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Research Article

Real-life Comparison of FOLFOX-6 and Modified DCF Regimens for the First-Line Treatment of HER-2 Negative Metastatic Gastric Cancer

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Abstract

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related mortality worldwide. Chemotherapy improves survival and quality of life in unresectable locally advanced or metastatic gastric cancer (mGC). The present study aimed to compare the efficacy of modified DCF and FOLFOX-6 for the first-line treatment of HER-2-negative mGC. This retrospective study included 254 patients. Demographic and clinicopathologic features were recorded. Patients were categorized into two groups according to the first-line chemotherapy regimens. Survival analysis was performed with the Kaplan-Meier method. Median follow-up duration was 12 months (IQR: 6.7–22). Median progression-free survival was 6.9 months in the FOLFOX-6 group and 7.1 months in the mDCF group. There was no statistically significant difference between the groups. Median overall survival (OS) was 11.1 months in patients receiving FOLFOX-6 and 13.4 months in patients receiving mDCF. No significant difference was observed between the two regimens in terms of OS. We found no difference between the two chemotherapy regimens in terms of survival outcomes and response rates.

Keywords: Gastric cancer, survival, triplet regimen, dual combination, chemotherapy, response rate

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Gastric cancer (GC) remains one of the most common malignancies worldwide and is among the leading causes of cancer-related mortality.[1] East Asia, South and Central America, and Eastern Europe are the regions with the highest incidence of GC.[2] It is categorized into two subtypes based on the histological Lauren classification: diffuse and intestinal types, whereas anatomical localization classifies it as cardia/proximal or non-cardia/intestinal tumors. The vast majority (95%) of gastric carcinomas are adenocarcinomas.[3] Helicobacter pylori infection, smoking, and a high-salt diet play important roles in the etiopathogenesis of GC. While most GCs are sporadic, inherited GC predisposition syndromes account for only 3–5% of cases.[4–6] There has been a significant change in the location and histological subtype of upper gastrointestinal tract tumors in North America and Europe in recent years. As a result of improved living standards, food preservation, and the eradication of Helicobacter pylori, there has been a marked decline in intestinal-type distal GC, whereas the incidence of proximal diffuse-type GC has increased.[2] Systemic chemotherapy has been shown to prolong survival and improve quality of life in patients with unresectable or metastatic disease. Patients treated with combination chemotherapy regimens have a median survival of approximately one year, compared with only 3–4 months for patients receiving best supportive care alone.[7,8]

The overall HER2 (Human Epidermal Growth Factor Receptor 2) positivity rate in GC is highly variable, ranging from 12% to 23%.[9] Chemotherapy combined with HER2-targeted therapy has improved survival in patients with HER2-positive metastatic GC. In addition, immune checkpoint inhibitors combined with platinum- and fluoropyrimidine-based chemotherapy have become a standard first-line treatment option for selected patients with HER2-negative metastatic GC. Nevertheless, platinum- and fluoropyrimidine-based chemotherapy remains the backbone of first-line systemic treatment, either alone or in combination with immunotherapy.[10] Although the NCCN (National Comprehensive Cancer Network) guidelines recommend platinum- and fluoropyrimidine-based doublet chemotherapy as the preferred first-line treatment for metastatic GC, three-drug combination regimens may be considered for medically fit patients with good performance status.[11]

There are conflicting results in the literature regarding the comparison of dual and triplet chemotherapy regimens in the first-line treatment of metastatic GC. Wang et al.[12] reported that the modified DCF (docetaxel, cisplatin, and fluorouracil) regimen improved progression-free survival (PFS) and overall survival (OS) compared with the CF (cisplatin and fluorouracil) regimen. Hacibekiroğlu et al.[13] demonstrated comparable efficacy between FOLFOX-6 and DCF in patients with metastatic GC. Similarly, the JCOG1013 trial reported that the addition of docetaxel to cisplatin plus S-1 did not improve overall survival compared with cisplatin plus S-1 alone in previously untreated advanced gastric cancer.[14] More recently, the phase III PRODIGE 51-FFCD-GASTFOX trial demonstrated that the modified FLOT (TFOX) regimen significantly improved progression-free survival, overall survival, and objective response rate compared with FOLFOX in patients with HER2-negative advanced gastric and gastro-oesophageal junction adenocarcinoma, although at the expense of increased treatment-related toxicity.[15]

Despite these recent advances, the optimal role of taxane-containing triplet chemotherapy in the first-line treatment of HER2-negative metastatic GC remains an important clinical question. Therefore, we aimed to compare the effectiveness of modified DCF and FOLFOX-6 as first-line treatment in a real-world cohort of patients with HER2-negative metastatic gastric cancer.

Methods

We retrospectively reviewed the records of patients who were diagnosed with mGC between 2012 and 2019 at our institution. Inclusion criteria were a histological/cytological diagnosis of HER2-negative GC, age ≥18 years, metastatic disease, receipt of first-line systemic chemotherapy (FOLFOX-6 or modified DCF), and complete medical records. Patients diagnosed with multiple malignancies other than GC were excluded to minimize potential confounding effects on treatment response and survival outcomes. The final study population included 254 patients, of whom 154 received FOLFOX-6 and 100 received modified DCF as first-line treatment.

Demographic, clinicopathologic, and laboratory data were extracted from the institutional electronic medical records. Patients with incomplete medical records were excluded from the study.

Chemotherapy Regimens

A. FOLFOX-6 (5-Fluorouracil 2400 mg/m2 48-hour infusion, 5-Fluorouracil 400mg/m2 bolus, Folinic acid 400mg/m2, and Oxaliplatin 85mg/m2 on day 1, repeated every 14 days)

B. Modified DCF (Cisplatin 40mg/m2, Docetaxel 40mg/m2, 5-Fluorouracil 2000 mg/m2 48-hour infusion, and 5-Fluorouracil 400mg/m2 bolus on day 1, repeated every 14 days)

Statistical Analysis

Descriptive statistics were used to present demographic and clinical features. Comparison of demographic features between treatment groups was carried out using Pearson's $\chi 2$ test. PFS was defined as the time from the start of sys-

temic treatment until radiological progression or death/last visit date. OS was defined as the time from the start of systemic treatment until death from any cause or the last visit date. Survival analysis was performed with the Kaplan-Meier method. Prognostic factors were compared using the log-rank test in univariate analysis. Multivariate analysis was carried out using the Cox proportional hazards model to assess the effect of prognostic factors on OS. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. All p values were two-sided, and p values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, version 22.0 (Armonk, NY: IBM Corp., USA).

Results

Demographic and clinicopathologic characteristics of patients

Ninety-two of 254 patients were female (36%), and the median age was 62 years (range, 22–78). While 154 patients received the mFOLFOX6 regimen, 100 patients were treated with the mDCF regimen. There was no difference between the two groups in terms of age, gender, tumor localization, and the presence of primary tumor surgery. Baseline demographics and clinicopathologic findings according to treatment groups are shown in Table 1.

Treatment Efficacy and Survival Outcomes

Median follow-up duration was 12 months (IQR: 6.7–22). Treatment efficacy was found to be similar in both groups. Disease control rate (DCR) was 47% in patients receiving FOLFOX-6 and 57% in those receiving mDCF, and no significant difference was detected between the groups (p=0.13). Overall response rate (ORR) was 32% in the FOLFOX-6 group and 43% in the mDCF group (p=0.1). For the entire cohort, median PFS was 7 months (95% CI, 6.1–7.8), and median OS was 11.5 months (95% CI, 10.1–12.9) **(**Fig. 1,2).

Median PFS was 6.9 months (95% CI, 5.8–8.0) and 7.1 months (95% CI, 5.9–8.3) in patients receiving FOLFOX-6 and mDCF, respectively. There was no statistically significant difference between the two regimens in terms of PFS (p=0.92) **(**Fig. 3**)**. Median OS was 11.1 months (95% CI, 9.6–12.5) in the FOLFOX-6 group and 13.4 months (95% CI, 10.5–16.3) in the mDCF group. No statistically significant difference was observed between the two regimens in terms of OS (p=0.23, Fig. 4).

Prognostic factors affecting OS were evaluated with Cox regression analysis. In univariate analysis, ECOG PS, CEA, and chemotherapy response were found to be significant predictors of OS. In multivariate analysis, ECOG PS (HR: 2.02) and chemotherapy response (HR: 4.1) were determined as independent prognostic factors. Cox regression analysis results are shown in Table 2. In the ECOG PS 0–1 group and ECOG PS 2–3 group, median OS was 12 months (95% CI: 10.5–13.4) and 6.9 months (95% CI: 3–10.9), respectively (p=0.005) **(**Fig. 5**)**. The median OS was 18 months (95% CI: 13.5–22.4) in patients who responded to chemotherapy, while it was 8.4 months (95% CI: 7.1–9.7) in the unresponsive group (p<0.001) **(**Fig. 6**)**.

Table 1. Baseline demographic and clinicopathologic characteristics of patients

	FOLFOX (n=154)	mDCF (n=100)	p
Gender			
Male	95	67	0.39
Female	59	33	
Age, years			
≥60	97	56	0.27
<60	57	44	
Location of primary tumor			
Cardia	71	58	0.27
Corpus	49	24	
Antrum	32	16	
Diffuse	2	2	
Surgery for primary tumor			
Yes	47	22	0.14
No	107	78	
Carcinoembryonic antigen (Median)	3,6 ng/ml (min 0.8-max 1500)	5,3 ng/ml (min 0,5-max 1500)	0,9
CA19-9 (Median)	52.1 U/ml (min 0,8-max 1400)	16,6 U/ml (min 0,2-max1200)	0,2
Metastatic sites			
Single	101	45	**0.001**
Multiple	53	55	
ECOG-PS			
0-1	122	91	**0.01**
2-3	32	9	
Response Type			
CR	3	4	
PR	46	39	0,2
SD	24	24	
PD	81	43	
Best response			
CR/PR/SD	73	57	0.13
PD	81	43	
Progression			
Yes	144	97	0.22
No	10	3	
Death			
Yes	135	88	0.93
No	19	12	

CA19-9: Carbohydrate antigen 19-9; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CR: Complete response, PR: Partial response , SD: Stable disease, PD: Progressive disease.

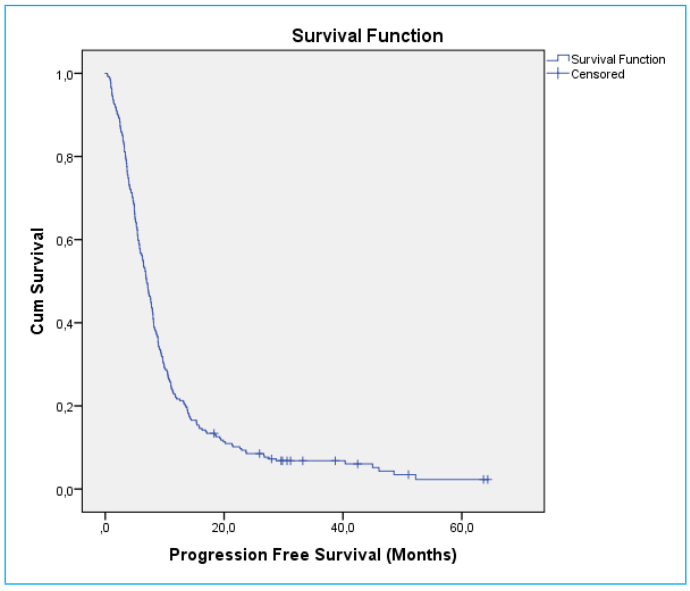

Figure 1. Progression free survival graphic all cohort by Kaplan-Meier.

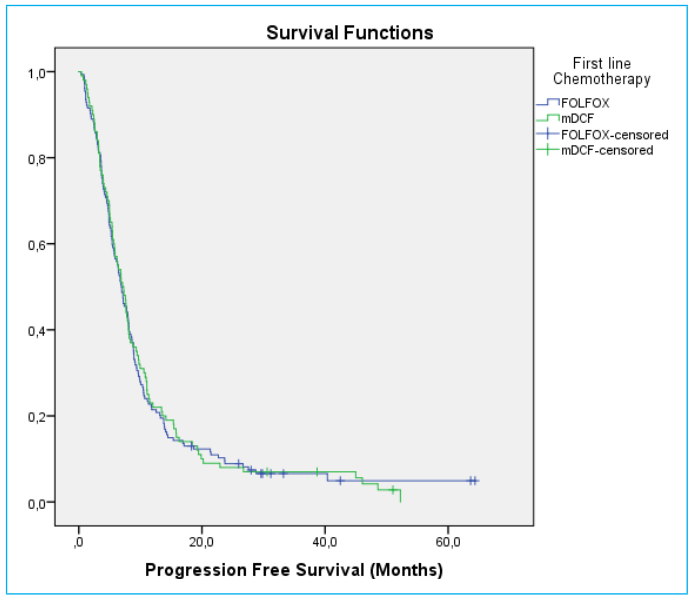

Figure 3. Progression free survival graphic according to treatment regimens by Kaplan-Meier.

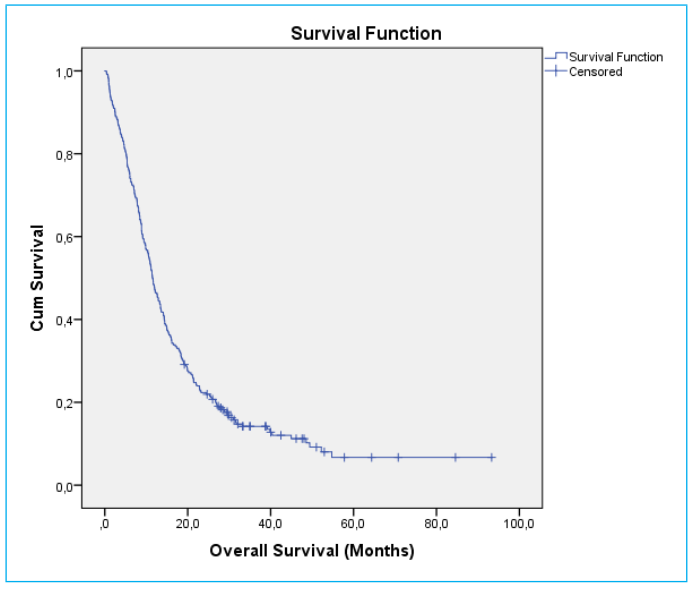

Figure 2. Overall survival graphic all cohort by Kaplan-Meier.

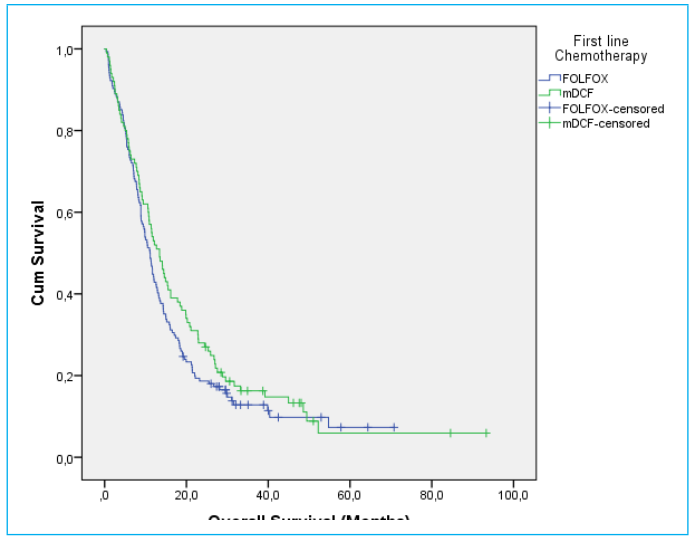

Figure 4. Overall survival graphic according to treatment regimens by Kaplan-Meier.

Discussion

Chemotherapy remains the cornerstone of first-line treatment for patients with HER2-negative metastatic gastric cancer. Platinum- and fluoropyrimidine-based doublet regimens are the current standard of care and may be combined with immune checkpoint inhibitors in selected patients. Whether the addition of a taxane to platinum–fluoropyrimidine chemotherapy provides additional clinical benefit remains an important clinical question. In the present study, we found no significant differences between the modified DCF and FOLFOX-6 regimens with respect to progression-free survival, overall survival, objective response rate, or disease control rate. These findings suggest that both regimens provide comparable clinical efficacy as first-line treatment for HER2-negative metastatic gastric cancer in routine clinical practice.

Systemic treatment provides improved survival and enhanced palliation of disease burden. In this study, there was no statistically significant difference in overall survival between the FOLFOX-6 and modified DCF groups (11.1 vs. 13.4 months, p=0.23). Similarly, median progression-free survival was 6.9 months in the FOLFOX-6 group and 7.1 months in the modified DCF group, with no statistically significant difference between the two regimens (p=0.92).

Table 2. Cox regression models of overall survival

		Univariate Analysis				Multivariate Analysis			
		HR	95% CI		P	HR	95 % CI		P
			Lower	Upper			Lower	Upper	
Age	<60	0.9	0.70	1.19	0,50				
	≥ 60								
ECOG PS	0-1	1.6	1.1	2.3	**0,005**	2.02	1.1	3.6	**0,02**
	2-4								
Gender	Female	0,9	0,7	1.3	0.9				
	Male								
CEA	<5 ng/ml	1.6	1.01	2.6	**0.04**				
	≥5ng/ml								
CA19-9	<35 U/ml	1.3	0.8	2.2	0.2				
	≥ 35 U/ml								
Histology	Signet ring cell	1,02	0,7	1,4	0,8				
	Adenocarcinoma								
Systemic treatment	FOLFOX	0,84	0,6	1,12	0,2				
	DCF								
Response Type	CR/PR	1,6	1,4	1,9	**0,001**	4.1	2.4	7.0	**0.001**
	SD/PD								

CA19-9: Carbohydrate antigen 19-9; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CEA: Cox regression analysis; CR: Complete response, PR: Partial response , SD: Stable disease, PD: Progressive disease; DCF: Docetaxel, cisplatin, and fluorouracil.

Overall, previous retrospective studies have consistently demonstrated comparable efficacy between FOLFOX- and DCF-based regimens in the first-line treatment of metastatic gastric cancer. Hacibekiroğlu et al.[13] and Pourghasemian et al.[14] reported no significant differences in overall survival or progression-free survival between the two regimens, findings that are consistent with our results. Similarly, studies evaluating FOLFOX-4 as first-line treatment have report-

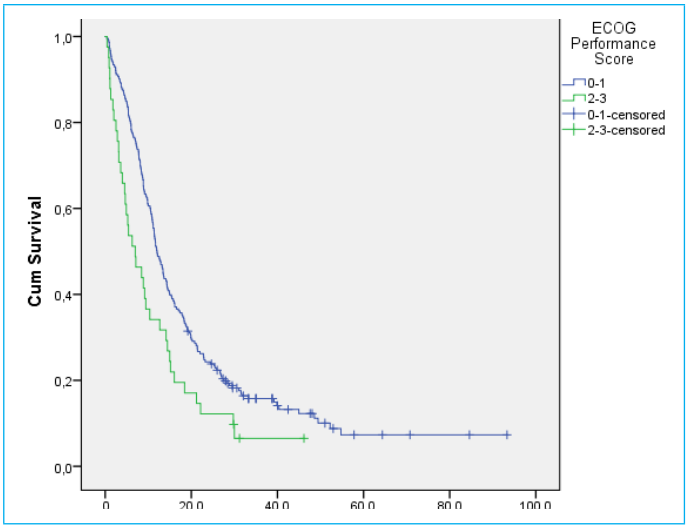

Figure 5. Overall survival graphic accorging to ECOG PS by Kaplan-Meier.

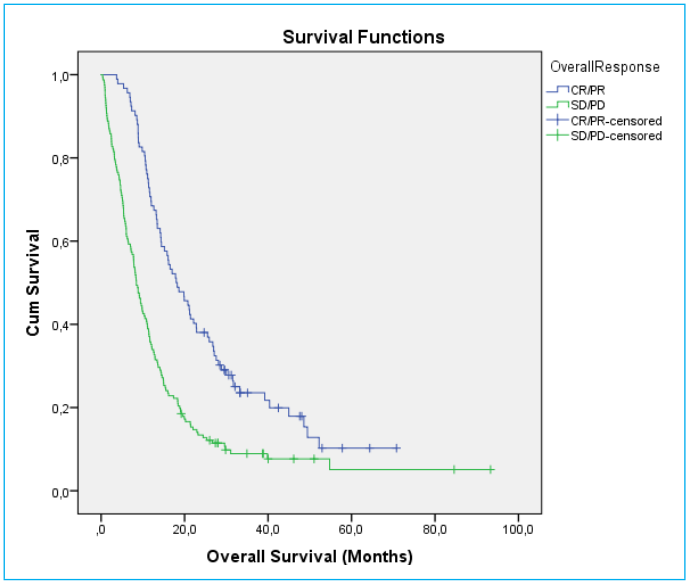

Figure 6. Overall survival graphic according to response type by Kaplan-Meier.
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

ed median overall survival ranging from 9.3 to 11.9 months and median progression-free survival ranging from 4.9 to 7.3 months, which are comparable to those observed in our cohort.[16,17] These differences across studies may reflect variations in patient characteristics, study design, and treatment protocols.

Recently, the phase III PRODIGE 51-FFCD-GASTFOX trial demonstrated that the modified FLOT (TFOX) regimen significantly improved progression-free survival (7.6 vs. 6.0 months), overall survival (15.1 vs. 12.7 months; HR 0.82, 95% CI 0.68–0.99; p=0.048), and objective response rate (62.3% vs. 53.4%) compared with FOLFOX in previously untreated patients with HER2-negative advanced gastric and gastro-oesophageal junction adenocarcinoma. However, these efficacy benefits were accompanied by a higher incidence of grade 3–4 toxicities, including diarrhoea, peripheral neuropathy, neutropenia, and fatigue, as well as a higher rate of serious treatment-related adverse events. [15] Direct comparison between the GASTFOX trial and our study should be interpreted with caution, as the triplet regimen evaluated in GASTFOX (TFOX) differs from the modified DCF regimen used in our study. In addition, differences in study design, patient characteristics, and eligibility criteria, particularly the inclusion of only patients with ECOG performance status 0–1 in the GASTFOX trial, may have contributed to the discrepant findings. Therefore, although the GASTFOX trial supports the use of taxane-containing triplet chemotherapy in carefully selected patients, our findings provide complementary real-world evidence demonstrating comparable effectiveness of modified DCF and FOLFOX-6 in routine clinical practice.

In the present study, the ORR was 32% in the FOLFOX-6 group and 43% in the modified DCF group, whereas the DCR was 47% and 57%, respectively, with no statistically significant differences between the two treatment arms. Objective response and disease control are clinically meaningful efficacy endpoints, as improved tumor response and disease stabilization may translate into better symptom control, delayed disease progression, and improved quality of life in patients receiving palliative systemic therapy. These findings are consistent with previous studies evaluating FOLFOX- and DCF-based regimens. Pourghasemian et al.[14] similarly reported no significant differences in ORR between the FOLFOX and modified DCF groups. Likewise, studies evaluating FOLFOX-4 as first-line treatment reported ORRs ranging from 52.5% to 72.6%, although these studies included different patient populations, particularly elderly patients, which may partly explain the higher response rates observed.[16,18,19] In our study, the FOLFOX-6 regimen was more frequently administered to patients with poorer performance status; ECOG PS 2–3 was observed in 20% of patients receiving FOLFOX-6 compared with 9% of those receiving modified DCF, which may also have influenced treatment outcomes.

This study has several limitations that should be considered when interpreting the findings. First, the retrospective design is inherently subject to selection bias, information bias, and residual confounding. In addition, treatment allocation was based on physician discretion and patients' clinical characteristics rather than randomization, which may have contributed to baseline imbalances between the treatment groups. Second, although this is the largest retrospective comparison of FOLFOX-6 and modified DCF reported to date, the sample size may still have limited the statistical power to detect small differences between treatment groups. Third, toxicity data were not consistently available because of the retrospective nature of data collection, precluding a comprehensive comparison of treatment-related adverse events and dose modifications. Comprehensive toxicity assessment is an essential component of chemotherapy evaluation, as treatment-related adverse events directly influence treatment selection, dose modifications, treatment adherence, and patients' quality of life, particularly in the palliative setting. Future prospective, adequately powered randomized studies are warranted to validate our findings and to better define the optimal first-line chemotherapy regimen for patients with HER2-negative metastatic gastric cancer. Such studies should incorporate comprehensive toxicity assessments and balanced baseline characteristics to minimize potential bias and strengthen the evidence for clinical decision-making. Despite these limitations, the major strength of our study is that it represents the largest retrospective comparison of modified DCF and FOLFOX-6 reported to date. While previous retrospective comparative studies included 126 and 104 patients, respectively, our study evaluated 254 patients, providing a larger real-world cohort for assessing the comparative effectiveness of these two first-line regimens in HER2-negative metastatic gastric cancer.

In conclusion, no statistically significant differences in progression-free or overall survival were observed between the FOLFOX-6 and modified DCF regimens. These findings suggest that both regimens represent reasonable first-line treatment options for patients with HER2-negative metastatic gastric cancer in routine clinical practice. Given the comparable efficacy, treatment selection should be individualized based on patients' performance status, comorbidities, expected toxicity profile, and physician judgment. Future prospective studies are warranted to identify patient subgroups that may derive greater benefit from either FOLFOX-6 or modified DCF and to clarify the optimal role of these regimens in first-line treatment.

Abbreviations

The following abbreviations are used in this manuscript:

ECOG PS: Eastern Cooperative Oncology Group Performance Score

CR: Complete Response

GC: Gastric cancer

HER-2: Human Epidermal Groft Factor Receptor 2

mGC: Metastatik Gastric

NCCN: National Comprehensive Cancer Network

PD: Progressive Disease

PFS: Progression-free survival

PR: Partial Response

OS : Overall survival

SD: Stable Disease,

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Disclosure

Ethics Committe Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Marmara University Faculty of Medicine Clinical Reseaarch Ethic Committee Review Board approval was obtained from the local Institutional Ethics Committee (Approval No: 08.10.2021.1126).

Informed Consent: Patient consent was waived due to the retrospective design of this study, which posed no additional risk to participants and did not require direct patient interaction, in accordance with the approval of the local ethics committee.

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