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Original Article

Perioperative Chemotherapy Could Not Improve the Prognosis of Gastric Cancer Patients With Mismatch Repair Deficiency: A Multicenter, Real-World Study

Lulu Zhao[1,‡], Yongliang Fu[1,‡], Penghui Niu[1,‡], Fan Zhang[2,‡], Fuzhi Jiao[3,‡], Xiadong Zhou[4,‡], Zhenkun Wu[1], Wanqing Wang[1], Xiaoyi Luan[1], Xue Han[1], Mingyan He[*,4], Quanlin Guan[*,3], Yumin Li[*,2], Dongbing Zhao[*,1], Jidong Gao[*,5], Yingtai Chen[*,1]

[1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China
[2]Lanzhou University Second Hospital, Lanzhou, People's Republic of China
[3]The First Hospital of Lanzhou University, Lanzhou, People's Republic of China
[4]Gansu Provincial Cancer Hospital, Lanzhou, People's Republic of China
[5]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union College, Shenzhen, People's Republic of China

*Corresponding author: Mingyan He, Gansu Provincial Cancer Hospital, Lanzhou, People's Republic of China. Email: 119273873@qq.com; or, Quanlin Guan, The First Hospital of Lanzhou University, Lanzhou, People's Republic of China. Email: guanquanlin@163.com; or, Yumin Li, Lanzhou University Second Hospital, Lanzhou, People's Republic of China. Email: liym@lzu.edu.cn, or, Dongbing Zhao, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China. Email: dbzhao2003@sina.com; or, Jidong Gao, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union College, Shenzhen, People's Republic of China. Email: ab168@cicams.ac.cn; or, Yingtai Chen, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China. Email: yingtaichen@126.com
‡Contributed equally.

Abstract

Introduction: To date, the role of deficient mismatch repair (dMMR) remains to be proven in gastric cancer, and it is difficult to judge its value in clinical application. Our study aimed to investigate how MMR status affected the prognosis in patients with gastrectomy, as well as the efficacy of neoadjuvant chemotherapy and adjuvant chemotherapy in patients with dMMR with gastric cancer.

Materials and Methods: Patients with gastric cancer with certain pathologic diagnosis of dMMR or proficient MMR (pMMR) using immunohistochemistry from 4 high-volume hospitals in China were included. Propensity score matching was used to match patients with dMMR or pMMR in 1:2 ratios. Overall survival (OS) and progression-free survival (PFS) curves were plotted using the Kaplan-Meier method and compared statistically using the log-rank test. Univariate and multivariate Cox proportional hazards models based on hazard ratios (HRs) and 95% confidence intervals (CIs) were used to determine the risk factors for survival.

Results: In total, data from 6176 patients with gastric cancer were ultimately analyzed, and loss of expression of one or more MMR proteins was observed in 293 patients (293/6176, 4.74%). Compared to patients with pMMR, patients with dMMR are more likely to be older (≥66, 45.70% vs. 27.94%, $P < .001$), distal location (83.51% vs. 64.19%, $P < .001$), intestinal type (42.21% vs. 34.46%, $P < .001$), and in the earlier pTNM stage (pTNM I, 32.79% vs. 29.09%, $P = .009$). Patients with gastric cancer with dMMR showed better OS than those with pMMR before PSM ($P = .002$); however, this survival advantage was not observed for patients with dMMR after PSM ($P = .467$). As for perioperative chemotherapy, results of multivariable Cox regression analysis showed that perioperative chemotherapy was not an independent prognostic factor for PFS and OS in patients with dMMR with gastric cancer (HR = 0.558, 95% CI, 0.270-1.152, $P = .186$ and HR = 0.912, 95% CI, 0.464-1.793, $P = .822$, respectively).

Conclusion: In conclusion, perioperative chemotherapy could not prolong the OS and PFS of patients with dMMR with gastric cancer.

Key words: gastric cancer; deficient mismatch repair; perioperative chemotherapy; prognosis.

Implications for Practice

This multicenter study investigated systematically how mismatch repair (MMR) status affected the prognosis in patients with gastrectomy with gastric cancer, as well as the efficacy of neoadjuvant chemotherapy and adjuvant chemotherapy in patients with deficient MMR (dMMR) with gastric cancer. To the best of our knowledge, our analysis represented the largest evaluation of perioperative chemotherapy to survival outcomes in patients with dMMR. A primary finding was that perioperative chemotherapy could not prolong the survival of patients with dMMR compared with surgery alone, suggesting that perioperative chemotherapy might not be considered for patients with dMMR with gastric cancer.

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Introduction

Deficient mismatch repair (dMMR) tumors, also known as high-frequency microsatellite instability (MSI-H) tumors, are characterized by loss of mismatch repair (MMR) proteins in tumor cell nuclei and/or that of MMR activity.[1] The MMR status can be detected by using immunohistochemistry (IHC) and MSI test using tumor DNA.[1] Many studies have shown that dMMR exhibited a better anti-tumor immune response and inhibit the growth of tumor cells growth in colorectal cancer due to mutation or epigenetic changes of DNA MMR genes.[2,3] However, the role of dMMR remains to be proven in gastric cancer, and it is difficult to judge its value in clinical application.

Some studies have reported that dMMR status was associated with improved long-term survival for patients with gastric cancer who underwent gastrectomy,[4-9] whereas 2 post hoc analyses of clinical trials demonstrated that dMMR was not an independent factor affecting patients with gastric cancer.[10,11] In addition, the prognostic effects of perioperative chemotherapy at diagnosis of gastric cancer are also contradictory. Smyth et al[11] and Choi et al[8] showed that dMMR had a differentially negative prognostic effect on patients treated with chemotherapy, although others did not confirm this finding.[12-14] An et al[15] has identified that aggressive chemotherapy after recurrence should be considered for patients with gastric cancer with gastrectomy. To date, some large-scale randomized trials targeting the same issue are currently underway, and we are all awaiting the results.

As such, we conducted this multicenter, hospital-based retrospective study with the primary aim of comparing the overall survival (OS) and progression-free survival (PFS) between patients with gastric cancer with dMMR or proficient MMR (pMMR) based on China National Cancer Center, the first hospital of Lanzhou University, the second hospital of Lanzhou University and Gansu Cancer Hospital. The secondary aim of this study was to assess the impact of perioperative chemotherapy, including both neoadjuvant and adjuvant chemotherapy, for patients with dMMR following gastrectomy, in order to provide evidences for the development of guiding strategies for patients with dMMR with gastric cancer.

Materials and Methods

Study Population and Data Source

All patient records were abstracted from a multicenter gastric cancer cohort from China of China National Cancer Center 2015-2019, the first hospital of Lanzhou University 2014-2020, Lanzhou University Second Hospital 2015-2020, and Gansu Cancer Hospital 2015-2020. These 4 centers were high-volume hospitals with extensive experience in gastric cancer surgery and comprehensive treatment.

The inclusion criteria were as follows: (1) patients were 18 years of age or older, (2) histologically confirmed gastric adenocarcinoma, (3) patients received distal, proximal, or total gastrectomy, (4) patients diagnosed as pTanyNanyM0, (5) patients with complete date on MMR status. The exclusion criteria were as follows: (1) other types of malignancies in the stomach, (2) patients with M1, (3) patients who did not received gastrectomy, (4) patients missed significant varies or unknown MMR status. After selecting, 6176 patients with gastric cancer with certain pathologic diagnosis with dMMR or pMMR using IHC during were included (Fig. 1).

IHC for MMR Proteins

All tissue samples were fixed with 10% formalin solution, embedded in paraffin, and then was performed by IHC on MMR protein. Monoclonal antibodies of MLH1 (clone number: ES05), PMS2 (clone number: EP51), MSH2 (clone number: RED2), and MSH6 (clone number: EP49) were used

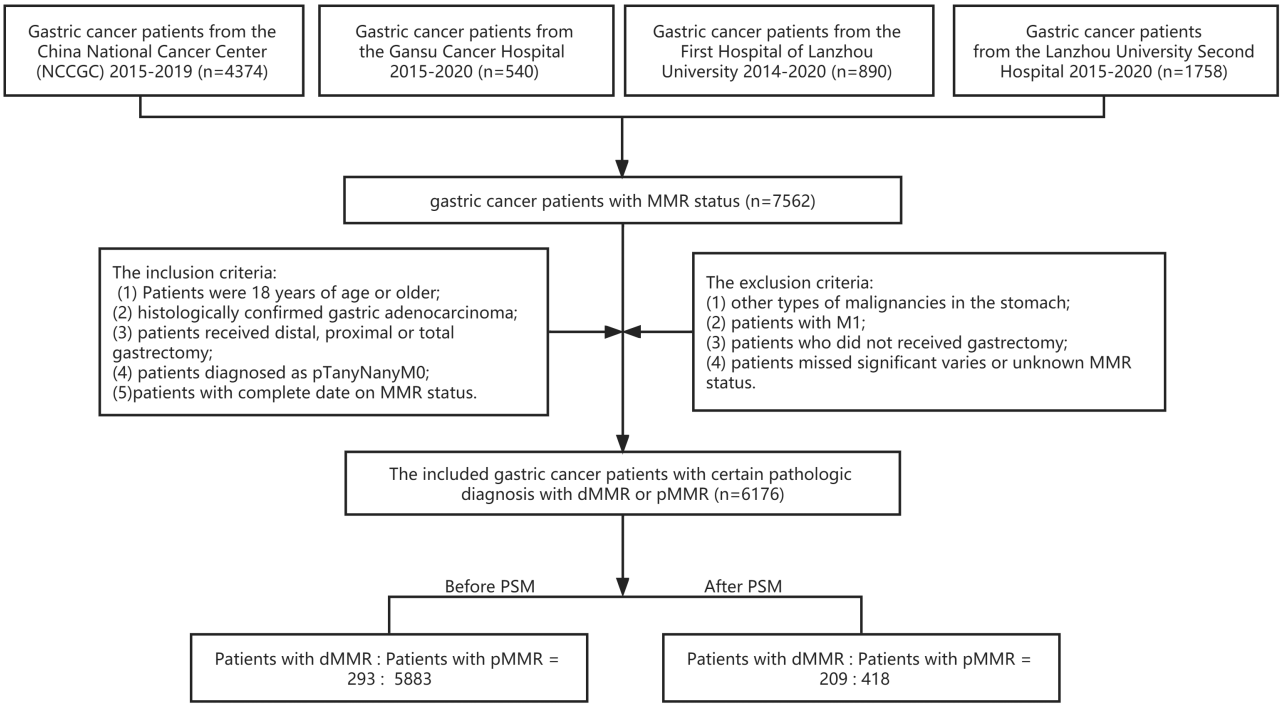

Figure 1. Flow diagram of the patient selection process in this study.

Table 1. The characteristics of patients with gastric cancer with dMMR or pMMR.

Characteristics	Before PSM			After PSM		
	dMMR (*n* = 293)	pMMR (*n* = 5883)	*P*-value	dMMR (*n* = 209)	pMMR (*n* = 418)	*P*-value
	N (%)	*N* (%)		*N* (%)	*N* (%)	
Age at diagnosis (years)			<.001			.790
Younger (≤35)	5 (1.72)	160 (2.73)		4 (1.91)	5 (1.20)	
Middle aged (36-65)	153 (52.58)	4063 (69.33)		119 (56.94)	238 (56.94)	
Older (≥66)	133 (45.70)	1637 (27.94)		86 (41.15)	175 (41.87)	
Gender			<.001			1.000
Male	185 (63.14)	4465 (75.90)		135 (64.59)	270 (64.59)	
Female	108 (36.86)	1418 (24.10)		74 (35.41)	148 (35.41)	
Smoking history			.005			1.000
Yes	78 (26.80)	2022 (34.78)		67 (32.06)	134 (32.06)	
No	213 (73.20)	3792 (65.22)		142 (67.94)	284 (67.94)	
Alcohol history			.107			.507
Yes	74 (25.43)	1737 (30.00)		64 (30.62)	139 (33.25)	
No	217 (74.57)	4083 (70.00)		145 (69.38)	279 (66.75)	
Tumor location			<.001			.884
Proximal	33 (11.34)	1629 (28.05)		27 (12.92)	56 (13.40)	
Distal	243 (83.51)	3728 (64.19)		175 (83.73)	348 (83.25)	
Total	15 (5.15)	451 (7.76)		7 (3.35)	14 (3.34)	
Lauren classification			.446			.072
Intestinal	111 (42.21)	1794 (34.46)		83 (42.13)	178 (46.23)	
Diffuse	67 (25.47)	1966 (37.76)		50 (25.38)	120 (31.17)	
Mixed	85 (32.32)	1446 (27.78)		64 (32.49)	87 (22.60)	
Pathologic T stage			.351			.061
T1	57 (20.88)	1366 (25.04)		51 (24.40)	138 (33.01)	
T2	57 (20.88)	654 (11.99)		43 (20.57)	72 (17.22)	
T3	62 (22.71)	1230 (22.54)		44 (21.05)	96 (22.98)	
T4	97 (35.53)	2206 (40.43)		71 (33.97)	112 (26.79)	
Pathologic N stage			<.001			.098
N0	145 (52.92)	2176 (40.69)		110 (52.63)	195 (46.67)	
N1	60 (21.90)	859 (16.06)		47 (22.49)	80 (22.00)	
N2	27 (9.85)	948 (17.73)		19 (9.09)	75 (12.22)	
N3	42 (15.33)	1365 (25.52)		33 (15.79)	68 (19.11)	
pTNM			.009			.759
I	81 (32.79)	1422 (29.09)		77 (36.84)	162 (38.76)	
II	78 (31.58)	1062 (21.72)		61 (29.18)	115 (27.51)	
III	88 (35.63)	2405 (49.19)		71 (33.97)	141 (33.73)	
Surgical margin			.326			.346
Negative	285 (99.30)	5653 (98.43)		205 (99.03)	387 (97.72)	
Positive	2 (0.70)	90 (1.57)		2 (0.97)	9 (2.28)	
Linitis plastic			.887			.260
Yes	2 (0.70)	50 (1.00)		2 (0.98)	1 (0.25)	
No	285 (99.30)	4931 (99.00)		203 (99.02)	407 (99.75)	
Histologic type			.606			.108
Well	18 (6.29)	400 (7.11)		156 (76.47)	316 (77.45)	
Moderately	52 (18.18)	1048 (18.62)		39 (19.12)	111 (27.21)	
Poorly	216 (75.52)	4179 (74.27)		9 (4.41)	23 (5.64)	
Signet ring cell carcinoma			<.001			.876
Yes	38 (14.45)	1552 (29.72)		32 (15.31)	66 (15.79)	
No	225 (85.55)	3670 (70.28)		177 (84.69)	352 (84.21)	
Vascular invasion			.546			.443
Yes	106 (40.46)	2221 (42.35)		72 (35.12)	157 (38.29)	
No	156 (59.54)	3024 (57.65)		133 (64.88)	253 (61.71)	

Table 1. Continued

Characteristics	Before PSM			After PSM		
	dMMR (n = 293)	pMMR (n = 5883)	P-value	dMMR (n = 209)	pMMR (n = 418)	P-value
	N (%)	N (%)		N (%)	N (%)	
Nerve invasion			.004			.650
Yes	130 (48.69)	3138 (57.69)		97 (46.41)	186 (44.50)	
No	137 (51.31)	2301 (42.31)		112 (53.59)	232 (55.50)	
Neoadjuvant chemotherapy			.353			.991
Yes	42 (15.38)	716 (13.41)		31 (14.90)	62 (14.87)	
No	231 (84.62)	4622 (86.59)		177 (85.10)	355 (85.13)	
Adjuvant chemotherapy			.274			.493
Yes	149 (70.14)	3406 (73.68)		95 (66.43)	195 (63.11)	
No	63 (29.86)	1217 (26.32)		48 (33.57)	114 (36.89)	

PSM for age at diagnosis, gender, smoking history, tumor location, pTNM stage, signet ring cell carcinoma, and nerve invasion.
Abbreviation: PSM: propensity score matching; dMMR: deficient mismatch repair; pMMR: proficient mismatch repair; pTNM: pathologic TNM.

for IHC staining with VENTANA fully automated IHC platform. The positive result means that some of the tumor cells have brown nuclei (Supplementary Fig. S1A, S1C, S1E, and 1G). Negative judgment means that the tumor cell nucleus is unstained, while the nucleus of normal cells (such as fibroblasts and lymphocytes) near the tumor cells is brown (Supplementary Fig. S1B, S1D, S1F, and S1H). Notably, Supplementary Fig. S1A, S1C, S1E and S1G was from the same patient with dMMR, while Supplementary Fig. S1B, S1D, S1F, and S1H were from the same patient with pMMR. Two senior pathologists will evaluate the results. If the results are inconsistent, a third senior pathologist will be invited to evaluate.

A published study has investigated that IHC method shows comparable performance characteristics and high concordance rate (>90%) with MSI detection with PCR.[16] Hence, IHC allows the determination which of the MMR genes is defective and supports the decision about further genetic analysis.

Statistical Methods

Categorical variables were compared using the Chi-squared test, and continuous variables were analyzed by Student's t test. OS and PFS curves were plotted for dMMR and pMMR groups, respectively, using the Kaplan-Meier method and compared statistically using the log-rank test.

Given the inherent differences between patients in dMMR and pMMR groups, we calculated a propensity score for following variables: age at diagnosis, gender, smoking history, tumor location, pTNM stage, signet ring cell carcinoma (SRC), and nerve invasion. The propensity score was estimated using a logit model. Propensity score matching (PSM) was performed using 1:2 optimal matching method with 0.05 of caliper value.

Univariate and multivariate Cox proportional hazards models based on Hazard ratios (HRs) and 95% confidence intervals (CIs) was used to determine the risk factors for OS and PFS. Variables with a P-value of < .10 on the univariate analysis were included for the multivariate analysis.

A P-value of < .05 was considered statistically significant. All statistical analyses were performed using the SPSS Version 25 (College Station, TX, USA) and R software version 3.6.4 (http://www.r-project.org/).

Results

Clinicopathologic Characteristics of Patients With dMMR and pMMR

In total, data from 6176 patients gastric cancer from 4 high-volume hospitals were ultimately analyzed, and loss of expression of one or more MMR proteins was observed in 293 patients (293/6176, 4.74%). Among the patients with dMMR, 82.94% patients showed loss of MLH1, 9.90% patients showed loss of MSH2, 10.24% patients showed loss of MSH6, and 86.35% patients showed loss of PMS2 (Supplementary Fig. S2).

The clinicopathologic characteristics of the pMMR and dMMR groups are shown in Table 1. Compared to patients with pMMR, patients with dMMR are more likely to be older (≥66, 45.70% vs. 27.94%, P < .001), female (36.86% vs. 24.10%, P < .001), distal location (83.51% vs. 64.19%, P < .001), intestinal type (42.21% vs. 34.46%, P < .001), and in the earlier pathologic TNM stage (pTNM I, 32.79% vs. 29.09%; and pTNM II, 31.58% vs. 21.72%, P =.009).] Relatively higher percentages of smoking history (34.78% vs. 26.80%, P = .005), SRC (29.72% vs. 14.45%, P < .001), and nerve invasion (57.69% vs. 48.69%, P = .004) were shown in patients with pMMR as compared to patients with dMMR.

After PSM, 627 (209:418) matched patients with dMMR or pMMR status were selected. There was no significant difference between the 2 groups in age at diagnosis, gender, smoking history, alcohol history, tumor location, Lauren classification, pathologic T stage, pathologic N stage, pTNM stage, surgical margin, linitis plastica, histologic type, SRC, vascular invasion, nerve invasion, neoadjuvant chemotherapy, and adjuvant chemotherapy (all P > .05).

OS and PFS Analysis of Patients With dMMR and pMMR

Figure 2 showed the Kaplan-Meier curves for OS and PFS before and after PSM. Patients with gastric cancer with dMMR showed better OS outcomes than those with pMMR before PSM (Fig. 2A, P = .002); however, this survival advantage was not observed for patients with dMMR after PSM (Fig. 2B, P = .466). The comparison of PFS in the matched patients with dMMR and pMMR also did not reach a

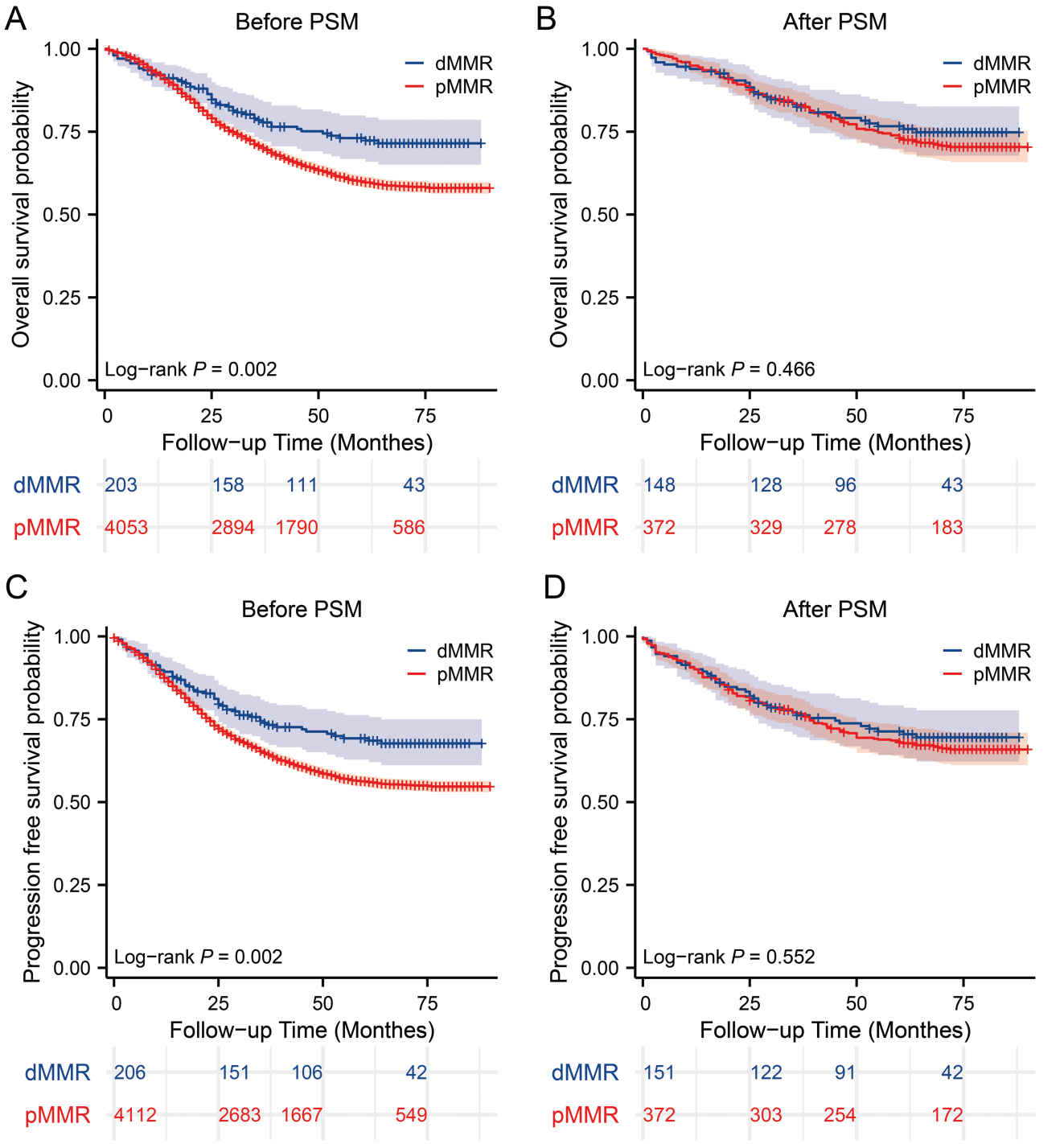

Figure 2. Overall survival (OS) and progression-free survival (PFS) of patients with gastric cancer with dMMR and pMMR before and after PSM. (**A**) OS before PSM, $P = .002$; (**B**) OS after PSM, $P = .466$; (**C**) PFS before PSM, $P = .002$; (**D**) PFS after PSM, $P = .552$. dMMR: deficient mismatch repair; pMMR: proficient mismatch repair; OS: overall survival; PFS: progression-free survival; PSM: propensity score matching.

statistically significant difference, as indicated in Fig. 2C and 2D ($P = .002$ before PSM and $P = .552$ after PSM).

Furthermore, the univariate and multivariate Cox proportional hazards models were used to determine the prognostic factors for OS and PFS in patients with matched gastric cancer (Tables 2). Variables with a P value of less than .10 in the univariate analysis were involved in the multivariate analysis, including age at diagnosis, tumor location, pTNM stage, surgical margin, histologic type, vascular invasion, nerve invasion, neoadjuvant chemotherapy, adjuvant chemotherapy, and MMR status. The independent predictor for OS included pTNM stage (HR = 4.121, 95% CI, 1.970-8.622, $P = .002$; HR = 8.816, 95% CI, 4.207-18.477, $P < 0.001$), vascular invasion (HR = 1.657, 95% CI, 1.118-2.456, $P = .035$), neoadjuvant chemotherapy (HR = 0.476, 95% CI, 0.291-0.779, $P = .003$), and adjuvant therapy (HR = 0.459, 95% CI, 0.293-0.718, $P = .003$). However, dMMR was not an independent prognostic factor for both OS (HR = 0.773,

Table 2. Univariate and multivariate analysis of OS and PFS in total patients with gastric cancer after PSM.

Characteristics	OS						PFS					
	Unadjusted			Adjusted*			Unadjusted			Adjusted*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age at diagnosis (years)												
Younger (≤35)	—			—			—			—		
Middle-aged (36-65)	1			1			1			1		
Older (≥66)	1.524	1.156-2.009	0.012	1.162	0.814-1.660	0.488	1.396	1.031-1.891	0.031	1.024	0.738-1.421	0.905
Gender												
Male	1			—			1			—		
Female	0.792	0.583-1.077	0.212				0.845	0.607-1.177	0.319			
Smoking history												
No	1			—			1			—		
Yes	0.926	0.690-1.241	0.665				1.012	0.736-1.391	0.941			
Alcohol history												
No	1			—			1			—		
Yes	1.055	0.791-1.407	0.758				1.148	0.840-1.568	0.388			
Tumor location												
Proximal	1			1			1			1		
Distal	0.587	0.420-0.820	0.020	0.673	0.430-1.053	0.145	0.605	0.415-0.882	0.009	0.748	0.491-1.141	0.258
Total				—			0.177	0.024-1.294	0.088	—		
Lauren classification												
Intestinal	1			—			1			—		
Diffuse	1.275	0.902-1.802	0.248				1.035	0.712-1.502	0.859			
Mixed	0.988	0.681-1.436	0.959				0.777	0.515-1.172	0.229			
pTNM												
I	1			1			1			1		
II	3.182	1.906-5.312	<0.001	4.121	1.970-8.622	0.002	2.352	1.420-3.896	<0.001	3.257	1.786-5.940	0.001
III	8.237	5.280-12.852	<0.001	8.816	4.207-18.477	<0.001	5.347	3.478-8.221	<0.001	6.201	3.360-11.444	<0.001
Surgical margin												
Negative	1			1			1			1		
Positive	3.305	1.745-6.259	0.002	0.914	0.362-2.306	0.873	2.645	1.240-5.643	0.012	0.920	0.369-2.292	0.881
Linitis plastica												
No	1			—			1			—		
Yes	1.911	0.367-9.967	0.519				1.402	0.196-10.020	0.736			
Histologic type												
Well	1			1			1			1		
Moderately	0.940	0.670-1.317	0.762	0.687	0.416-1.148	0.229	1.013	0.702-1.460	0.946	0.838	0.536-1.310	0.516
Poorly	0.400	0.153-1.050	0.118	1.312	0.470-3.661	0.663	0.765	0.337-1.739	0.523	1.197	0.492-2.914	0.739
Signet ring cell carcinoma												
No	1			—			1			—		
Yes	1.342	0.944-1.908	0.169				1.045	0.801-1.765	0.39			
Vascular invasion												
No	1			1			1			1		
Yes	2.616	1.963-3.486	<0.001	1.657	1.118-2.456	0.035	1.989	1.463-2.705	<0.001	1.257	0.890-1.776	0.276
Nerve invasion												
No	1			1			1			1		
Yes	2.327	1.750-3.094	<0.001	1.163	0.775-1.744	0.540	1.946	1.431-2.647	<0.001	1.147	0.798-1.650	0.534
Neoadjuvant chemotherapy												
No	1			1			1			1		
Yes	2.251	1.643-3.083	<0.001	0.476	0.291-0.779	0.003	2.137	1.590-2.873	<0.001	0.542	0.345-0.851	0.008

Table 2. Continued

Characteristics	OS						PFS					
	Unadjusted			Adjusted*			Unadjusted			Adjusted*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Adjuvant chemotherapy												
No	1			1			1			1		
Yes	1.777	1.220-2.589	0.012	0.459	0.293-0.718	0.003	1.655	1.188-2.306	0.013	0.598	0.395-0.906	0.042
Group												
dMMR	1			1			1			1		
pMMR	0.867	0.627-1.198	0.467	0.773	0.511-1.168	0.305	0.9	0.673-1.204	0.548	0.896	0.629-1.278	0.611

*Adjusted factors: age at diagnosis, tumor location, pTNM stage, surgical margin, histologic type, vascular invasion, nerve invasion, neoadjuvant chemotherapy, adjuvant chemotherapy and MMR status.
OS: overall survival; PFS: progression-free survival; HR: Hazard ratios; PSM: propensity score matching; dMMR: deficient mismatch repair; pMMR: proficient mismatch repair; pTNM: pathologic TNM.

95 CI%, 0.511-1.168, *P* = .305) and PFS (HR = 0.896, 95 CI%, 0.629-1.278, *P* = 0.611).

Clinicopathologic Characteristics of Patients With dMMR

We further reported the clinicopathologic features of patients with dMMR with different perioperative chemotherapy status (Table 3). Compared to patients received treatment, patients without perioperative chemotherapy had a higher percentage of older (≥66, 64.81% vs. 34.81%, *P* = .001), pT1 stage (39.62% vs. 7.04%, *P* < .001), pN0 stage (71.70% vs. 42.57%, *P* = .018), and pTNM I stage (60.78% vs. 17.32%, *P* <.001). In addition, a smaller percentage of patients without perioperative chemotherapy had poorly grade (60.38% vs. 79.22%, *P* = .005) and nerve invasion (36.00% vs. 60.28%, *P* = .003).

OS and PFS Analysis of Patients With dMMR

The comparison of survival between the perioperative chemotherapy and nonperioperative chemotherapy groups in the total patients with dMMR was shown in Fig. 3A and 3B. There was no significantly difference between the 2 groups not only in OS but also in PFS (*P* = .417 and *P* = .189, respectively).

As indicated in Table 4, the multivariable Cox regression analysis showed that perioperative chemotherapy was not an independent predictive factor for PFS and OS in patients with dMMR with gastric cancer (HR = 0.558, 95% CI, 0.270-1.152, *P* = .186; and HR = 0.912, 95% CI, 0.464-1.793, *P* = .822, respectively). We further evaluated the subgroups stratified by detailed therapeutic schedule, and results showed that the 2 groups (adjuvant chemotherapy only, and neoadjuvant and adjuvant chemotherapy group) were not associated with improved OS (HR = 0.515, 95% CI, 0.209-1.268, *P* = .149; and HR = 0.370, 95% CI, 0.093-1.463, *P* = .156, respectively) and PFS (HR = 0.729, 95% CI, 0.312-1.702, *P* = .465; and HR = 1.032, 95% CI, 0.359-2.965, *P* = .953, respectively).

Discussion

This multicenter study investigated systematically how MMR status affected the prognosis in gastrectomy patients with gastric cancer, as well as the efficacy of neoadjuvant chemotherapy and adjuvant chemotherapy in patients with dMMR with gastric cancer. To the best of our knowledge, our analysis represented the largest evaluation of perioperative chemotherapy to survival outcomes in patients with dMMR. A primary finding was that perioperative chemotherapy could not prolong the survival of patients with dMMR compared with surgery alone, suggesting that perioperative chemotherapy might not be considered for patients with dMMR with gastric cancer.

The Cancer Genome Atlas (TCGA) project has first provided a systematic classification of gastric cancer, focusing on genetic profiling, defining 4 molecular subtypes.[17] The MSI category, presenting a typical lack of function of MMR genes, was of clinical interest because of the favorable prognostic profile in some tumors compared with their pMMR counterpart.[18,19] However, previous study has reported that the mechanism of dMMR occurrence in gastric cancer is distinct from that in other tumors, such as colorectal carcinoma.[20] In this study, we conducted this multicenter hospital-based retrospective study to investigate the OS and PFS outcomes of patients with pMMR and dMMR with gastric cancer, as well as the efficacy of perioperative chemotherapy for patients with dMMR following gastrectomy.

Our study demonstrated that the clinicopathological characteristics of patients with dMMR presented differently with patients with pMMR, where dMMR was associated with older age, female sex, distal stomach location, intestinal type, and earlier pTNM stage. Some published studies were in agreement with our study.[6,7,11,15,21] Nakajima et al has reported that the loss of expression of MLH1 gene was related to aging.[22] In addition, some studies have argued that the better prognosis of patients with dMMR was attributed to its earlier pTNM stage and intestinal type.[1,21]

A post hoc analyses of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial has reported the association among MSI-H or dMMR, clinical features, and survival in patients with non-metastatic gastric cancer.[11] Patients from MAGIC trial treated with surgery alone who had MSI-H or dMMR had a median OS that was not reached (95% CI, 11.5 months to not reached) compared with a median OS among those who had neither MSI-H or dMMR of 20.5 months (95% CI, 16.7-27.8 months; HR = 0.42; 95% CI, 0.15-1.15, *P* = .09). Some researchers reported that dMMR tumors are strongly associated with a vigorous immune infiltration[23,24] and highly

Table 3. The characteristics of patients with dMMR with different perioperative chemotherapy.

Characteristics	Perioperative chemotheraoy ($n = 159$)	Non-perioperative chemotheraoy ($n = 55$)	*P* value
	N (%)	*N* (%)	
Age at diagnosis (years)			.001
Younger (≤35)	3 (1.90)	1 (1.85)	
Middle-aged (36-65)	100 (63.29)	18 (33.33)	
Older (≥66)	55 (34.81)	35 (64.81)	
Gender			.222
Male	107 (67.30)	32 (58.18)	
Female	52 (32.70)	23 (41.82)	
Smoking history			.557
Yes	41 (25.79)	12 (21.82)	
No	118 (74.21)	43 (78.18)	
Alcohol history			.880
Yes	36 (22.64)	13 (23.64)	
No	123 (77.36)	42 (76.36)	
Tumor location			.215
Proximal	22 (14.01)	4 (7.27)	
Distal	123 (78.34)	49 (89.09)	
Total	12 (7.64)	2 (3.64)	
Lauren classification			.221
Intestinal	49 (34.75)	23 (47.92)	
Diffuse	41 (29.08)	13 (27.08)	
Mixed	51 (36.17)	12 (25.00)	
Pathologic T stage			<.001
T1	10 (7.04)	21 (39.62)	
T2	30 (21.13)	12 (22.64)	
T3	41 (28.87)	11 (20.75)	
T4	61 (42.96)	9 (16.98)	
Pathologic N stage			.018
N0	63 (42.57)	38 (71.70)	
N1	41 (27.70)	6 (11.32)	
N2	15 (10.14)	2 (3.77)	
N3	29 (19.59)	7 (13.21)	
pTNM			<.001
I	22 (17.32)	31 (60.78)	
II	48 (37.80)	9 (17.65)	
III	57 (44.88)	11 (21.57)	
Surgical margin			.406
Negative	156 (98.73)	54 (100.00)	
Positive	2 (1.27)	0 (0.00)	
Linitis plastica			.489
Yes	1 (0.72)	1 (1.85)	
No	137 (99.28)	53 (98.15)	
Histologic type			.005
Well	7 (4.55)	9 (16.98)	
Moderately	25 (16.23)	12 (22.64)	
Poorly	122 (79.22)	32 (60.38)	
Signet ring cell carcinoma			.050
Yes	24 (17.02)	3 (5.88)	
No	117 (82.98)	48 (94.12)	
Vascular invasion			.226
Yes	70 (51.09)	21 (41.18)	
No	67 (48.91)	30 (58.82)	

Table 3. Continued

Characteristics	Perioperative chemotheraoy (n = 159)	Non-perioperative chemotheraoy (n = 55)	P value
	N (%)	N (%)	
Nerve invasion			.003
Yes	85 (60.28)	18 (36.00)	
No	56 (39.72)	32 (64.00)	
Neoadjuvant chemotherapy			—
Yes	42 (29.17)	0 (0.00)	
No	102 (70.83)	55 (100.00)	
Adjuvant chemotherapy			—
Yes	149 (97.39)	0 (0.00)	
No	4 (2.61)	55 (100.00)	

dMMR: deficient mismatch repair; pTNM: pathologic TNM.

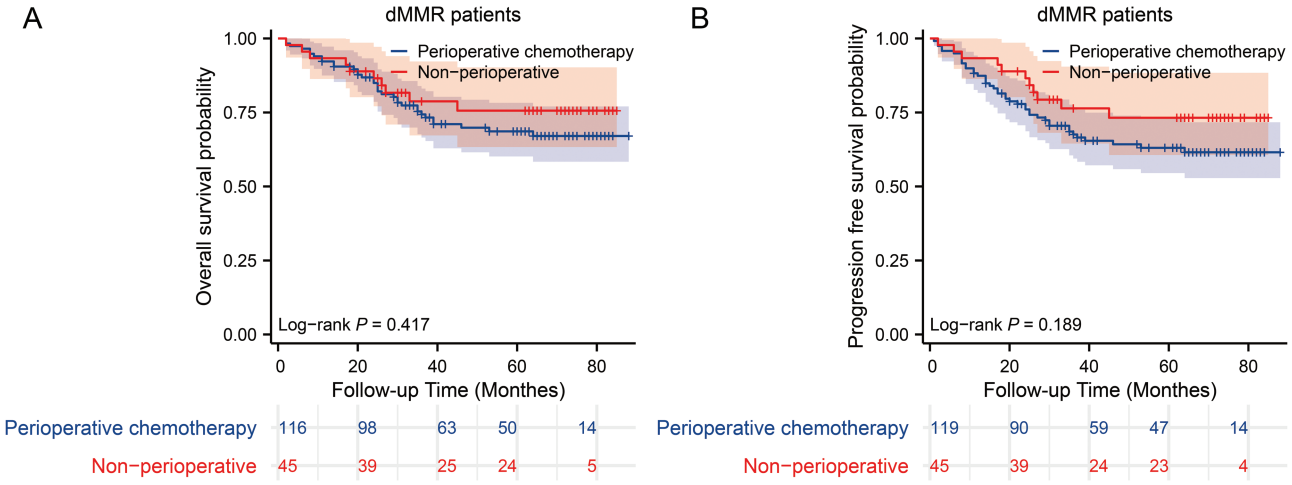

Figure 3. Overall survival (OS) and progression-free survival (PFS) of patients with dMMR with different perioperative chemotherapy status. (**A**) OS for perioperative chemotherapy status, P = .417; (**B**) PFS for neoadjuvant chemotherapy status, P = .189. dMMR: deficient mismatch repair; OS: overall survival; PFS: progression-free survival.

express some immune molecules, such as CTLA-4, PD-1, PD-L1, LAG-3, and IDO,[23,25] which may suppress the residual micrometastasis following gastrectomy and get favorable survival. In this study, we showed that patients with dMMR had a relatively improved OS and PFS before PSM, although no difference was found between the 2 groups in statistics after PSM (P = .467 for OS and P = .551 for PFS, respectively). In addition, results from multivariate analyses showed that dMMR was not an independent indicator for prognosis of patients with gastric cancer, which was similar with another recently published study in China.[26] As we have mentioned earlier, the survival benefits of patients with dMMR mainly attributed to the intestinal type and earlier pTNM stage.

In addition, the prognostic value of perioperative chemotherapy for patients with dMMR with gastric cancer was still controversial. In 2019, a meta-analysis from 4 large randomized clinical trials (MAGIC, CLASSIC, ARTIST, and ITACA-S) showed that patients with dMMR/MSI-H with gastric cancer did not benefit from adjuvant chemotherapy after radical surgery.[27] After that, many clinicians did not recommend that patients with MSI-H to receive adjuvant chemotherapy after radical surgery, but to observe or involve adjuvant immunotherapy. Interestingly, a recently published meta-analysis with 7 clinical studies confirmed the benefit of adjuvant chemotherapy for patients with dMMR/MSI-H. An et al[15] indicated that aggressive chemotherapy after recurrence should be considered for patients with dMMR with gastric cancer following gastrectomy. In this multicenter real-world study with the largest cohort of individual of patients with dMMR, we found that perioperative chemotherapy could not prolong the survival of patients with dMMR compared with surgery alone, even in the subgroup of adjuvant chemotherapy only or those received both neoadjuvat chemotherapy and adjuvant chemotherapy. In this context, a clear correlation between dMMR and perioperative chemotherapy in gastric cancer requires additional study.

In addition, increasing clinical trials showed that patients with dMMR or MSI-H gastric cancer could reach survival benefits from perioperative immunotherapy and manageable safety across a range of heavily treated.[28-31] Specifically, MSI-H tumors display high infiltration with CD8 + T cells, presumably due to the recognition of a high number of neoantigens and its corresponding expression of immune checkpoints,

Table 4. The univariate and multivariate analysis of PFS and OS in of patients with dMMR with different perioperative chemotherapy.

Characteristics	Univariate				Multivariate*			
	HR	95% CI		*P* value	HR	95% CI		*P* value
OS for patients with dMMR								
Perioperative chemotherapy								
No	1				1			
Yes	1.339	0.741	2.420	.417	0.558	0.270	1.152	.186
Subgroup								
No-neo AND no-adjuvant chemotherapy	1				1			
No-neo AND adjuvant chemotherapy	1.352	0.654	2.796	.416	0.515	0.209	1.268	.149
Neo AND no-adjuvant chemotherapy	—				—			
Neoadjuvant AND adjuvant chemotherapy	0.978	0.334	2.863	.968	0.370	0.093	1.463	.156
PFS for patients with dMMR								
Perioperative chemotherapy								
No	1				1			
Yes	1.554	0.890	2.714	.193	0.912	0.464	1.793	.822
Subgroup								
No-neo AND No-adjuvant chemotherapy	1				1			
No-neo AND adjuvant chemotherapy	1.425	0.716	2.836	.313	0.729	0.312	1.702	.465
Neo AND No-adjuvant chemotherapy	—				—			
Neoadjuvant AND adjuvant chemotherapy	1.780	0.737	4.298	.200	1.032	0.359	2.965	.953

*Adjusted factors: pTNM stage, surgical margin, histologic type, vascular invasion, and perioperative chemotherapy.
OS: overall survival; PFS: progression-free survival; HR: Hazard ratios; dMMR: deficient mismatch repair; pTNM: pathologic TNM.

such as PD-L1 in the tumor microenvironment,[32] which might lead to a favorable response to Immune checkpoint inhibitors. In this context, it is possible to prioritize perioperative immunotherapy for patients with dMMR rather than chemotherapy in the future.

Several limitations need to be considered in this study. First, our multicenter retrospective study may potentially have introduced selection bias. Although we have attempted to simulate randomization by using PSM analysis for survival analyses, there remains a possibility of uncontrolled confounding factors. Second, our study was lacking in engagement of detailed chemotherapy drugs and the information of immunotherapy status for patients with gastric cancer. Third, the small sample size of 293 patients with dMMR could be the reason for non-significant *P*-value with regard to evaluate the effect of perioperative chemotherapy, research with large sample volume needs to be verified in the future. Despite all this, our multicenter hospital-based study was the largest one to evaluation of MMR status to survival outcomes for gastric cancer patients to data, as well as the efficacy of neoadjuvant chemotherapy and adjuvant chemotherapy in patients with dMMR.

In conclusion, perioperative chemotherapy could not prolong the OS and PFS of patients with dMMR gastric cancer. Although it is too early to consider any potential clinical recommendations, we will continue to focus on patients with dMMR who underwent gastrectomy and perform further medical research to explore the relevant mechanisms.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: L.Z., M.H., Q.G., Y.L., D.Z., J.G., Y.C. Provision of study material or patients: L.Z., F.Z., F.J., X.Z. Collection and/or assembly of data: Y.F., P.N. Data analysis and interpretation: Z.W., W.W., X.L., X.H. Final approval of manuscript: All authors.

Data Availability

The data used to support these findings of this study is included within the article in Tables.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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