653
N3	1.379 (0.779-2.441)	0.270	1.508 (0.800-2.844)	0.204
LN examined				
≤10	Reference		Reference	
>10	0.755 (0.579-0.984)	0.038	0.825 (0.612-1.112)	0.206
RT				
No	Reference		Reference	
Post-RT	0.583 (0.377-0.901)	0.015	0.693 (0.434-1.109)	0.126
Pre-RT	2.034 (0.504-8.199)	0.318	1.996 (0.462-8.622)	0.355
Surgery				
No	Reference		Reference	
Yes	0.744 (0.598-0.927)	0.008	0.689 (0.538-0.881)	0.003

8140=Adenocarcinoma; 8144=Adenocarcinoma, intestinal type; 8145=Adenocarcinoma, diffuse type; 8490=Signet ring cell adenocarcinoma. HR=Hazard ratio; LN=Lymph node; RT=Radiotherapy; CI=Confidence interval

The major strength of our study lies in rigorous inclusion criteria and a large number of eligible patients from the SEER database. Moreover, we also used both PSM analysis and multivariable Cox regression analysis to adjust the potential bias caused by confounding factors. This doubly robust estimation combines two approaches to evaluate the causal effect of exposures on outcomes, which encourages researchers to more fully interpret their findings on both scales. Hence, the power of our study is still convincing.

CONCLUSION

Based on the results of PSM analysis, surgery showed significant survival benefits for the patients with distant metastatic GC. Surgery was also identified as an independent protective factor for favorable prognosis. Our study has provided additional evidence to recommend PTR for such patients in clinical practice, which hopefully optimizes the current policy-making for them.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

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