

Received: 2020.02.28

Accepted: 2020.04.24

Available online: 2020.05.08

Published: 2020.05.15

A Population-Based Analysis of Distant Metastasis in Stage IV Gastric Cancer

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Source of support:

The present study was supported by Chongqing Natural Science Foundation Program (cstc2019jcyj-msxmX0466), the Top Talent Training Program of the First Affiliated Hospital of PLA Army Medical University (SWH2018BJKJ-12), and the Natural Science Foundation of China (No. 81802508 and No. 81903398)

Background:

Distant metastasis (DM) is a crucial problem in management of patients with gastric cancer. Identification of the risk factors for development of DM and the prognostic factors for patients with DM is essential in development of individualized treatment of patients at the advanced stage with specific metastasis.

Material/Methods:

Records of patients with gastric cancer were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Survival duration of patients with specific DM was estimated, and the prognostic factors were investigated using the Cox proportional hazard regression model. The logistic regression model was used to reveal the inherent risk factors for development of DM.

Results:

Eventually, 32.6% (11,918 out of 36,588) of gastric cancer patients were diagnosed with DM between 2010 and 2015, among whom 5,361, 1,778, 1,495, and 231 patients were diagnosed with liver, lung, bone, and brain metastasis, respectively. The median overall survival for patients with DM was 5.0 (95% CI: 4.8–5.2) months, with a 5-year survival rate of 3.9%. Primary tumor site, histology types, tumor grade, T stage, N stage, surgery, chemotherapy, and the number of metastases were associated with worse survival. Younger age and higher tumor grade were positively associated with the development of DM.

Conclusions:

Initial DM was found in 32.6% of patients with gastric cancer. Homogenous and heterogenous predictive factors were identified for patients with a specific metastatic site, which can be used in targeted screening and individualized treatment.

MeSH Keywords:

Neoplasm Metastasis • Prognosis • Risk Factors • SEER Program • Stomach Neoplasms

Full-text PDF:

<https://www.medscimonit.com/abstract/index/idArt/923867>

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Background

As one of most common cancers worldwide, gastric cancer causes many death every year, imposing a huge burden on economic and medical resources [1]. In the latest cancer statistics (2019) in the United States, it was reported that there were 17,230 newly diagnosed cases of gastric cancer and 11,140 deaths caused by gastric cancer [2]. With the development of new treatment strategies, the long-term survival outcome of patients with gastric cancer has significantly improved, especially for pre-metastatic patients, with a 5-year survival rate of approximate 70% [3]. However, the prognosis of patients with distant metastasis has remained poor.

Distant metastasis is the main criterion for stage IV gastric cancer diagnosis, and distant metastasis is correlated with worse survival [4]. The percentage of metastasis in gastric cancer patients was reported to have increased from 24% in 1990 to 44% in 2011 in the Netherlands [5]. Due to the absence of early specific clinical symptoms, many patients are diagnosed with distant metastasis. Among all patients with gastric cancer, 40.1% were found to have synchronous distant metastasis [6]. The National Comprehensive Cancer Network (NCCN) recommends that different treatments should be administered to gastric cancer patients in different stages. For gastric cancer patients in stage IV, palliative therapy is suggested [7,8]. Due to the various symptoms associated with different metastatic sites, targeted treatment should be given in a specialized department. Thus, it is important to perform distant metastasis screening, and research on the risk factors for distant metastasis is needed.

Although it is important for guiding individualized treatment, prediction of prognosis of gastric cancer patients with distant metastasis is often difficult. Compared with other organs, the liver is more likely to develop metastasis in gastric cancer patients. A previous study found that 2.43% of gastric cancer patients who received gastrectomy subsequently developed liver metastases [9]. The 2-year survival rate in gastric cancer patients with synchronous liver-only metastases was reported to be 17.2% [10]. Favorable prognostic factors for patients with gastric cancer after radical hepatectomy were reported to be: lower T and N stage, less metastases, lesions smaller than 5 cm, and negative resection margins [11]. The pulmonary metastasis rate for gastric cancer patients was reported to be 0.96%, and the median survival was 4.0 months after diagnosis of pulmonary metastasis [12]. In a study of a cohort of patients with metastatic or recurrent gastric cancer, the initial bone metastasis rate was 6.7%, and the median survival was 4.4 months after diagnosis of bone metastasis [13]. Brain metastasis has seldom been studied [14], with a reported occurrence rate of 2.33% in gastric cancer patients [15].

However, the research cited above studied specific metastasis in gastric cancer and had limited sample sizes. To thoroughly study the relative risk factors and prognosis in stage IV gastric cancer, research exploring different patterns of distant metastasis on gastric cancer in a large population is needed.

The present study assessed a gastric cancer patient cohort extracted from the Surveillance, Epidemiology, and End Results (SEER) Program database to thoroughly investigate distant metastasis in gastric cancer patients. Our analysis of the risk factors, prognostic factors, and prognosis may help develop targeted specific metastatic screening and guide individualized treatment.

Material and Methods

Study population

Data were extracted from the National Cancer Institute SEER cohort (<https://seer.cancer.gov/data/>). SEER*Stat Software version 8.3.6 was used to generate the data.

Patients who were initially diagnosed with gastric cancer between 2010 to 2015 were selected because sites of metastases were available after 2010. In the patients we enrolled from the SEER database, all had been followed up until at least 2018 (i.e., minimum 3-year follow-up). The primary site label was used to identify patients with gastric cancer (C16.0–C16.9). Patients diagnosed at autopsy or via death certificate and those without detailed records on distant metastasis were excluded. To investigate the prognostic factors for gastric cancer patients with distant metastasis, patients diagnosed without distant metastasis were excluded after logistic regression analysis (Figure 1).

Statistical analysis

The following patient-related characteristics were included: age (<65 and ≥65 years); sex (female and male); marital status (unmarried and married); race (white, black, and others); insurance status (insured and uninsured); histological type (adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, and others/unknown); primary site (proximal third, middle third, distal third, stomach, NOS, and overlapping lesion); tumor grade (I to IV: well, moderately, poorly, and undifferentiated, respectively); T stage (T0/Tis/T1, T2, T3, and T4); N stage (N0, N1, N2, and N3); the presence of lung, liver, brain, or bone metastasis; surgical treatment (no, yes); radiation treatment (no/unknown, yes); and treatment with chemotherapy (no/unknown, yes). To investigate the prognostic factors for patients with distant metastasis, the variables of 'Number of mets' (the sum of metastases sites) and 'Other mets (metastasis for other sites)' were defined. The homogenous predictive

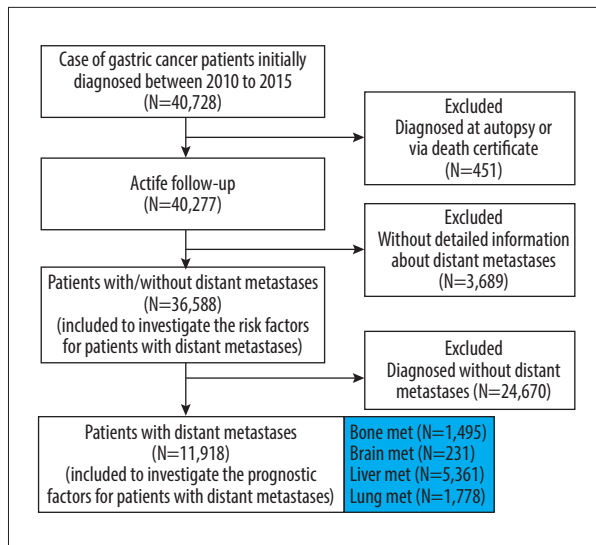


Figure 1. Flowchart of patient selection.

factors are variables which exert the same effect on disease development or survival prediction in subgroup analysis, while heterogeneous factors are those affecting a specific subgroup.

Categorical variables were presented as number and percentage (N,%), and Pearson chi-square (χ^2) or Fisher's exact test was used to evaluate the differences between demographic and clinicopathological variables. To identify risk factors for specific metastasis, logistic regression analysis was performed in our initial population. Variables with statistical differences in univariate logistic regression analysis were further analyzed by multivariate analysis. To identify risk factors for patients at M1 stage, patients who presented any distant metastatic sites (including liver, lung, bone, brain, and other non-specific sites) were defined as 'M-Met'. To identify risk factors for organ-specific metastasis, patients with only liver, lung, bone, and brain metastasis were regarded as having specific metastasis. For example, to identify risk factors for liver metastasis, patients who were diagnosed with only liver metastasis were regarded as 'Liver-Met' and were compared with those without any metastasis and those who had other metastatic sites. Overall survival (OS) was the primary outcome in the present study, which was defined as the time from diagnosis of gastric cancer to death due to any cause. Kaplan-Meier analysis were performed to estimate the length of survival, and the differences were assessed with log-rank test. To identify the prognostic factors for patients with distant metastasis, patients at M0 stage were excluded. We tested the proportional hazards assumption. Univariate Cox proportional hazards regression analysis was performed for patients at M1 stage. Variables with statistically significant differences were further analyzed by multivariate analysis to identify the prognostic factors.

IBM SPSS Statistics (version 23.0, Armonk, NY, USA) was used for statistical analyses, and survival curves were generated using MedCalc 15.2.2 (MedCalc Software, Ostend, Belgium). All statistical tests were 2-sided, and $P < 0.05$ was considered significant.

Ethnic statement

The SEER dataset is freely available and the data released by SEER do not require informed patient consent because cancer is a reportable disease in every state in the USA. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Patient characteristics

According to the pre-defined inclusion and exclusion criteria, a total of 36,588 gastric cancer patients were selected, among whom 11,918 (32.6%) cases were diagnosed at M1 stage. There were 5,361, 1,778, 1,495, and 231 patients diagnosed with liver, lung, bone, and brain metastasis, respectively. The mean age was 67.2 ± 14.0 years, with a predominance for male patients ($N=22,421$, 61.3%) in the total cohort. After excluding patients without detailed information, more than half of the patients were of white race ($N=25,930$, 71.3%) and married ($N=20,317$, 58.9%), and almost of the patients were insured ($N=34,269$, 96.3%). The main histological subtype was adenocarcinoma ($N=23,245$, 63.5%), and proximal third was the most common tumor site ($N=12,898$, 35.3%), following by stomach, NOS ($N=10,158$, 27.8%) and distal third ($N=7,079$, 19.3%). Almost half of patients ($N=17,266$, 47.2%) underwent surgical treatment, and the percentage of patients receiving radiation and chemotherapy were 23.0% and 47.8%, respectively. Table 1 shows additional information on patient characteristics.

Survival estimation and prognostic factors for patients with metastasis

For patients without distant metastasis, the median overall survival was 32.0 (95% CI: 30.7–33.3) months, and the 1-, 2-, 3-, and 5-year survival rates were 69.3%, 55.4%, 47.9%, and 39.8%, respectively. On the contrary, the median overall survival for metastatic patients was 5.0 (95% CI: 4.8–5.2) months, and the 1-, 2-, 3-, and 5-year survival rates were 25.9%, 11.6%, 6.7%, and 3.9%, respectively. The 1-year survival rates for patients with liver, lung, bone, and brain metastasis were 24.0%, 18.0%, 14.0%, and 16.2%, respectively. The corresponding 5-year survival rates were 4.4%, 1.6%, 1.2%, and 0%, respectively. The survival curves for gastric cancer patients with or without metastasis to liver (Figure 2A), lung (Figure 2B), bone (Figure 2C), and brain (Figure 2D) are illustrated in Figure 2.

Table 1. Description of the SEER population of patients with gastric cancer by distant metastasis at diagnosed between 2010–2015.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)
Age (χ^2 , P)	378.42	<0.001	7.34	0.007	7.96	0.005	76.11	<0.001	18.35	<0.001
<65	9,094 (61.6)	5,662 (38.4)	12,504 (84.7)	2,252 (15.3)	13,928 (94.8)	774 (5.2)	13,991 (94.8)	765 (5.2)	14,631 (99.2)	125 (0.8)
≥65	15,576 (71.3)	6,256 (28.7)	18,723 (85.8)	3,109 (14.2)	20,828 (95.4)	1,004 (4.6)	21,102 (96.7)	730 (3.3)	21,726 (99.5)	106 (0.5)
Gender (χ^2 , P)	64.13	<0.001	236.58	<0.001	39.84	<0.001	17.82	<0.001	12.84	<0.001
Male	14,768 (65.9)	7,653 (34.1)	18,629 (83.1)	3,792 (16.9)	21,205 (94.6)	1,216 (5.4)	21,427 (95.6)	994 (4.4)	22,253 (99.3)	168 (0.7)
Female	9,902 (69.9)	4,265 (30.1)	12,598 (88.9)	1,569 (11.1)	13,605 (96.0)	562 (4.0)	13,666 (96.5)	501 (3.5)	14,104 (99.6)	63 (0.4)
Race (χ^2 , P)	33.20	<0.001	73.48	<0.001	24.34	<0.001	20.56	<0.001	14.62	0.002
White	17,308 (66.7)	8,622 (33.3)	22,070 (85.1)	3,860 (14.9)	24,583 (94.8)	1,347 (5.2)	24,802 (95.6)	1,128 (4.4)	25,740 (99.3)	190 (0.7)
Black	3,450 (67.7)	1,647 (32.3)	4,228 (83.0)	869 (17.0)	4,882 (95.8)	215 (4.2)	4,938 (96.9)	159 (3.1)	5,078 (99.6)	19 (0.4)
Others	3,742 (70.0)	1,601 (30.0)	4,731 (88.5)	612 (11.5)	5,131 (96.0)	212 (4.0)	5,139 (96.2)	204 (3.8)	5,322 (99.6)	21 (0.4)
Unknown	170 (78.0)	48 (22.0)	198 (90.8)	20(9.2)	214 (98.2)	4 (1.8)	214 (98.2)	4 (1.8)	217 (99.5)	1 (0.5)
Marital status (χ^2 , P)	40.00	<0.001	16.02	<0.001	9.34	0.009	7.48	0.024	0.79	0.674
Married	13,557 (66.7)	6,760 (33.3)	17,276 (85.0)	3,041 (15.0)	19,335 (95.2)	982 (4.8)	19,469 (95.8)	848 (4.2)	20,183 (99.3)	134 (0.7)
Unmarried	9,565 (67.5)	4,600 (32.5)	12,092 (85.4)	2,073 (14.6)	13,444 (94.9)	721 (5.1)	13,580 (95.9)	585 (4.1)	14,079 (99.4)	86 (0.6)
Unknown	1,548 (73.5)	558 (26.5)	1,859 (88.3)	247 (11.7)	2,031 (96.4)	75(3.6)	2,044 (97.1)	62 (2.9)	2,095 (99.5)	11 (0.5)
Insurance status (χ^2 , P)	191.62	<0.001	29.22	<0.001	12.06	0.002	17.82	<0.001	2.86	0.239
Insured	23,203 (67.7)	11,066 (32.3)	29,265 (85.4)	5,004 (14.6)	32,622 (95.2)	1,647 (4.8)	32,878 (95.9)	1,391 (4.1)	34,057 (99.4)	212 (0.6)
Uninsured	680 (52.0)	627 (48.0)	1,061 (81.2)	246 (18.8)	1,218 (93.2)	89 (6.8)	1,229 (94.0)	78 (6.0)	1,294 (99.0)	13 (1.0)
Unknown	787 (77.8)	225 (22.2)	901 (89.0)	111 (11.0)	970 (95.8)	42 (4.2)	986 (97.4)	26 (2.6)	1,006 (99.4)	6 (0.6)
Year of diagnosis (χ^2 , P)	11.67	0.040	11.81	0.038	4.34	0.501	13.33	0.020	1.84	0.871
2010	3,935 (67.8)	1,871 (32.2)	4,983 (85.8)	823 (14.2)	5,524 (95.1)	282 (4.9)	5,599 (96.4)	207 (3.6)	5,769 (99.4)	37 (0.6)
2011	3,994 (68.6)	1,830 (31.4)	4,956 (85.1)	868 (14.9)	5,566 (95.6)	258 (4.4)	5,601 (96.2)	223 (3.8)	5,787 (99.4)	37 (0.6)
2012	4,197 (68.2)	1,958 (31.8)	5,316 (86.4)	839 (13.6)	5,866 (95.3)	289 (4.7)	5,913 (96.1)	242 (3.9)	6,121 (99.4)	34 (0.6)
2013	4,134 (67.2)	2,020 (32.8)	5,214 (84.7)	940 (15.3)	5,850 (95.1)	304 (4.9)	5,903 (95.9)	251 (4.1)	6,119 (99.4)	35 (0.6)
2014	4,231 (66.9)	2,094 (33.1)	5,411 (85.5)	914 (14.5)	6,003 (94.9)	322 (5.1)	6,054 (95.7)	271 (4.3)	6,281 (99.3)	44 (0.7)

Table 1 continued. Description of the SEER population of patients with gastric cancer by distant metastasis at diagnosed between 2010–2015.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)
2015	4,179 (66.1)	2,145 (33.9)	5,347 (84.6)	977 (15.4)	6,001 (94.9)	323 (5.1)	6,023 (95.2)	301 (4.8)	6,280 (99.3)	44 (0.7)
Primary site (χ^2 , P)	221.36	<0.001	310.33	<0.001	176.00	<0.001	82.92	<0.001	70.87	<0.001
Proximal third	8,619 (66.8)	4,279 (33.2)	10,469 (81.2)	2,429 (18.8)	12,045 (93.4)	853 (6.6)	12,265 (95.1)	633 (4.9)	12,763 (99.0)	135 (1.0)
Mid	2,715 (69.7)	1,178 (30.3)	3,439 (88.3)	454 (11.7)	3,768 (96.8)	125 (3.2)	3,746 (96.2)	147 (3.8)	3,882 (99.7)	11 (0.3)
Distal third	5,184 (73.2)	1,895 (26.8)	6,323 (89.3)	756 (10.7)	6,883 (97.2)	196 (2.8)	6,915 (97.7)	164 (2.3)	7,066 (99.8)	13 (0.2)
Stomach, NOS	6,640 (65.4)	3,518 (34.6)	8,792 (86.6)	1,366 (13.4)	9,674 (95.2)	484 (4.8)	9,708 (95.6)	450 (4.4)	10,093 (99.4)	65 (0.6)
Overlapping	1,512 (59.1)	1,048 (40.9)	2,204 (86.1)	356 (13.9)	2,440 (95.3)	120 (4.7)	2,459 (96.1)	101 (3.9)	2,553 (99.7)	7 (0.3)
Histology (χ^2 , P)	758.44	<0.001	570.14	<0.001	88.15	<0.001	173.99	<0.001	13.26	0.004
Adenocarcinoma	15,256 (65.6)	7,989 (34.4)	19,139 (82.3)	4,106 (17.7)	21,951 (94.4)	1,294 (5.6)	22,288 (95.9)	957 (4.1)	23,078 (99.3)	167 (0.7)
Mucous carcinoma	381 (65.7)	199 (34.3)	517 (89.1)	63 (10.9)	546 (94.1)	34 (5.9)	557 (96.0)	23 (4.0)	578 (99.7)	2 (0.3)
Signet-ring cell carcinoma	3,497 (59.3)	2,401 (40.7)	5,553 (94.2)	345 (5.8)	5,647 (95.7)	251 (4.3)	5,513 (93.5)	385 (6.5)	5,859 (99.3)	39 (0.7)
Unknown	5,536 (80.6)	1,329 (19.4)	6,018 (87.7)	847 (12.3)	6,666 (97.1)	199 (2.9)	6,735 (98.1)	130 (1.9)	6,842 (99.7)	23 (0.3)
Grade (χ^2 , P)	1231.98	<0.001	305.40	<0.001	93.89	<0.001	227.91	<0.001	27.33	<0.001
I	2,766 (92.1)	236 (7.9)	2,868 (95.5)	134 (4.5)	2,958 (98.5)	44 (1.5)	2,986 (99.5)	16(0.5)	3,001 (100.0)	1 (0.0)
II	5,655 (73.5)	2,038 (26.5)	6,400 (83.2)	1,293 (16.8)	7,310 (95.0)	383 (5.0)	7,515 (97.7)	178 (2.3)	7,641 (99.3)	5 (0.7)
III	10,775 (62.5)	6,475 (37.5)	14,753 (85.5)	2,497 (14.5)	16,374 (94.9)	876 (5.1)	16,346 (94.8)	904 (5.2)	17,149 (99.4)	101 (0.6)
IV	483 (68.2)	225 (31.8)	595 (84.0)	113 (16.0)	686 (96.9)	22 (3.1)	687 (97.0)	21 (3.0)	701 (99.0)	7 (1.0)
Unknown	4,991 (62.9)	2,944 (37.1)	6,611 (83.3)	1,324 (16.7)	7,482 (94.3)	453 (5.7)	7,559 (95.3)	376 (4.7)	7,865 (99.1)	70 (0.9)
T stage (χ^2 , P)	4691.69	<0.001	2339.40	<0.001	803.09	<0.001	840.77	<0.001	155.81	<0.001
T1	7,401 (77.8)	2,112 (22.2)	8,438 (88.7)	1,075 (11.3)	9,146 (96.1)	367 (3.9)	9,245 (97.2)	268 (2.8)	9,473 (99.6)	40 (0.4)
T2	3,471 (84.8)	622 (15.2)	3,891 (95.1)	202 (4.9)	4,031 (98.5)	62 (1.5)	4,039 (98.7)	54 (1.3)	4,084 (99.8)	9 (0.2)
T3	6,845 (80.0)	1,711 (20.0)	7,906 (92.4)	650 (7.6)	8,365 (97.8)	191 (2.2)	8,369 (97.8)	187 (2.2)	8,529 (99.7)	27 (0.3)
T4	3,697 (59.3)	2,535 (40.7)	5,280 (84.7)	952 (15.3)	5,931 (95.2)	301 (4.8)	6,031 (96.8)	201 (3.2)	6,207 (99.6)	25 (0.4)

Table 1 continued. Description of the SEER population of patients with gastric cancer by distant metastasis at diagnosed between 2010–2015.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)
Unknown	3,256 (39.7)	4,938 (60.3)	5,712 (69.7)	2,482 (30.3)	7,337 (89.5)	857 (10.5)	7,409 (90.4)	785 (9.6)	8,064 (98.4)	130 (1.6)
N stage (χ^2 , P)	2899.94	<0.001	1388.41	<0.001	590.22	<0.001	471.15	<0.001	80.68	<0.001
N0	14,807 (76.0)	4,677 (24.0)	17,422 (89.4)	2,062 (10.6)	18,844 (96.7)	640 (3.3)	18,959 (97.3)	525 (2.7)	19,407 (99.6)	77 (0.4)
N1	4,557 (53.1)	4,020 (46.9)	6,607 (77.0)	1,970 (23.0)	7,908 (92.2)	669 (7.8)	7,993 (93.2)	584 (6.8)	8,493 (99.0)	84 (1.0)
N2	2,171 (76.8)	654 (23.2)	2,572 (91.0)	253 (9.0)	2,756 (97.60)	69 (2.4)	2,762 (97.8)	63 (2.2)	2,815 (99.6)	10 (0.4)
N3	2,034 (74.9)	683 (25.1)	2,503 (92.1)	214 (7.9)	2,650 (97.5)	67 (2.5)	2,655 (97.7)	62 (2.3)	2,704 (99.5)	13 (0.5)
Unknown	1,101 (36.9)	1,884 (63.1)	2,123 (71.1)	862 (28.9)	2,652 (88.8)	333 (11.2)	2,724 (91.3)	261 (8.7)	2,938 (98.4)	47 (1.6)
Surgery (χ^2 , P)	8952.99	<0.001	3808.23	<0.001	1391.97	<0.001	1199.06	<0.001	163.73	<0.001
None	8,707 (45.4)	10,488 (54.6)	14,298 (74.5)	4,897 (25.5)	17,496 (91.1)	1,699 (8.9)	17,756 (92.5)	1,439 (7.5)	18,977 (98.9)	218 (1.1)
Yes	15,853 (91.8)	1,413 (8.2)	16,808 (97.3)	458 (2.7)	17,189 (99.6)	77 (0.4)	17,212 (99.7)	54 (0.3)	17,253 (99.9)	13 (0.1)
Unknown	110 (86.6)	17 (13.4)	121 (95.3)	6(4.7)	125 (98.4)	2 (1.6)	125 (98.4)	2 (1.6)	127 (100.0)	0 (0.0)
Radiation therapy (χ^2 , P)	510.46	<0.001	244.63	<0.001	20.13	<0.001	44.61	<0.001	190.20	<0.001
No/unknown	18,148 (64.4)	10,031 (35.6)	23,605 (83.8)	4,574 (16.2)	26,732 (94.9)	1,447 (5.1)	27,134 (96.3)	1,045 (3.7)	28,089 (99.7)	90 (0.3)
Yes	6,522 (77.6)	1,887 (22.4)	7,622 (90.6)	787 (9.4)	8,078 (96.1)	331 (3.9)	7,959 (94.6)	450 (5.4)	8,268 (98.3)	141 (1.7)
Chemical therapy (χ^2 , P)	782.93	<0.001	171.88	<0.001	39.20	<0.001	62.04	<0.001	8.09	0.005
No/unknown	14,124 (74.0)	4,965 (26.0)	16,735 (87.7)	2,354 (12.3)	18,290 (95.8)	799 (4.2)	18,458 (96.7)	631 (3.3)	18,990 (99.5)	99 (0.5)
Yes	10,546 (60.3)	6,953 (39.7)	14,492 (82.8)	3,007 (17.2)	16,520 (94.4)	979 (5.6)	16,635 (95.1)	864 (4.9)	17,367 (99.2)	132 (0.8)
Vital status (χ^2 , P)	5077.26	<0.001	1866.53	<0.001	725.16	<0.001	643.67	<0.001	75.14	<0.001
Alive	11,792 (91.0)	1,166 (9.0)	12,457 (96.1)	501 (3.9)	12,858 (99.2)	100 (0.8)	12,888 (99.5)	70 (0.5)	12,939 (99.9)	19 (0.1)
Dead	12,878 (54.5)	10,752 (45.5)	18,770 (79.4)	4,860 (20.6)	21,952 (92.9)	1,678 (7.1)	22,205 (94.0)	1,425 (6.0)	23,418 (99.1)	212 (0.9)
Number of mets (χ^2 , P)	3248.96	<0.001	6493.04	<0.001	16646.25	<0.001	7459.10	<0.001	1968.49	<0.001
≤1	24,670 (70.3)	10,413 (29.7)	31,025 (88.4)	4,058 (11.6)	34,432 (98.1)	651 (1.9)	34,299 (97.8)	784 (2.2)	34,995 (99.7)	88 (0.3)
>1	0 (0.0)	1,505 (100.0)	202 (13.4)	1,303 (86.6)	378 (25.1)	1,127 (74.9)	794 (52.8)	711 (47.2)	1,362 (90.5)	143 (9.5)

SEER – Surveillance, Epidemiology, and End Results; Met – metastases; NOS – not otherwise specified.

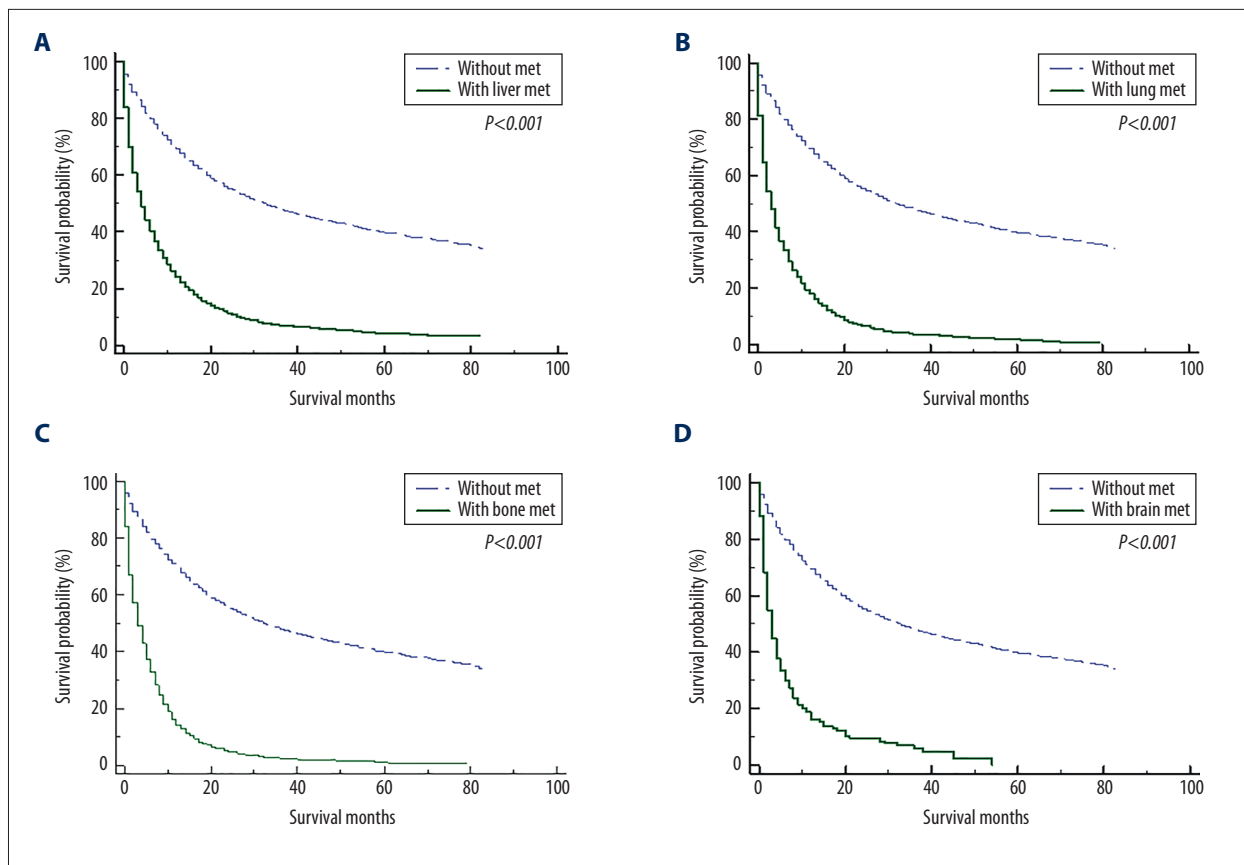


Figure 2. The overall survival for gastric cancer patients with or without metastasis to liver (A), lung (B), bone (C), and brain (D).

Supplementary Table 1 shows P values for results of testing the proportion hazards assumption. Most of the factors did not violate the proportional hazards assumption. As shown in Supplementary Table 2, primary site, T stage, and treatment by surgery and chemotherapy were associated with survival in univariate Cox regression analysis. Other variables, such as age, marital status, histology types, tumor grade, N stage, radiation treatment, and presence or absence of other metastasis, were associated with specific metastasis patients. After adjusting all these characteristics in multivariate analysis, factors significantly associated with survival outcome for patients with liver metastasis were: age ≥ 65 years (HR=1.19, 95% CI 1.12–1.26); tumor grade (II HR=1.64, 95% CI 1.21–2.22; III HR=2.23, 95% CI 1.66–3.00; IV HR=1.91, 95% CI 1.21–2.82); T stage (T2 HR=0.80, 95% CI 0.64–0.99; T3 HR=0.88, 95% CI 0.77–1.00); N3 stage (HR=1.23, 95% CI 1.01–1.50); surgery (HR=0.45, 95% CI 0.38–0.52); chemotherapy (HR=0.30, 95% CI 0.27–0.34); and more other metastases (HR=1.38, 95% CI 1.24–1.55). In patients with lung metastasis, the following factors were associated with overall survival: tumor grade III (HR=1.53, 95% CI 1.02–2.29); T4 stage (HR=1.27, 95% CI 1.06–1.53); surgery (HR=0.74, 95% CI 0.55–0.99); chemotherapy (HR=0.31, 95% CI 0.26–0.37); and more other metastases (HR=1.51, 95% CI 1.28–1.77). Table 2 provides additional information on the results of multivariate Cox regression analysis.

Risk factors for distant metastases

In our cohort, there were 11,918 patients presenting distant metastasis. The number of cases with bone, brain, liver, and lung metastasis was 1495, 231, 5361, and 1778, respectively. As shown in Supplementary Table 3, the following factors were significantly associated with developing distant metastasis and bone, liver, or lung metastasis: age, sex, race, insurance status, primary tumor site, histological type, grade, T stage, and N stage, and all of these variables except insurance status and T stage were also associated with developing brain metastasis.

The multivariate regression analysis suggested several independent risk factors. Younger age and higher tumor grade were positively associated with developing distant metastasis, including all four organs. Proximal third of stomach was the most common primary site for tumor metastasis. Patients without insurance were more likely to have distant metastasis. T stage and N stage were independent risk factors. More details on the results of the multivariate analysis are provided in Table 3.

Table 2. Multivariable Cox regression for analyzing the prognostic factors for gastric cancer patients with distance metastases.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age										
<65	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
≥65	1.19 (1.12–1.26)	<0.001	1.16 (1.06–1.28)	0.002	0.94 (0.81–1.11)	0.479	0.96 (0.82–1.13)	0.652	NA	NA
Marital status										
Married	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Unmarried	1.02 (0.96–1.08)	0.631	0.95 (0.86–1.04)	0.244	1.10 (0.94–1.29)	0.233	0.95 (0.81–1.12)	0.544	NA	NA
Primary site										
Proximal third	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mid	1.09 (0.98–1.22)	0.107	0.99 (0.83–1.18)	0.880	1.12 (0.81–1.56)	0.490	1.55 (1.17–2.05)	0.002	2.90 (0.86–9.85)	0.088
Distal third	0.93 (0.85–1.02)	0.135	0.91 (0.79–1.04)	0.167	1.02 (0.79–1.31)	0.892	1.30 (0.98–1.74)	0.071	2.32 (1.00–5.41)	0.051
Stomach, NOS	0.96 (0.89–1.04)	0.349	0.93 (0.82–1.05)	0.241	1.11 (0.91–1.37)	0.306	0.98 (0.81–1.19)	0.837	1.13 (0.69–1.85)	0.625
Overlapping	1.17 (1.05–1.30)	0.004	1.29 (1.08–1.55)	0.005	1.25 (0.93–1.67)	0.137	1.09 (0.81–1.46)	0.575	0.42 (0.09–1.96)	0.272
Histology										
Adenocarcinoma	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mucous carcinoma	1.05 (0.82–1.34)	0.696	1.42 (0.89–2.28)	0.142	NA	NA	NA	NA	NA	NA
Signet-ring cell carcinoma	1.03 (0.95–1.11)	0.514	1.02 (0.85–1.23)	0.843	NA	NA	NA	NA	NA	NA
Unknown	0.74 (0.65–0.84)	<0.001	0.80 (0.68–0.95)	0.012	NA	NA	NA	NA	NA	NA
Grade										
I	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
II	1.55 (1.24–1.92)	<0.001	1.64 (1.21–2.22)	0.001	1.08 (0.71–1.64)	0.726	NA	NA	NA	NA
III	2.00 (1.62–2.48)	<0.001	2.23 (1.66–3.00)	<0.001	1.53 (1.02–2.29)	0.039	NA	NA	NA	NA
IV	1.84 (1.39–2.43)	<0.001	1.91 (1.29–2.82)	0.001	1.04 (0.51–2.13)	0.920	NA	NA	NA	NA
T stage										
T1	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
T2	0.83 (0.73–0.93)	0.002	0.80 (0.64–0.99)	0.039	0.98 (0.69–1.39)	0.904	0.54 (0.39–0.74)	<0.001	1.67 (0.79–3.53)	0.184

Table 2 continued. Multivariable Cox regression for analyzing the prognostic factors for gastric cancer patients with distance metastases.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
T3	0.92 (0.84–1.00)	0.042	0.88 (0.77–1.00)	0.048	1.16 (0.93–1.44)	0.183	0.89 (0.73–1.09)	0.262	1.34 (0.74–2.40)	0.333
T4	1.15 (1.06–1.24)	0.001	1.07 (0.95–1.21)	0.241	1.27 (1.06–1.53)	0.011	1.11 (0.91–1.36)	0.309	2.28 (1.28–4.07)	0.005
N stage										
N0	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
N1	1.06 (0.99–1.31)	0.122	1.05 (0.95–1.17)	0.350	NA	NA	NA	NA	NA	NA
N2	1.11 (0.99–1.24)	0.074	1.15 (0.95–1.38)	0.146	NA	NA	NA	NA	NA	NA
N3	1.19 (1.06–1.34)	0.003	1.23 (1.01–1.50)	0.040	NA	NA	NA	NA	NA	NA
Surgery										
No	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	0.43 (0.39–0.47)	<0.001	0.45 (0.38–0.52)	<0.001	0.74 (0.55–0.99)	0.045	0.54 (0.38–0.75)	<0.001	0.32 (0.13–0.79)	0.014
Radiation										
No/unknown	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	0.93 (0.86–1.00)	0.053	NA	NA	0.99 (0.81–1.20)	0.903	0.94 (0.80–1.12)	0.499	0.91 (0.56–1.46)	0.683
Chemotherapy										
No/unknown	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	0.32 (0.30–0.35)	<0.001	0.30 (0.27–0.34)	<0.001	0.31 (0.26–0.37)	<0.001	0.28 (0.24–0.34)	<0.001	0.24 (0.14–0.42)	<0.001
Number of mets										
≤1	1.00 (Reference)	1.00	–	–	–	–	–	–	–	–
>1	1.48 (1.35–1.63)	<0.001	–	–	–	–	–	–	–	–
Other mets										
No	–	–	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	–	–	1.38 (1.24–1.55)	<0.001	1.51 (1.28–1.77)	<0.001	NA	NA	1.47 (0.90–2.38)	0.123

Met – metastases; HR – hazard ratio; CI – confidence interval; NOS – not otherwise specified; NA – not available.

Table 3. Multivariable logistic regression for analyzing the risk factors for developing distant metastases in patients with gastric cancer.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age										
<65	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
≥65	0.68 (0.63–0.72)	<0.001	0.87 (0.79–0.96)	0.005	0.80 (0.68–0.94)	0.008	0.71 (0.59–0.85)	<0.001	0.50 (0.35–0.71)	<0.001
Gender										
Male	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Female	0.94 (0.87–1.01)	0.076	0.73 (0.66–0.82)	<0.001	0.90 (0.75–1.07)	0.215	0.82 (0.67–1.00)	0.056	0.80 (0.52–1.21)	0.287
Race										
White	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Black	1.01 (0.92–1.12)	0.817	1.37 (1.20–1.57)	<0.001	0.99 (0.77–1.27)	0.947	0.69 (0.50–0.95)	0.022	0.49 (0.23–1.07)	0.073
Others	0.82 (0.74–0.90)	<0.001	0.82 (0.71–0.95)	0.008	0.89 (0.70–1.13)	0.330	0.96 (0.74–1.25)	0.760	0.62 (0.32–1.20)	0.154
Insurance status										
Insured	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Uninsured	1.48 (1.25–1.75)	<0.001	1.48 (1.18–1.85)	0.001	1.52 (1.06–2.16)	0.021	1.39 (0.93–2.08)	0.107	NA	NA
Primary site										
Proximal third	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mid	1.05 (0.93–1.18)	0.446	0.79 (0.66–0.94)	0.009	0.53 (0.39–0.73)	<0.001	0.64 (0.46–0.91)	0.012	0.25 (0.10–0.63)	0.003
Distal third	0.70 (0.63–0.77)	<0.001	0.62 (0.54–0.72)	<0.001	0.37 (0.28–0.48)	<0.001	0.29 (0.21–0.41)	<0.001	0.17 (0.08–0.37)	<0.001
Stomach, NOS	1.04 (0.94–1.14)	0.465	0.71 (0.63–0.82)	<0.001	0.65 (0.52–0.80)	<0.001	0.88 (0.70–1.11)	0.267	0.39 (0.23–0.65)	<0.001
Overlapping	1.32 (1.16–1.50)	<0.001	0.86 (0.72–1.04)	0.125	0.77 (0.57–1.04)	0.085	0.81 (0.58–1.14)	0.229	0.30 (0.12–0.74)	0.009
Histology										
Adenocarcinoma	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mucous carcinoma	0.78 (0.59–1.02)	0.720	0.43 (0.26–0.69)	0.001	0.80 (0.41–1.56)	0.508	0.97 (0.45–2.08)	0.938	NA	NA
Signet-ring cell carcinoma	0.95 (0.86–1.03)	0.218	0.31 (0.26–0.38)	<0.001	0.78 (0.61–0.98)	0.035	1.34 (1.07–1.67)	0.011	1.03 (0.62–1.72)	0.918
Unknown	0.82 (0.71–0.94)	0.003	1.22 (1.04–1.45)	0.018	0.66 (0.47–0.93)	0.018	1.05 (0.72–1.53)	0.797	0.61 (0.27–1.37)	0.233

Table 3 continued. Multivariable logistic regression for analyzing the risk factors for developing distant metastases in patients with gastric cancer.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Grade										
I	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
II	3.53 (2.89–4.32)	<0.001	4.14 (3.16–5.43)	<0.001	2.26 (1.47–3.48)	<0.001	4.72 (2.14–10.40)	<0.001	11.32 (1.53–83.77)	0.017
III	5.46 (4.49–6.66)	<0.001	4.41 (3.37–5.78)	<0.001	2.64 (1.72–4.04)	<0.001	9.49 (4.37–20.62)	<0.001	9.20 (1.25–67.85)	0.029
IV	4.93 (3.77–6.44)	<0.001	4.90 (3.41–7.05)	<0.001	1.53 (0.73–3.22)	0.263	5.15 (1.90–14.02)	0.001	20.76 (2.47–174.32)	0.005
T stage										
T1	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
T2	0.48 (0.43–0.54)	<0.001	0.29 (0.23–0.35)	<0.001	0.33 (0.23–0.45)	<0.001	0.40 (0.28–0.56)	<0.001	NA	NA
T3	0.56 (0.51–0.62)	<0.001	0.41 (0.36–0.47)	<0.001	0.40 (0.32–0.49)	<0.001	0.45 (0.36–0.58)	<0.001	NA	NA
T4	1.59 (1.44–1.75)	<0.001	1.14 (1.00–1.30)	0.048	1.11 (0.90–1.37)	0.329	0.78 (0.61–1.01)	0.054	NA	NA
N stage										
N0	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
N1	2.17 (2.00–2.35)	<0.001	2.24 (2.00–2.50)	<0.001	2.05 (1.71–2.46)	<0.001	2.35 (1.91–2.90)	<0.001	1.81 (1.23–2.66)	0.003
N2	0.91 (0.80–1.02)	0.116	0.95 (0.79–1.15)	0.595	0.77 (0.55–1.07)	0.119	1.01 (0.70–1.45)	0.967	0.70 (0.33–1.49)	0.354
N3	0.85 (0.75–0.96)	0.008	0.88 (0.73–1.06)	0.182	0.64 (0.45–0.91)	0.013	0.91 (0.63–1.31)	0.608	1.40 (0.73–2.67)	0.315

Met – metastases; OR – odds ratio; CI – confidence interval; NOS – not otherwise specified; NA – not available.

Discussion

Distant metastasis is a serious problem during cancer management. The median overall survival time for gastric cancer patients with distant metastasis was approximately 4.0 months in our analysis. Synchronous metastasis was present in 32.6% of patients with primary gastric cancer. The poor survival and high metastasis rate in gastric cancer suggested that further research should be performed to thoroughly investigate the related predictive factors for prognosis and prevalence of distant metastasis.

To promote the survival of patients at stage IV, developing a comprehensive treatment strategy has been the global focus. Surgery of the primary cancer and chemotherapy can improve survival for patients with metastasis to liver, lung, bone, and

brain. In the present study, chemotherapy was the main treatment for patients with distant metastasis and it was offered to 56.1% of patients with liver metastasis, while surgery of primary gastric cancer was performed in only 8.5% of patients. The proportion of gastric resection and chemotherapy was consistent with a previous study in Europe [16]. As previously reported, chemotherapy was the main treatment for patients with liver metastasis, and conversion surgery can be considered in some selected patients [17]. Similarly, according to a survey from two European and Japanese gastric cancer study groups, preoperative chemotherapy followed by resection of both primary and liver lesions was the recommended option for patients without extrahepatic metastasis [18], an similar percentages of chemotherapy and surgery were performed in patients with metastasis to lung and bone. Based on the records from the Metastatic Lung Tumor Study Group of Japan,

the 5-year survival rate was 28% after pulmonary metastatic tumor resection [19]. For bone metastasis in gastric cancer, a metastasis rate of 3.8% was reported, and palliative chemotherapy was a significant factor for improved survival [20]. Brain metastasis was rare and no prediction was made in large cohort. In our study, based on the analysis of 231 patients with brain metastasis, we found similar benefits from surgery and chemotherapy. Currently, chemotherapy is the standard first-line treatment for advanced gastric cancer patients and has shown good performance [21]. More than 50 years since chemotherapy was first introduced, infusional 5-FU has been accepted as the main component of most combination regimens in stage IV gastric cancer [22], while paclitaxel is a widely used second-line chemotherapy drug [23]. Adverse effects and resistance to chemotherapy in clinical practice have recently focused attention on developing combination therapy [23,24]. Further study is needed to reveal the underlying causes of adverse effects and chemotherapy resistance.

Except for the homogenous prognostic factors for all metastatic sites in our analysis, age older than 65 years, higher grade (II, III, and IV), and N4 were associated with worse survival in patients with liver metastasis. Tumor grade III and T4 stage were independent factors associated with pulmonary metastasis. T4 stage was also associated with worse survival for patients with brain metastasis. All these negative factors should be considered in the prediction of survival in patients with specific metastasis.

To improve long-term survival and quality of life, the negative influence of distant metastasis on survival must be determined. Thus, timely screening and early diagnosis of the possible metastasis is important before treatment. PET/CT has been the main strategy for distant metastasis screening in gastric cancer [25]. However, due to limited medical resources, the screening should be offered to gastric cancer patients with higher risk of distant metastasis. Thus, the prediction of possible distant metastasis is crucial in clinical practice.

Although many studies have evaluated the survival and related factors for gastric cancer patients with metastasis, few studies have investigated risk factors for distant metastasis. The risk factors for the development of bone metastasis were evaluated in a study including 1,342 patients with metastatic gastric cancer, in which 141 (10.5%) patients presented bone metastasis and predictive factors included age younger than 65 years, signet ring cell histology and location than 2/3 of stomach [13]. In our study, homogenous risk factors for all the metastatic sites were age less than 65 years, tumor in the proximal third of the stomach, higher grade, and N1 stage. Male sex, black race, and uninsured status were also associated with higher risk of liver metastasis. Histological type showed different effects on metastasis. The clinicopathological factors

revealed in our study can guide the identification of patients with distant metastasis.

In addition to predictive clinicopathological characteristics, some blood tests can also be used for prediction; for example, the serum level of the bone alkaline phosphatase was reported to be correlated with bone metastasis [26]. More advanced techniques have been developed to predict distant metastasis, including high-quality image-based artificial intelligence technologies [27]. Based on radiomics analysis and selected clinical characteristics, constructed nomograms can be used to predict metastasis to the liver [28], lymph nodes [29], and peritoneum [30]. Gene expression [31] and metastasis-associated protein [32] have been studied for their value as potential predictive biomarkers for distant metastasis in gastric cancer. All these promising tools at different levels can be further applied and validated to assist prediction of metastasis.

Our work has some limitations. First, the SEER database only recorded synchronous metastatic patients; therefore, patients developing distant metastasis later in their course were not analyzed. Although our analysis revealed some important factors predicting distant metastasis in gastric cancer, only the liver, lung, bone, and brain metastatic sites were available, and the lack of data on other metastatic sites may impair the accuracy of our findings. The significant predictive factors need to be externally validated in different databases or multiple centers. Furthermore, other useful information such as genetic or clinical tests were not available in the SEER database, and these should be analyzed and incorporated into the predictive model to establish a more accurate and robust tool for patient stratification.

Conclusions

Initial distant metastasis was recorded in 32.6% of patients with gastric cancer in the SEER database. Patients with distant metastasis had significantly shorter survival than those without metastasis. Homogeneity and heterogeneity were identified in the risk factors for specific distant metastasis and the prognostic factors of gastric cancer patients. A series of factors were found to be correlated with distant metastasis, including: age, sex, race, insurance status, primary tumor site, histological type, grade, T stage, and N stage. These factors might be used in auxiliary individualized evaluation and prediction in the future. Our findings may improve individualized evaluation and prediction of gastric cancer patients.

Conflicts of interest

None.

Supplementary Data

Supplementary Table 1. P values for the results of proportion hazards assumption test.

Subject characteristics	M-Met	Liver-Met	Lung-Met	Bone-Met	Brain-Met
	P-value	P-value	P-value	P-value	P-value
Age	0.039	0.103	0.187	0.576	0.654
Gender	0.482	0.001	0.070	0.647	0.971
Race	0.802	0.956	0.813	0.147	0.562
Marital Status	0.716	0.091	0.516	0.226	0.845
Insurance Status	0.300	0.328	0.659	0.999	0.592
Primary site	0.381	0.475	0.695	0.329	0.568
Histology	0.263	0.587	0.218	0.718	0.993
Grade	0.097	0.160	0.006	0.904	0.340
T Stage	0.022	0.656	0.900	0.720	0.930
N Stage	0.170	0.430	0.548	0.432	0.674
Surgery	0.002	0.338	0.509	0.269	0.507
Radiation	0.178	0.243	0.043	0.804	0.462
Chemotherapy	<0.001	<0.001	0.004	0.066	0.600
Number of mets	0.244	–	–	–	–
Other mets	–	0.506	0.768	0.181	0.602

Supplementary Table 2. Univariable Cox regression for analyzing the prognostic factors for gastric cancer patients with distant metastases.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age										
<65	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
≥65	1.31 (1.26–1.36)	<0.001	1.34 (1.26–1.42)	<0.001	1.17 (1.06–1.29)	0.001	1.12 (1.01–1.24)	0.036	1.14 (0.87–1.49)	0.355
Gender										
Male	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Female	0.98 (0.94–1.02)	0.333	0.95 (0.89–1.01)	0.116	1.02 (0.92–1.13)	0.702	1.04 (0.94–1.17)	0.442	1.02 (0.75–1.38)	0.894
Race										
White	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Black	0.99 (0.93–1.04)	0.597	0.95 (0.88–1.02)	0.166	1.12 (0.97–1.30)	0.135	1.16 (0.98–1.37)	0.084	1.16 (0.72–1.87)	0.540
Others	0.99 (0.94–1.05)	0.746	0.99 (0.91–1.09)	0.850	1.14 (0.98–1.32)	0.950	1.06 (0.91–1.24)	0.460	1.29 (0.81–2.05)	0.290

Supplementary Table 2 continued. Univariable Cox regression for analyzing the prognostic factors for gastric cancer patients with distant metastases.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Marital status										
Married	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Unmarried	1.18 (1.13–1.23)	<0.001	1.15 (1.09–1.22)	<0.001	1.21 (1.10–1.34)	<0.001	1.13 (1.02–1.26)	0.025	1.03 (0.78–1.38)	0.825
Insurance status										
Insured	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Uninsured	1.05 (0.96–1.14)	0.303	1.14 (0.99–1.30)	0.067	1.07 (0.85–1.35)	0.562	1.08 (0.84–1.38)	0.548	1.54 (0.86–2.78)	0.148
Primary site										
Proximal third	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mid	1.06 (0.99–1.14)	0.084	1.04 (0.93–1.15)	0.495	1.18 (0.97–1.43)	0.100	1.29 (1.08–1.55)	0.006	1.69 (0.89–3.23)	0.112
Distal third	1.02 (0.97–1.08)	0.488	1.04 (0.96–1.14)	0.328	1.18 (1.01–1.38)	0.043	1.32 (1.10–1.57)	0.002	1.43 (0.81–2.54)	0.222
Stomach, NOS	1.06 (1.01–1.11)	0.017	1.00 (0.93–1.07)	0.983	1.19 (1.06–1.34)	0.003	1.18 (1.04–1.33)	0.010	1.44 (1.06–1.96)	0.021
Overlapping	1.17 (1.09–1.26)	<0.001	1.29 (1.15–1.44)	<0.001	1.32 (1.08–1.60)	0.006	1.17 (0.95–1.46)	0.147	0.97 (0.40–2.37)	0.944
Histology										
Adenocarcinoma	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mucous carcinoma	1.02 (0.88–1.17)	0.845	1.43 (1.11–1.85)	0.005	1.00 (0.70–1.42)	0.995	0.73 (0.47–1.14)	0.163	0.95 (0.24–3.85)	0.944
Signet-ring cell carcinoma	1.06 (1.01–1.11)	0.018	1.17 (1.04–1.31)	0.007	1.13 (0.99–1.30)	0.080	1.01 (0.90–1.14)	0.831	1.35 (0.95–1.92)	0.099
Unknown	0.67 (0.63–0.71)	<0.001	0.63 (0.58–0.69)	<0.001	1.07 (0.92–1.26)	0.372	1.07 (0.88–1.29)	0.502	1.11 (0.70–1.77)	0.665
Grade										
I	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
II	1.51 (1.30–1.77)	<0.001	1.57 (1.28–1.92)	<0.001	1.24 (0.89–1.73)	0.204	0.74 (0.44–1.24)	0.251	NA	NA
III	1.83 (1.57–2.12)	<0.001	2.02 (1.66–2.47)	<0.001	1.65 (1.20–2.28)	0.002	0.95 (0.58–1.55)	0.825	NA	NA
IV	1.34 (1.09–1.65)	0.005	1.46 (1.11–1.92)	0.008	1.12 (0.65–0.94)	0.691	0.88 (0.46–1.70)	0.700	NA	NA
T stage										
T1	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00

Supplementary Table 2 continued. Univariable Cox regression for analyzing the prognostic factors for gastric cancer patients with distant metastases.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
T2	0.71 (0.64–0.78)	<0.001	0.59 (0.50–0.70)	<0.001	0.90 (0.68–1.20)	0.456	0.58 (0.43–0.80)	0.001	1.30 (0.62–2.72)	0.486
T3	0.71 (0.66–0.76)	<0.001	0.68 (0.61–0.75)	<0.001	0.90 (0.75–1.07)	0.225	0.83 (0.69–1.01)	0.059	0.85 (0.50–1.46)	0.561
T4	0.92 (0.86–0.97)	0.004	0.91 (0.83–1.00)	0.043	1.18 (1.01–1.38)	0.042	1.01 (0.84–1.22)	0.932	1.72 (1.02–2.91)	0.043
N stage										
N0	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
N1	1.01 (0.97–1.06)	0.572	1.09 (1.02–1.16)	0.012	0.98 (0.88–1.10)	0.758	1.09 (0.97–1.23)	0.155	1.20 (0.87–1.67)	0.271
N2	0.84 (0.77–0.92)	<0.001	0.99 (0.86–1.13)	0.867	0.96 (0.75–1.24)	0.745	0.93 (0.71–1.21)	0.571	0.86 (0.43–1.73)	0.676
N3	0.86 (0.79–0.93)	<0.001	1.01 (0.87–1.17)	0.944	1.11 (0.86–1.44)	0.410	0.95 (0.72–1.24)	0.686	1.32 (0.71–2.44)	0.383
Surgery										
No	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	0.51 (0.48–0.55)	<0.001	0.51 (0.46–0.57)	<0.001	0.73 (0.57–0.92)	0.009	0.66 (0.50–0.87)	0.003	0.48 (0.25–0.91)	0.025
Radiation										
No/unknown	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	0.91 (0.87–0.96)	0.001	1.01 (0.93–1.09)	0.845	0.80 (0.71–0.91)	<0.001	0.89 (0.79–0.99)	0.036	0.67 (0.51–0.89)	0.005
Chemotherapy										
No/unknown	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	0.37 (0.36–0.39)	<0.001	0.37 (0.34–0.39)	<0.001	0.36 (0.32–0.40)	<0.001	0.38 (0.34–0.42)	<0.001	0.41 (0.31–0.55)	<0.001
Number of mets										
≤1	1.00 (Reference)	1.00	–	–	–	–	–	–	–	–
>1	1.44 (1.37–1.53)	<0.001	–	–	–	–	–	–	–	–
Other mets										
No	–	–	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Yes	–	–	1.41 (1.32–1.50)	<0.001	1.27 (1.15–1.40)	<0.001	1.01 (0.91–1.12)	0.813	1.34 (1.01–1.78)	0.040

Met – metastases; HR – hazard ratio; CI – confidence interval; NOS – not otherwise specified; NA – not available.

Supplementary Table 3. Univariable logistic regression for analyzing the risk factors for developing distant metastases in patients with gastric cancer.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age										
<65	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
≥65	0.65 (0.62–0.67)	<0.001	0.92 (0.87–0.98)	0.007	0.87 (0.79–0.96)	0.005	0.63 (0.57–0.70)	<0.001	0.57 (0.44–0.74)	<0.001
Gender										
Male	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Female	0.83 (0.79–0.87)	<0.001	0.61 (0.57–0.65)	<0.001	0.72 (0.65–0.80)	<0.001	0.79 (0.71–0.88)	<0.001	0.59 (0.44–0.79)	<0.001
Race										
White	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Black	0.96 (0.90–1.02)	0.193	1.18 (1.08–1.27)	<0.001	0.80 (0.69–0.93)	0.004	0.71 (0.60–0.84)	<0.001	0.51 (0.32–0.81)	0.005
Others	0.86 (0.81–0.92)	<0.001	0.74 (0.68–0.81)	<0.001	0.75 (0.65–0.87)	<0.001	0.87 (0.75–1.02)	0.080	0.54 (0.34–0.84)	0.007
Marital status										
Married	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Unmarried	0.96 (0.92–1.01)	0.121	0.97 (0.92–1.04)	0.392	1.06 (0.96–1.17)	0.279	0.99 (0.89–1.10)	0.841	0.92 (0.70–1.21)	0.548
Insurance status										
Insured	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Uninsured	1.93 (1.73–2.16)	<0.001	1.36 (1.18–1.56)	<0.001	1.45 (1.16–1.81)	0.001	1.50 (1.19–1.90)	0.001	1.61 (0.92–2.83)	0.096
Primary site										
Proximal third	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mid	0.87 (0.81–0.94)	0.001	0.57 (0.51–0.63)	<0.001	0.47 (0.39–0.57)	<0.001	0.76 (0.63–0.91)	0.003	0.27 (0.15–0.50)	<0.001
Distal third	0.74 (0.69–0.79)	<0.001	0.52 (0.47–0.56)	<0.001	0.40 (0.34–0.47)	<0.001	0.46 (0.39–0.55)	<0.001	0.17 (0.10–0.31)	<0.001
Stomach, NOS	1.07 (1.01–1.13)	0.020	0.67 (0.62–0.72)	<0.001	0.71 (0.63–0.79)	<0.001	0.90 (0.79–1.02)	0.089	0.61 (0.45–0.82)	0.001
Overlapping	1.40 (1.28–1.52)	<0.001	0.70 (0.62–0.79)	<0.001	0.69 (0.57–0.85)	<0.001	0.80 (0.64–0.99)	0.037	0.26 (0.12–0.56)	0.001
Histology										
Adenocarcinoma	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
Mucous carcinoma	1.00 (0.84–1.19)	0.977	0.57 (0.44–0.74)	<0.001	1.06 (0.74–1.50)	0.760	0.96 (0.63–1.47)	0.856	0.48 (0.12–1.93)	0.300

Supplementary Table 3 continued. Univariable logistic regression for analyzing the risk factors for developing distant metastases in patients with gastric cancer.

Subject characteristics	M-Met		Liver-Met		Lung-Met		Bone-Met		Brain-Met	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Signet-ring cell carcinoma	1.31 (1.24–1.39)	<0.001	0.29 (0.26–0.33)	<0.001	0.75 (0.66–0.87)	<0.001	1.63 (1.44–1.84)	<0.001	0.92 (0.65–1.31)	0.640
Unknown	0.46 (0.43–0.49)	<0.001	0.66 (0.61–0.71)	<0.001	0.51 (0.44–0.59)	<0.001	0.45 (0.37–0.54)	<0.001	0.47 (0.30–0.72)	0.001
Grade										
I	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
II	4.22 (3.66–4.87)	<0.001	4.32 (3.60–5.19)	<0.001	3.52 (2.57–4.83)	<0.001	4.42 (2.65–7.39)	<0.001	20.42 (2.82–147.80)	0.003
III	7.04 (6.15–8.07)	<0.001	3.62 (3.03–4.33)	<0.001	3.60 (2.65–4.88)	<0.001	10.32 (6.29–16.95)	<0.001	17.68 (2.47–126.74)	0.004
IV	5.46 (4.44–6.71)	<0.001	4.07 (3.12–5.30)	<0.001	2.16 (1.28–3.62)	0.004	5.71 (2.96–10.99)	<0.001	29.97 (3.68–243.96)	0.001
T stage										
T1	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
T2	0.63 (0.57–0.69)	<0.001	0.41 (0.35–0.48)	<0.001	0.38 (0.29–0.50)	<0.001	0.46 (0.34–0.62)	<0.001	0.52 (0.25–1.08)	0.078
T3	0.88 (0.82–0.94)	<0.001	0.65 (0.58–0.72)	<0.001	0.57 (0.48–0.68)	<0.001	0.77 (0.64–0.93)	0.007	0.75 (0.46–1.22)	0.248
T4	2.40 (2.24–2.58)	<0.001	1.42 (1.29–1.55)	<0.001	1.27 (1.08–1.48)	0.003	1.15 (0.96–1.38)	0.141	0.95 (0.58–1.57)	0.853
N stage										
N0	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00	1.00 (Reference)	1.00
N1	2.79 (2.65–2.95)	<0.001	2.52 (2.35–2.70)	<0.001	2.49 (2.23–2.79)	<0.001	2.64 (2.34–2.98)	<0.001	2.49 (1.83–3.40)	<0.001
N2	0.95 (0.87–1.05)	0.320	0.83 (0.73–0.95)	0.008	0.74 (0.57–0.95)	0.017	0.82 (0.63–1.07)	0.150	0.90 (0.46–1.73)	0.743
N3	1.06 (0.97–1.17)	0.196	0.72 (0.62–0.84)	<0.001	0.74 (0.58–0.96)	0.023	0.84 (0.65–1.10)	0.210	1.21 (0.67–2.18)	0.523

Met – metastases; OR – odds ratio; CI – confidence interval; NOS – not otherwise specified.

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