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Research Paper

The survival benefit of palliative gastrectomy and/or metastasectomy in gastric cancer patients with synchronous metastasis: a population-based study using propensity score matching and coarsened exact matching

Lu-Ping Yang*, Zi-Xian Wang*, Ming-Ming He*, Ying Jin, Chao Ren, Zhi-Qiang Wang, Feng-Hua Wang, Yu-Hong Li, Feng Wang, Rui-Hua Xu✉

Department of Medical Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China

* These authors contributed equally to this work.

✉ Corresponding author: Rui-Hua Xu, 651 Dong Feng Road East, Guangzhou 510060, China; Tel and Fax: +86-20-8734 3468; E-mail: xurh@sysucc.org.cn

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Abstract

Introduction: Palliative surgeries were controversial for asymptomatic metastatic gastric cancer (mGC) patients. This study was aimed to evaluate survival benefit of palliative surgeries to gastric and/or metastatic tumors in mGC patients based on U.S population.

Materials and Methods: A total of 8345 gastric cancer patients diagnosed with synchronous distal metastasis between 2004 to 2013 from the Surveillance, Epidemiology, and End Results Program (SEER) database were divided into four groups according to surgery strategies: surgeries to both primary and metastatic tumors (SPM), gastrectomy only (GO), metastasectomy only (MO) and no surgery performed (NS). Their clinicopathological characteristics and overall survival (OS) were analyzed before and after propensity score matching (PSM) and coarsened exact matching (CEM).

Results: The median OS of SPM and GO patients was both significantly higher than NS patients (11 months vs. 8 months vs. 5 months; P<0.001, respectively) while that of MO was not (6 months vs. 5 months; P= 0.286). In comparisons between surgery strategies, survival benefit was similar between SPM and GO groups (P=0.389) and both showed significantly better survival than MO patients (P<0.001). All surgery strategies were proved to be favorable prognostic factors over non-surgical treatment (Hazard ratio (HR) for SPM: 0.60, P<0.001; HR for GO: 0.62, P<0.001; HR for MO: 0.91, P=0.046). Similar results were obtained after matching by PSM and CEM except that prognostic impact of MO deteriorated.

Conclusions: Gastrectomy plus metastasectomy or gastrectomy alone could be adopted as a choice of improving survival in the U.S population. Metastasectomy alone is not generally recommended.

Key words: gastric cancer; gastrectomy; metastasectomy; survival; matching

1. Introduction

Gastric cancer (GC) ranks the fifth most common tumors and the fourth leading cause of cancer-related deaths in the United States, with approximately 22,220 new cases and 10,990 deaths in 2014. [1] Although an annual decline of the incidence rate of GC was observed since 1992 [2], the 5-year overall survival (OS) remained unimproved. Especially for metastatic GC (mGC), the median survival was only 7.9 to 13.8 months as assessed in several randomized clinical trials, which however consisted of more than one third of initially diagnosed GC patients. [3] Developing best treatment strategies for mGC is undoubtedly of vital importance. Systemic treatment strategies with chemotherapy, target therapy and immunotherapy are universally adopted while performing surgery is controversial. Current guidelines approved of palliative gastrectomy in terms of obstruction or uncontrolled bleeding, but palliative surgeries for the purpose of tumor reduction to either primary or metastatic sites were not mentioned for recommendation. [4] There were some studies finding that surgical resection with therapeutic intent in mGC patients was associated with a relatively poor prognosis, and the REGATTA trial conducted in Eastern population negated gastrectomy followed by chemotherapy could improve survival in mGC patients compared to chemotherapy alone. [5, 6] Nevertheless, in recent years many retrospective studies challenged the negative results and have shown survival benefit in patients treated with gastrectomy and/or metastasectomy with or without chemotherapy. [7-14] Moreover, the GYMSSA trial proved regional treatment including maximal cytoreductive surgery and regional hyperthermic intraperitoneal chemotherapy combined with systemic chemotherapy could achieve prolonged survival in selected patients. [15] For now, the survival impacts of surgeries to mGC patients in Western population are still under investigation, and there also lacks evidence in comparing different surgery strategies.

In this study, we searched the Surveillance, Epidemiology, and End Results Program (SEER) database to evaluate survival benefit from surgeries to primary and/or metastatic tumors in comparison with non-surgeryin the U.S. population.

2. Material and methods

2.1 Patients and data collection

The study population and their clinicopathological data were searched and collected from Surveillance, Epidemiology, and End Results Program (SEER) database. Patients initially diagnosed as gastric adenocarcinoma by microscopically confirmation with synchronous distal metastasis between 2004 to 2013 at the age of 18 to 79 were included. GC was defined according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) with codes C160/C161/C162/C163/C164/C165/C166/C168/C169 for primary tumor location and codes 8140/8144/8145/8211/8260/8480/8490 for histological type. Patients aged 80 or more are excluded because they are not usually considered for surgery and thus not fit in this topic. Patients diagnosed with more than one primary tumor and patients undergoing radiation therapy were excluded to avoid distraction from study objectives. It was necessary to clarify each patient's surgery strategy that whether one underwent primary or metastatic tumor resection, and thus those without such information would also be excluded. Additionally, patients who died within one month after diagnosis were excluded for more sufficient analysis. Figure 1 presents the inclusion and exclusion process. A total of 8345 eligible patients were divided into four groups according to the surgery strategy, that is one group of patients who underwent surgeries to both primary and metastatic tumors (SPM), one group with gastrectomy only (GO), one group with metastasectomy only (MO) and one group of the other patients who was not surgically operated (NS).

No institutional approval or informed consent was required because SEER is a public-use database.

2.2 Statistical analysis

Patient characteristics were compared by the chi-square test for categorical variables. Spearman rank correlation analysis was used to evaluate time trends of surgery strategies. Overall survival (OS) was the primary endpoint outcome and was evaluated by Kaplan–Meier method. Log-rank test was used to compare survival between groups. To analyze prognostic factors, the univariable Cox regression analysis was performed and hazard ratio (HR) with 95% confidence interval (CI) were assessed, followed by a multivariable Cox analysis to evaluate prognostic impact of palliative surgeries with risk adjustment for the other factors whose P value <0.05 in the univariable Cox analysis. Furthermore, two matching methods were introduced to guarantee better balance in baseline characteristics between groups and to reduce confounding impacts on survival analysis. One matched subanalysis was based on the propensity score with 1-to-1-to-1-to-1 matching (PSM). [16] Coarsened exact matching (CEM) method, which is less fitting-model dependent than PSM and could improve balance for each covariate without influencing the others to achieve maximum of the balance, was used in the other subanalysis. [17-19] Population after matching was analyzed as it was before matching.

Information on chemotherapy in the SEER database was limited to patients with or without/unknown receiving chemotherapy, and was suggested to be used with cautions due to its incompleteness and potential biases according to the official data use agreement. However, systemic chemotherapy is a major treatment for mGC patients and have a strong impact on their survival, therefore we carried out sensitivity analyses to verify the survival benefit of surgery strategies in combination of chemotherapy after excluding patients receiving no/unknown chemotherapy.

All data analyses were performed using SPSS Statistics 22.0 (IBM Corp., Version 22.0, Armonk, NY) and the "MatchIt" and "cem" R packages (The R Foundation, version 3.4.2). A two-sided *P* value <0.05 was considered to be statistically significant.

3. Results

3.1 Patient characteristics

Table 1 shows the demographic and clinicopathological characteristics of the patients enrolled. The median age of the whole cohort was 61 years old and 62.3% was male. Non-Hispanic white people and west-region residents took the most proportion, respectively.

Seventy-seven percent of patients had no surgery, followed by 12.1% of patients with gastrectomy only and 6.6% with metastatic tumors resected only, and smallest proportion of patients underwent SPM. Imbalance between groups was found in all characteristics investigated. In SPM and MO groups, there were more younger patients (< 50 years old) and female than that in other groups. NS patients had more primary tumor located in the upper one third whereas SPM and GO patients had more in the lower one third stomach. Besides, more and more patients received non-surgical treatment and an over-ten-percent increase was observed from 2004 to 2013 while the rate of mGC patients undergoing gastrectomy dropped significantly as time went by. (*P*<0.001, Figure 2)

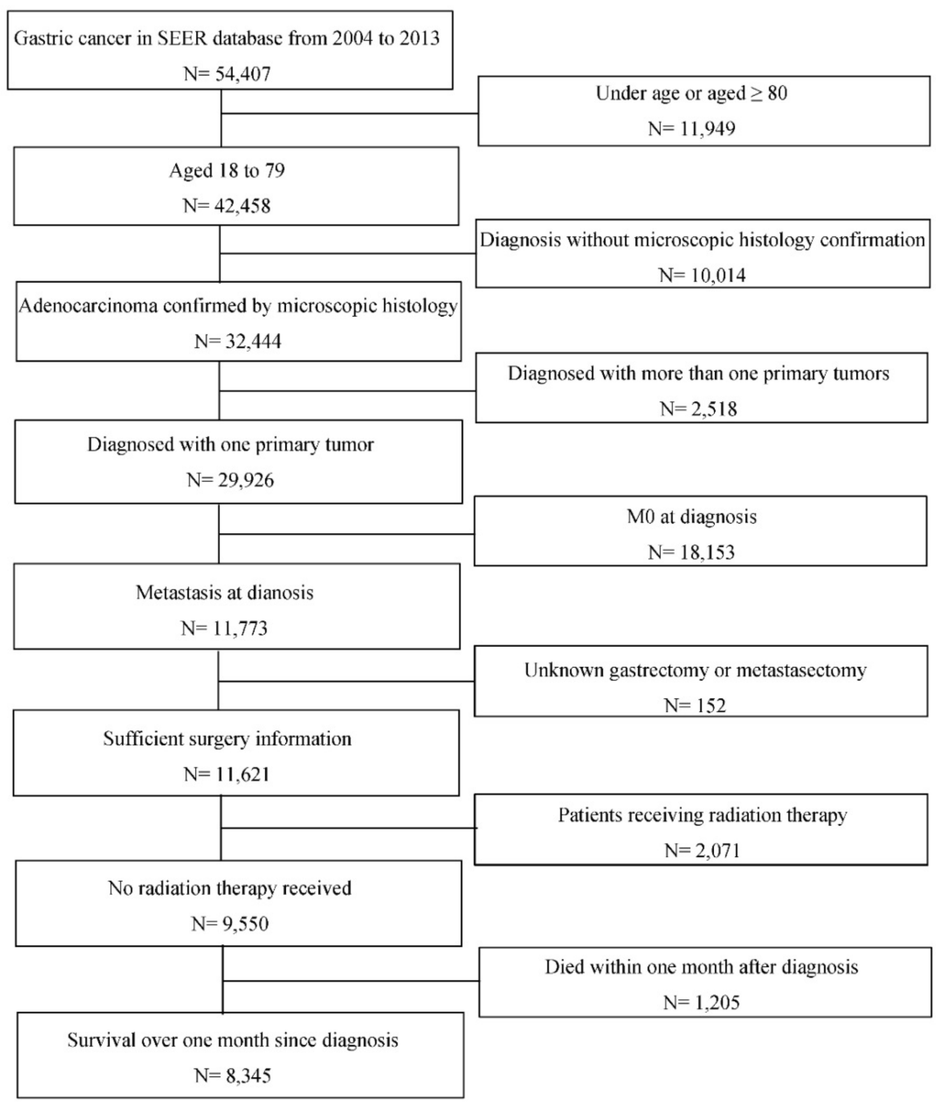


Figure 1. Flowchart of inclusion and exclusion process of the study population. Abbreviations: SEER, Surveillance, Epidemiology, and End Results; M0, without distant metastasis diagnosed.

Table 1. Baseline demographic and clinicopathological characteristics of the patients

Variable	Number (%)					*P* value
	All cohort	SPM	GO	MO	NS	
Total	8345 (100.0%)	359 (4.3%)	1006 (12.1%)	551 (6.6%)	6429 (77.0%)	
Age, years						<0.001
< 50	1819 (21.8%)	106 (29.5%)	207 (20.6%)	206 (37.4%)	1300 (20.2%)	
50−59	2028 (24.3%)	87 (24.2%)	254 (25.2%)	138 (25.0%)	1549 (24.1%)	
60−69	2449 (29.3%)	83 (23.1%)	297 (29.5%)	120 (21.8%)	1949 (30.3%)	
≥ 70	2049 (24.6%)	83 (23.1%)	248 (24.7%)	87 (15.8%)	1631 (25.4%)	
Sex						<0.001
Male	5195 (62.3%)	179 (49.9%)	629 (62.9%)	212 (38.5%)	4175 (64.9%)	
Female	3150 (37.7%)	180 (50.1%)	377 (37.5%)	339 (61.5%)	2254 (35.1%)	
Marriage status						0.012
Married	5005 (60.0%)	227 (63.2%)	631 (62.7%)	327 (59.3%)	3820 (59.4%)	
Widowed	670 (8.0%)	28 (7.8%)	97 (9.6%)	35 (6.4%)	510 (7.9%)	
Other	2670 (32.0%)	104 (29.0%)	278 (27.6%)	189 (34.3%)	2099 (32.6%)	
Race						<0.001
Non-Hispanic White	3973 (47.6%)	170 (47.4%)	389 (38.7%)	242 (43.9%)	3172 (49.3%)	
Non-Hispanic Black	1123 (13.5%)	42 (11.7%)	158 (15.7%)	67 (12.2%)	856 (13.3%)	
Hispanic	2030 (24.3%)	93 (25.9%)	271 (26.9%)	151 (27.4%)	1515 (23.6%)	
Other	1219 (14.6%)	54 (15.0%)	188 (18.7%)	91 (16.5%)	886 (13.8%)	
SEER region						<0.001
Mid-west	917 (11.0%)	43 (12.0%)	69 (6.9%)	71 (12.9%)	734 (11.4%)	
Northeast	1327 (15.9%)	62 (17.3%)	143 (14.2%)	71 (12.9%)	1051 (16.3%)	
South	1339 (16.0%)	67 (18.7%)	162 (16.1%)	85 (15.4%)	1025 (15.9%)	
West	4762 (57.1%)	187 (52.1%)	632 (62.8%)	324 (58.8%)	3619 (56.3%)	
Year of diagnosis						<0.001
2004−2006	2387 (28.6%)	130 (36.2%)	389 (38.7%)	179 (32.5%)	1689 (26.3%)	
2007−2009	2460 (29.5%)	114 (31.8%)	285 (28.3%)	145 (26.3%)	1916 (29.8%)	
2010−2013	3498 (41.9%)	115 (32.0%)	332 (33.0%)	227 (41.2%)	2824 (43.9%)	
Primary tumor location						<0.001
Upper one third	2537 (30.4%)	52 (14.5%)	138 (13.7%)	105 (19.1%)	2242 (34.9%)	
Middle one third	841 (10.1%)	35 (9.7%)	93 (9.2%)	64 (11.6%)	649 (10.1%)	
Lower one third	1568 (18.8%)	105 (29.2%)	333 (33.1%)	99 (18.0%)	1031 (16.0%)	
NOS	3399 (40.7%)	167 (46.5%)	442 (43.9%)	283 (51.4%)	2507 (39.0%)	
Tumor grade						<0.001
G1/G2	1484 (17.8%)	56 (15.6%)	177 (17.6%)	46 (8.3%)	1205 (18.7%)	
G3/G4	5121 (61.4%)	286 (79.7%)	764 (75.9%)	310 (56.3%)	3761 (58.5%)	
Unknown	1740 (20.9%)	17 (4.7%)	65 (6.5%)	195 (35.4%)	1463 (22.8%)	
Histology						<0.001
Adenocarcinoma NOS	5774 (69.2%)	219 (61.0%)	628 (62.4%)	270 (49.0%)	4657 (72.4%)	
Mucinous adenocarcinoma	135 (1.6%)	9 (2.5%)	31 (3.1%)	10 (1.8%)	85 (1.3%)	
Signet ring cell carcinoma	2436 (29.2%)	131 (36.5%)	347 (34.5%)	271 (49.2%)	1687 (26.2%)	
Gastrectomy						
Yes	1365 (16.4%)	359 (100.0%)	1006 (100.0%)	0 (0.0%)	0 (0.0%)	
Total gastrectomy surgery	401 (4.8%)	115 (32.0%)	286 (28.4%)	0 (0.0%)	0 (0.0%)	
Non-total gastrectomy surgery	907 (10.9%)	216 (60.2%)	691 (68.7%)	0 (0.0%)	0 (0.0%)	
Not specified	57 (0.7%)	28 (7.8%)	29 (2.9%)	0 (0.0%)	0 (0.0%)	
No	6980 (83.6%)	0 (0.0%)	0 (0.0%)	551 (100.0%)	6429 (100.0%)	
Metastasectomy						
Yes	910 (10.9%)	359 (100.0%)	0 (0.0%)	551 (100.0%)	0 (0.0%)	
No	7435 (89.1%)	0 (0.0%)	1006 (100.0%)	0 (0.0%)	6429 (100.0%)	

Abbreviation: SPM, surgeries to both primary and metastatic tumors; GO, gastrectomy only; MO, metastasectomy only; NS, no surgery; SEER, Surveillance, Epidemiology, and End Results.

3.2 Survival analysis

The OS of SPM and GO patients was both significantly higher than NS patients, with an improved median OS (mOS) of 6.0 months and 3.0 months, respectively. However, the mOS of MO only exceeded that of NS by 1.0 month, which was not a significant difference (*P*=0.286). In terms of comparisons between surgery strategies, survival benefit was similar between SPM and GO groups (*P*=0.389), while both showed significantly better survival than MO patients (*P* <0.001, respectively). Figure 3 depicts survival curves of patients stratified by surgical strategies.

3.3 Univariable and multivariable Cox regression analysis

Age at diagnosis, marriage status, race, SEER region, location and histology of primary tumor, year of diagnosis and surgery strategies were proven to be independent prognostic factors (Table 2). After adjusting for these factors in multivariable Cox analysis, all surgery strategies were proved to have significantly better prognosis than NS ones (HR for SPM: 0.60, *P*<0.001; HR for GO: 0.62, *P*<0.001; HR for MO: 0.91, *P*=0.046), and gastrectomy with or without metastasectomy remained superior over MO.

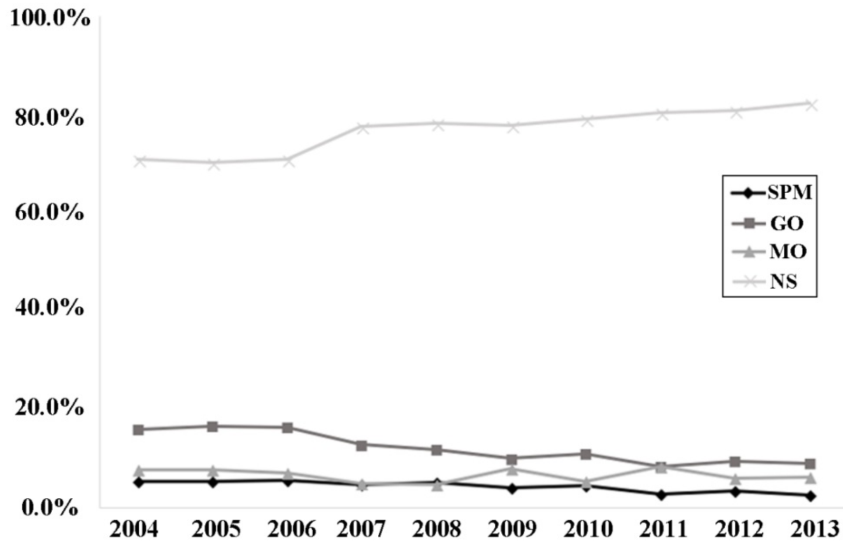
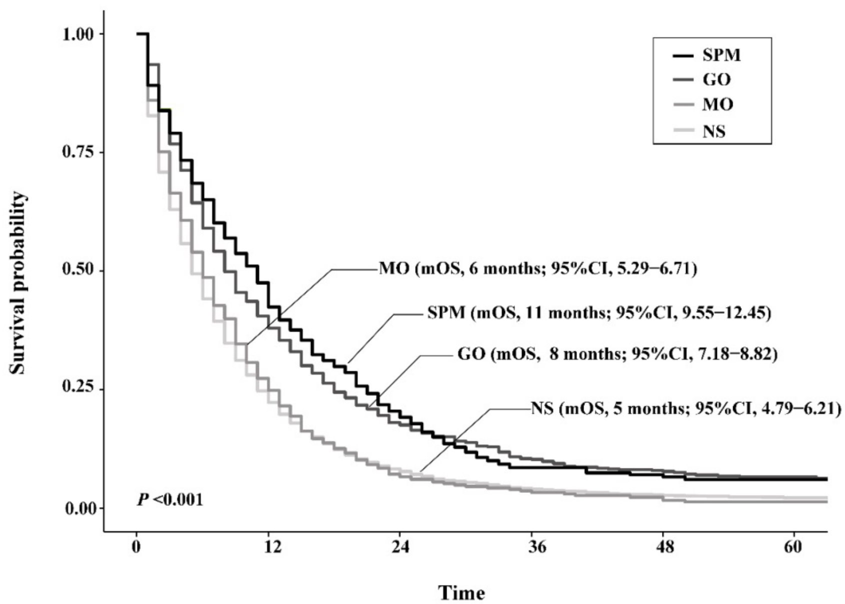


Figure 2. Proportions of surgery strategies performed in each year from 2004 to 2013. Abbreviations: SPM, surgeries to both primary and metastatic tumors; GO, gastrectomy only; MO, metastasectomy only; NS, no surgery.



Number at risk

	0	12	24	36	48	60
SPM	359	159	61	24	16	8
GO	1006	367	146	72	44	28
MO	551	129	28	11	7	4
NS	6429	1338	360	141	72	41

Figure 3. Kaplan–Meier survival curves of patients stratified according to their surgery strategies. Abbreviations: SPM, surgeries to both primary and metastatic tumors; GO, gastrectomy only; MO, metastasectomy only; NS, no surgery; mOS, median overall survival.

3.4 Propensity score matching and coarsened exact matching analysis

By PSM and CEM, the patient characteristics were well balanced between groups to diminish selection bias (Supplementary Table 1). The survival analyses based upon the matched population both showed consistent results with that upon the unmatched cohort, except in CEM-weighted analysis MO group presented poorer yet not significant survival than NS group (Figure 4).

In the univariable and multivariable Cox analysis, surgery strategies were demonstrated to be a prognostic factor (Table 3). Surgeries to the primary and/or metastatic tumors lowered the death risk from non-surgery, however MO did not function significantly in both matched subanalyses. Inbetween surgery strategies, SPM and GO held comparable survival impacts and both were more favorable than MO.

Table 2. Results of univariable and multivariable Cox regression analysis

Variable	Univariable Cox analysis		Multivariable Cox analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years				
< 50	Reference	< 0.001	Reference	< 0.001
50−59	0.97 (0.91, 1.04)		0.99 (0.93, 1.07)	
60−69	1.05 (0.98, 1.12)		1.09 (1.02, 1.17)	
≥ 70	1.22 (1.14, 1.30)		1.25 (1.16, 1.35)	
Sex				
Male	Reference	0.309	- [a]	- [a]
Female	1.03 (0.98, 1.07)		- [a]	
Marriage status				
Widowed	Reference	< 0.001	Reference	< 0.001
Married	0.79 (0.72, 0.86)		0.85 (0.77, 0.92)	
Other	0.86 (0.78, 0.94)		0.93 (0.85, 1.02)	
Race				
Non-Hispanic White	Reference	0.005	Reference	0.002
Non-Hispanic Black	1.09 (1.02, 1.17)		1.06 (0.98, 1.15)	
Hispanic	1.01 (0.96, 1.07)		0.99 (0.93, 1.06)	
Other	0.93 (0.87, 0.99)		0.90 (0.83, 0.96)	
SEER region				
Mid-west	Reference	< 0.001	Reference	< 0.001
Northeast	0.83 (0.76, 0.90)		0.83 (0.76, 0.91)	
South	1.02 (0.93, 1.11)		1.03 (0.94, 1.13)	
West	0.99 (0.92, 1.07)		1.02 (0.94, 1.11)	
Year of diagnosis				
2004−2006	Reference	< 0.001	Reference	< 0.001
2007−2009	0.86 (0.81, 0.91)		0.83 (0.78, 0.88)	
2010−2013	0.81 (0.76, 0.86)		0.77 (0.73, 0.82)	
Primary tumor location				
Upper one third	Reference	< 0.001	Reference	< 0.001
Middle one third	1.09 (1.01, 1.18)		1.08 (0.99, 1.18)	
Lower one third	1.04 (0.98, 1.12)		1.11 (1.03, 1.19)	
NOS	1.16 (1.10, 1.23)		1.18 (1.12, 1.26)	
Histology				
Adenocarcinoma NOS	Reference	0.001	Reference	< 0.001
Mucinous adenocarcinoma	0.91 (0.76, 1.10)		0.95 (0.79, 1.13)	
Signet ring cell carcinoma	1.09 (1.04, 1.15)		1.11 (1.06, 1.18)	
Surgery strategies				
NS	Reference	< 0.001	Reference	< 0.001
GO	0.67 (0.62, 0.72)		0.62 (0.57, 0.67)	
MO	0.95 (0.87, 1.05)		0.91 (0.83, 1.00)	
SPM	0.63 (0.57, 0.71)		0.60 (0.54, 0.68)	

[a] The variable was not include in the multivariable Cox analysis because of its *P* value ≥ 0.05 in the univariable Cox analysis.

Abbreviations: HR, hazard ratio; SEER, the Surveillance, Epidemiology, and End Results Program; NS, no surgery; GO, gastrectomy only; MO, metastasectomy only; SPM, surgery to both primary and metastatic tumor; NOS, not otherwise specified.

Table 3. Multivariable Cox regression analysis with propensity score matching and coarsened exact matching method weighting

Surgery strategies	Propensity score matching cohort		Coarsened exact matching method weighted cohort	
	HR[a] (95% CI)	*P* value	HR[b] (95% CI)	*P* value
NS	Reference		Reference	
GO	0.59 (0.51, 0.69)	<0.001	0.57 (0.43, 0.77)	<0.001
MO	0.94 (0.80, 1.10)	0.412	0.89 (0.65, 1.22)	0.464
SPM	0.60 (0.51, 0.70)	<0.001	0.50 (0.35, 0.72)	<0.001

[a] After adjustment for age, year of diagnosis, primary tumor location and histology whose *P* value <0.05 in the univariable Cox regression analysis.

[b] After adjustment for age, sex, race, SEER region, year of diagnosis, primary tumor location and histology whose *P* value <0.05 in the univariable Cox regression analysis.

Abbreviations: HR, hazard ratio; CI, confidence interval; NS, no surgery; SPM, surgery to both primary and metastatic tumor; GO, gastrectomy only; MO, metastasectomy only.

3.5 Sensitivity analyses

A total of 5347 patients were enrolled in the sensitivity analyses, and the demographic and clinicopathological characteristics were still different between groups (Supplementary Table 2). Survival analyses found that mOS of SPM (13 months vs. 8 months; *P*<0.001) and GO (12 months vs. 8 months; *P*<0.001) patients were both significantly higher than that of NS patients, and MO was not (8 months vs. 8 months; *P* = 0.893). SPM and GO groups showed comparable survival (*P* = 0.748) and both were significantly better than MO patients (*P*<0.001). After matching by PSM and CEM, similar results were obtained. Table 4 illustrates death risks of surgery strategies over NS among patients receiving chemotherapy, that is SPM and GO rather than MO were proven to be favorable for survival over non-surgical treatment, even after matching by PSM or CEM. These consistent results implied that SPM and GO could also improve survival from MO or NS in patients who received chemotherapy.

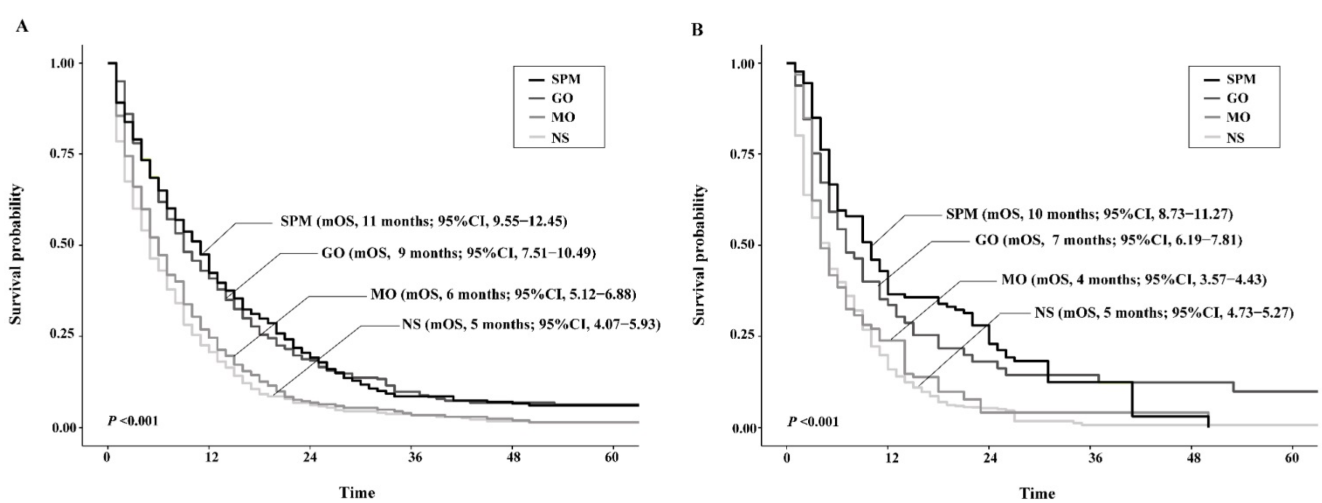


Figure 4. Kaplan–Meier survival curves of patients stratified according to their surgery strategies after propensity score matching (A) or coarsened exact matching (B). Abbreviations: SPM, surgeries to both primary and metastatic tumors; GO, gastrectomy only; MO, metastasectomy only; NS, no surgery; mOS, median overall survival.

Table 4. Death risks of surgery strategies over NS among patients receiving chemotherapy for the sensitivity analyses

Surgery strategies	All cohort		Propensity score matching cohort		Coarsened exact matching method weighted cohort	
	HR [a] (95% CI)	*P* value	HR [b] (95% CI)	*P* value	HR [c] (95% CI)	*P* value
NS	Reference		Reference		Reference	
GO	0.61 (0.55, 0.67)	<0.001	0.56 (0.46, 0.69)	<0.001	0.64 (0.58, 0.70)	<0.001
MO	0.92 (0.82, 1.03)	0.154	0.94 (0.77, 1.15)	0.524	1.02 (0.95, 1.11)	0.557
SPM	0.59 (0.51, 0.69)	<0.001	0.60 (0.49, 0.73)	<0.001	0.63 (0.57, 0.69)	<0.001

[a] After adjustment for age, race, SEER region, year of diagnosis, marriage status, primary tumor location and histology whose *P* value <0.05 in the univariable Cox regression analysis.

[b] After adjustment for year of diagnosis, primary tumor location and histology whose *P* value <0.05 in the univariable Cox regression analysis.

[c] After adjustment for age, sex, race, SEER region, year of diagnosis, marriage status, primary tumor location and histology whose *P* value <0.05 in the univariable Cox regression analysis.

Abbreviations: HR, hazard ratio; CI, confidence interval; NS, no surgery; GO, gastrectomy only; MO, metastasectomy only; SPM, surgery to both primary and metastatic tumor.

4. Discussion

In this study, we included 8345 patients from the SEER database and divided them into four groups according to the surgery strategies to evaluate survival benefit from surgeries to primary and/or metastatic tumors in comparison with non-surgery in the U.S. population.

Up to date, surgery has not been widely considered to treat mGC patients given that there was no solid evidence available to support its survival benefit. And high surgery-related mortality and morbidity rates and short life span of mGC patients have prevented aggressive treatment strategies from application. But with the progress of preoperative imaging diagnosis, anesthesia and surgical techniques, and nutritional support, the surgery-related mortality rate dropped markedly from more than 20% two decades ago to 4%. [20-23] Except the safety and feasibility of surgery, increasing awareness of clinical decision-making by the multidisciplinary team (MDT) [24, 25] also led to re-consideration of surgery as part of treatment to mGC.

Previous studies investigated whether gastrectomy and/or metastasectomy could be beneficial and the results were inconclusive. The most common surgery strategy investigated is gastrectomy. Although the negative result was drawn from the REGATTA trial, there are still doubts on its combination pattern of surgery followed by chemotherapy and also its validation in Western population, and therefore many researchers kept studying on it. Warschkow et al. carried out a study based on a large sample of 7026 mGC patients diagnosed within 2006–2012 from the National Cancer Database and suggested gastrectomy could improve survival from chemotherapy alone. [26] A systematic review and meta-analysis by Lasithiotakis, K. et al. implied a possible benefit of gastrectomy compared to non-resectional treatment for stage IV gastric cancer, and 40-70% of the patients received postoperative chemotherapy. [21] MO is also an option of surgery strategies. There were pooled studies showing long-term survival after metastasectomy, but the indication was quite restricted with solitary metastatic lesions in limited organs. [27-31] As a relatively aggressive and extensive surgery strategy, SPM was cautiously investigated and used, and obtained improved survival in several studies. He, M. M. et al. and Kim, K. H. et al. found gastrectomy or gastrectomy plus metastasectomy combined with systemic chemotherapy could improve survival for advanced GC or mGC patients, respectively, based on the Asian population. [7, 8] The GYMSSA trial indicated that maximal cytoreductive surgery combined with regional hyperthermic intraperitoneal chemotherapy and systemic chemotherapy could achieve prolonged survival, but the trial prematurely ended up with a small sample size and a deteriorated evidence level. [15] On the other hand, few studies compared different surgery strategies. Yang, S. W. et al.'s study which excluded chemotherapy-receivers implied better prognosis of patients with SPM than that with GO, but Chen, J. et al. found the advantage not significant based on SEER-based population. [9, 11]

In the present study, the survival of the SPM and GO patients was demonstrated significantly better than MO and NS patients, respectively, and conducting metastasectomy did not improve survival significantly from gastrectomy or non-surgical treatment. Surgery strategies was proved as an independently favorable prognostic factor. Inbetween surgery strategies, SPM and GO held comparable survival impacts which were more favorable than MO. Chen, J. et al. obtained similar findings, but imbalanced baseline characteristics were not handled and consequent selection bias was aggravated by including factors like T and N stages, whose definition differed with or without resection, in the Cox regression analysis. [11] At an advantage, the present study removed post-surgery factors out of adjustment analysis and used PSM and CEM methods to avoid confounding effects, and also analyzed metastasectomy in addition. Furthermore, because chemotherapy is the mainstay of treatment for mGC patients, we carried out sensitivity analyses after excluding patients receiving no/unknown chemotherapy and obtained consistent results. To the best of our knowledge, this is the first study to demonstrate and compare survival benefits of palliative surgery strategies including gastrectomy and/or metastasectomy with PSM and CEM methods.

Results of the study cast light on the therapeutic role of palliative surgery strategies. Regional resection used to be applied for radical purpose, and it could be achieved in selected potentially resectable mGC patients after conversion chemotherapy with significant survival benefit. [13, 14, 32-36] However, since distal metastasis was a systemic manifestation, the complete resection of primary and metastatic tumors with proved survival benefit might actually be palliative as with a recurrence rate of more than 50%. [35, 37] Palliative gastrectomy with or without metastasectomy improved survival probably due to the debulking or cytoreductive effect at its source. Relieving symptoms caused by either the primary or metastatic tumors might as well positively influence mGC patients. However, metastasectomy seemed to obtain little additional survival improvement in the study, which might be attributed to heterogeneity of metastatic loci status of the study population. One research held the view that only metastasectomy could distinguish second primary tumors from metastasis. [29] Thus, MO is not recommended for general application and might be a choice among cautiously selected patients, and SPM could be adopted after adequate cost-and-effectiveness weighing for its numerically better OS compared with GO.

The study has several limitations. First, data on patient comorbidities and performance status, postoperative mortality and morbidity, quality of life, and detailed chemotherapy information are unavailable. Further studies are needed to explore the extra influence of these variables on survival and to select suitable surgery candidates. Second, the circumstances under which surgeries were conducted, like the surgeries are emergent or not and the patients are asymptomatic or not, were not specified in the SEER database. Such information could had better distinguished surgeries as a treatment alternative from emergency operations. Third, PSM and CEM analysis only deal with observable factors, thus other unobservable factors might be confounding and unmatched. Also, part of information is lost during the process of matching. Combination of the results of the two matching methods and multivariate Cox regression analysis in the present study is a dependable solution. Despite these limitations, given the large sample size and the population-based nature of the SEER database, we are able to perform adequately powerful survival analyses.

5. Conclusions

Poor prognosis of metastatic gastric cancer promotes oncologists to spare no effort finding and evaluating various treatment strategies for survival prolongation, and the present study demonstrated gastrectomy plus metastasectomy or gastrectomy alone could be adopted as a choice of improving survival in the U.S population. Metastasectomy alone is not recommended except for highly selected patients.

Abbreviations

GC: gastric cancer; mGC: metastatic GC; SEER: Surveillance, Epidemiology, and End Results Program; SPM: surgeries to both primary and metastatic tumors; GO: gastrectomy only; MO: metastasectomy only; NS: not surgically operated; PSM: propensity score matching; CEM: coarsened exact matching; MDT: multidisciplinary team.

Supplementary Material

Supplementary tables.
http://www.jcancer.org/v10p0602s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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