ORIGINAL ARTICLE

Outcome evaluation of ECF, DCF, FOLFOX, and FLOT chemotherapy regimens as perioperative treatment in elderly patients with resectable gastric cancer; A retrospective comparative study

Ali Forouhari[1], Azadeh Moghaddas[2], Ali Darakhshandeh[3]

[1]Isfahan Eye Research Center, Department of Ophthalmology, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Clinical Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Medical Oncology and Hematology, Isfahan University of Medical Sciences, Isfahan, Iran

Background: The incidence of gastric cancer is known to be high in the elderly population. Identification of the best perioperative chemotherapy regimen is challenging in patients with resectable gastric cancer. In this study, we aimed to evaluate and compare the outcomes and safety of epirubicin, cisplatin, and 5-fluorouracil (ECF), docetaxel, cisplatin, and 5-fluorouracil (DCF), oxaliplatin plus 5-Fluorouracil and leucovorin (FOLFOX), and docetaxel, oxaliplatin, leucovorin, and 5-Fluorouracil (FLOT) chemotherapy regimens to identify the most appropriate treatment option for elderly patients with resectable gastric cancer. **Materials and Methods:** In this retrospective observational cohort study, data were extracted from the medical archives (2017–2021) of Omid Hospital, which is a tertiary oncology referral hospital in Isfahan, Iran. Patients with resectable gastric cancer, above 60 years of age, who were perioperatively treated with one of the mentioned chemotherapy regimens and met the inclusion criteria, were enrolled in this study. The survival parameters and safety profile of the regimens were evaluated and compared in this population. **Results:** A total of 63 patients were included in this study. The median follow-up period of the patients was 24 months (range, 7–51 months). The results of survival analysis revealed that the FLOT and DCF regimens were significantly associated with longer overall survival (OS) as compared to the other regimens (median OS: 38 and 33 months, respectively). Based on the results, the progression-free survival was longer in the DCF regimen (median: 24 months) compared to the other regimens; however, only the difference with the ECF regimen (median: 14 months) was significant. The results of Cox regression analysis showed no significant difference in the overall adjusted hazard ratio of mortality between the FLOT and DCF regimens ($P = 0.802$). The DCF and FOLFOX regimens accounted for the highest and lowest rates of adverse events (e.g., neutropenia and mucositis), respectively. **Conclusion:** Considering the higher rate of adverse events in the DCF group, besides the significant improvement of OS and the acceptable adverse event profile of patients treated with the FLOT regimen, it can be proposed that this chemotherapy regimen is the most appropriate treatment option for elderly patients with resectable gastric cancer.

Key words: Aged, antineoplastic agents, perioperative care, resectable gastric cancer, stomach neoplasms

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INTRODUCTION

Gastric cancer, also known as stomach cancer, is the fifth-most commonly diagnosed cancer and the fourth-leading cause of cancer mortality in the world.[1-3] Based on the GLOBOCAN 2020 data, the age-standardized incidence rate of gastric cancer is 11.1/100,000 population worldwide.[3] It is stated that 72% of all new gastric cancer cases are above 60 years of age globally.[3] The cutoff age of 60 years is selected based on the World Health Organization-suggested classification and recent articles.[4,5] In this regard, a retrospective cohort study

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Address for correspondence: Dr. Ali Darakhshandeh, Department of Medical Oncology and Hematology, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: alidarakhshandeh@yahoo.com
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reported significant differences in the overall survival (OS) and relapse-free survival of patients with advanced (locally advanced or metastatic) gastric cancer using a cutoff age of 60 years.[4]

Various studies revealed the priority of perioperative chemotherapy compared to surgical removal alone.[6-11] Furthermore, a recent review of clinical trials recommended perioperative chemotherapy and radical surgery for the management of elderly patients with locally advanced gastric cancer.[12] Different clinical trials have reported the efficacy of the following perioperative chemotherapy regimens in resectable gastric cancer patients;[13] epirubicin, cisplatin, and 5-fluorouracil (ECF) regimen,[14] docetaxel, cisplatin, and 5-fluorouracil (DCF),[15,16] oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX),[17,18] docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil (FLOT).[19,20] Nonetheless, it is challenging to determine the optimal perioperative chemotherapy regimen for elderly patients with resectable gastric cancer due to their comorbidities, organ dysfunctions, and increased risk of chemotherapy regimen-related toxicities.

To the best of our knowledge, there is no comparative study in the literature on the aforementioned chemotherapy regimens for resectable gastric cancer in patients above 60 years of age. Therefore, in the present study, we aimed to evaluate the outcome parameters and toxicity profile of ECF, FOLFOX, DCF, and FLOT chemotherapy regimens in a perioperative setting to recommend the most effective treatment with lower toxicity for patients with resectable gastric cancer, aged above 60 years.

METHODS

General information

This retrospective observational cohort study was performed according to the principles of the Declaration of Helsinki. The Institutional Review Board waived the need for informed consent due to the retrospective design (i.e., anonymous analysis of the existing data) of the study. The clinical data of the patients, admitted to Omid Hospital, Isfahan, Iran, from July 2017 to October 2021, were collected from the medical archives of the hospital. Omid Hospital is a tertiary referral center that delivers specialized oncology services to patients. The available medical records were explored to extract the following demographic and clinical information of patients who met the inclusion criteria of the study; age, sex, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, history of *Helicobacter pylori* infection, smoking history, familial gastric cancer history, tumor site and size, chemotherapy regimen, tumor histology and pathology, tumor, node and metastasis stage, type of surgery, and follow-up data.

The inclusion criteria were as follows: (1) age above 60 years at the time of diagnosis; (2) diagnosis of primary gastric adenocarcinoma through histopathological examination and computed tomography (CT) scan; (3) undergoing partial or total gastrectomy; and (4) receiving any of the ECF, FOLFOX, DCF, or FLOT chemotherapy regimens as the first-line pre- and postoperative chemotherapy plan. On the other hand, the exclusion criteria were as follows: (1) any concurrent active malignancies; (2) a history of malignant tumor or receiving antitumor treatments, such as chemotherapy, immunotherapy, or radiotherapy; (3) receiving the aforementioned chemotherapy regimens for palliative therapy; and (4) missing pathological and clinical data.

In the treatment setting, patients with gastric cancers are considered eligible for surgery (resectable gastric cancer) when they have no or limited metastasis (without distant metastases); (i) Only abdominal or retroperitoneal lymph node metastasis, or an incurable organ site (including unilateral or bilateral adrenal gland metastases or Krukenberg tumors, extra-abdominal lymph node metastases such as supraclavicular) with or without retroperitoneal lymph node metastases; (ii) No clinically visible (due to ascites or on CT scan) or symptomatic carcinomatosis of peritoneum or pleura and no diffuse peritoneal carcinomatosis on diagnostic laparoscopy; and (iii) Fewer than five liver metastases if the single organ is the liver.[13]

Chemotherapy regimens

The patients had been treated with the following perioperative chemotherapy regimens:

- DCF regimen comprising docetaxel (75 mg/m^2, day 1), cisplatin (75 mg/m^2, day 1), and fluorouracil (750 mg/m^2/day, day 1–5)[16]
- ECF regimen comprising epirubicin (50 mg/m^2, day 1), cisplatin (60 mg/m^2, day 1), and fluorouracil (200 mg/m^2/day through continuous infusion, days 1–21)[21,22]
- FOLFOX regimen comprising oxaliplatin (85 mg/m^2, day 1), leucovorin (400 mg/m^2, day 1), and fluorouracil (400 mg/m^2, day 1), (1200 mg/m^2 through continuous infusion over 24 h, days 1–2)[23,24]
- FLOT regimen comprising docetaxel (50 mg/m^2, day 1), oxaliplatin (85 mg/m^2, day 1), leucovorin (200 mg/m^2, day 1), fluorouracil (2600 mg/m^2 through continuous infusion over 24 h, day 1), (four cycles repeated every 2 weeks preoperatively and four cycles repeated postoperatively for a total of eight cycles).[25]

The bone marrow function was examined before and during each chemotherapy cycle. Two to three days after the end of chemotherapy treatment, the patients received

filgrastim (7.5 mg/kg). In the case of Grade 3–4 toxicity, the dosage of the regimen was reduced by 20% for the next cycle. Furthermore, in case of intolerable adverse events or disease progression, the chemotherapy regimen was terminated for change or modification.

Outcome evaluation and endpoints

During the follow-up, physicians evaluated the patients' tumor response every 8–12 weeks after the onset of perioperative chemotherapy by reviewing the CT scans based on the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). According to the criteria, perioperative treatment efficacy was classified as progressive disease, stable disease (SD), partial response, or complete response (CR).[26]

The OS and progression-free survival (PFS) of the chemotherapy regimens were the primary endpoints of this study. The OS was defined as the length of time from either the date of diagnosis or the onset of treatment until death for any reason (or the length of time that patients diagnosed with the disease are still alive). In addition, the PFS was defined as the length of time during and after treatment until disease progression. Secondary endpoints were (1) determining the rate of R0 resection (i.e., no microscopic or gross tumor remaining in the bed after a microscopically margin-negative resection) in each regimen and (2) evaluating the efficacy of chemotherapy regimens, as well as the rates of related adverse events.

Adverse events

Chemotherapy-related adverse events were investigated according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[27] In this study, the third and fourth grades of hematological (neutropenia) and gastrointestinal (mucositis) toxicities were considered. The rate of hospitalization due to adverse events was also recorded.

Statistical analysis

SPSS version 26.0 (IBM, Chicago, IL, USA) was used for all statistical analyses. Continuous variables, expressed as mean ± standard deviation), and categorical variables, presented as ratio (%), were compared using one-way ANOVA test and Chi-square test, respectively. The Kaplan–Meier method was also used to plot the survival curves, and Log-rank test was applied to compare the treatment regimens. A two-sided $P > 0.05$ was considered statistically significant. In addition, crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using univariate and multivariable Cox regression analyses. Each single variable was initially examined based on the univariate Cox regression analysis, and covariates with a $P < 0.1$ were included in the multivariate analysis. Finally, covariates that presented $P < 0.05$ were considered statistically significant confounders.

RESULTS

Sixty-three patients were included in this study based on the inclusion criteria. The median follow-up period of the participants was 24 months (range, 7–51 months). The majority of the patients were male (n = 48, 76.2%), and the mean age was 68.46 years. Overall, 20 (31.7%), 16 (25.4%), 14 (22.2%), and 13 (20.6%) patients had received FOLFOX, FLOT, DCF, and ECF chemotherapy regimens as perioperative treatments, respectively. The ECOG performance status was ≤2 in 88.9% of the patients.

A poorly differentiated pathology, tubular histological type, cardia anatomical location, and tumor size >4 cm were the dominant cancer features among the patients. A total of 59 patients (93.7%) underwent total gastrectomy in this study. Based on the results, age, ECOG status, and location of tumor invasion were significantly different among the chemotherapy regimens [Supplementary Table 1].

There was no significant difference in terms of tumor response between the treatment strategies. The free margin of surgery (R0 resection) was achieved in 69.8% of cases; the corresponding rate was 87.5% in the FLOT regimen. The results revealed that hospitalization rate was significantly higher in the ECF group compared to the other groups (P = 0.002) [Supplementary Table 2].

The survival analysis results are presented in Table 1 and Figure 1. The log-rank test revealed that OS differed significantly among the chemotherapy regimens (P = 0.002). Moreover, the pairwise comparisons showed that the FLOT (OS: 38 months) and DCF (OS: 33 months) regimens significantly resulted in a longer OS compared to the ECF (OS: 24 months) and FOLFOX (OS: 21 months) regimens. However, the difference in the OS of patients treated with the FLOT and DCF regimens was not significant (P = 0.936). Although the results of the log-rank test showed no significant difference regarding the PFS of chemotherapy regimens, the results of pairwise comparisons revealed that patients who were treated with the DCF regimen had a significantly longer PFS (PFS: 24 months) compared to those treated with the ECF regimen (PFS: 14 months) (P = 0.015). The 1- and 2-year OS and PFS are presented in Supplementary Table 3. Based on the results, the 2-year PFS of the evaluated chemotherapy regimens differed significantly (P = 0.001), and the DCF regimen had the highest rate (57.1%) of all regimens.

The HRs of significant covariates from the univariate Cox regression analysis, as well as the adjusted HRs in the adjusted models (multivariate analysis) for OS

and PFS, are presented in Tables 2 and 3. The results of univariate analysis showed that with each 1-year increase in age at the time of diagnosis, the risk of death due to cancer increased significantly by 5% (HR: 1.056; 95% CI: 1.004–1.110). Patients with a family history of gastric cancer had a significantly higher risk of disease progression (HR: 2.109) and death (HR: 2.448). According to the results, the total gastric involvement of the tumor increased the likelihood of death by 2.84 times compared to cardiac involvement. Furthermore, poorly-differentiated tumors increased the risk of death by 2.45 times compared to well-differentiated tumors. Moreover, the chemotherapy response category of SD was associated with a significantly higher risk of disease progression (HR: 15.554) than the CR category. However, none of the mentioned ones remained significant when included in the multivariate analysis. The results of the multivariate analysis revealed that R1 resection (i.e., microscopic residual tumor) increased the risk of disease progression and death by 2.372 and 2.897 times, respectively, when compared to R0 resection.

The adjusted HRs of chemotherapy regimens for OS and PFS are presented in Table 4. By considering ECF as the reference and adjusting for confounders, the FLOT (HR: 0.218, $P = 0.049$) and DCF (HR: 0.263, $P = 0.04$) regimens resulted in significantly lower overall mortality HRs. However, there was no significant difference in the overall mortality HRs of the FLOT and DCF regimens ($P = 0.802$). Besides, differences in disease progression-adjusted HR of the regimens were not significant.

Table 1: Kaplan–Meier survival analysis results

Chemotherapy regimen	OS					PFS				
	Mean (months)	95% CI	Median (months)	95% CI	*P*	Mean (months)	95% CI	Median (months)	95% CI	*P*
DCF	32.80	24.43–41.16	33	24.77–41.22	0.002	21.65	14.79–28.52	24	10.58–37.41	0.057
ECF	20.99	16.23–25.75	24	14.46–33.53		12.65	9.16–16.14	14	8.27–19.73	
FLOT	31.74	27.13–36.35	38	NA		21.19	15.74–26.63	18	10.40–25.59	
FOLFOX	24.71	21.02–28.4	21	16.16–25.83		16.93	13.49–20.38	15	5.24–24.75	
Overall	27.88	24.66–31.09	27	20.9–33.1		18.44	15.75–21.14	18	14.01–21.98	

OS=Overall survival; PFS=Progression-free survival; CI=Confidence interval; DCF=Docetaxel, cisplatin, and 5-fluorouracil; ECF=Epirubicin, cisplatin, and 5-fluorouracil; FLOT=Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; FOLFOX=Oxaliplatin plus 5-fluorouracil and leucovorin

Table 2: Cox-regression analysis of overall survival covariates

	Univariate analysis			Multivariable analysis		
	P	HR	95% CI	*P*	Adjusted HR	95% CI
Age	0.034	1.056	1.004–1.110	0.751	0.989	0.923–1.060
Pathology differentiation		0.018				
Well-differentiated	0.024			0.197		
Moderately differentiated	0.737	0.849	0.327–2.204	0.826	0.861	0.227–3.27
Poorly differentiated	0.044	2.455	1.025–5.883	0.152	2.538	0.709–9.079
Undifferentiated	0.881	1.128	0.231–5.504	0.894	1.178	0.108–12.894
Tumor site		0.01				
Cardia	0.015			0.566		
Noncardia	0.797	0.911	0.449–1.849	0.534	0.780	0.357–1.705
Total involvement	0.010	2.842	1.285–6.288	0.527	1.593	0.376–6.737
Response		0.008				
CR	0.013			0.665		
PR	0.003	3.005	1.449–6.230	0.367	1.778	0.51–6.202
SD	0.984	0.000	0	0.984	0	0
Resection rate		<0.001				
R0						
R1	<0.001	3.653	1.883–7.088	0.034	2.897	1.082–7.662
Familial gastric cancer history	0.008					
No						
Yes	0.011	2.448	1.231–4.866	0.672	1.231	0.47–3.226
ECOG	0.054					
0	0.069			0.275		
1	0.123	0.190	0.023–1.570	0.097	0.116	0.009–1.474
2	0.357	0.382	0.049–2.964	0.164	0.144	0.009–2.207
3	0.699	0.653	0.076–5.628	0.338	0.245	0.014–4.35

HR=Hazard ratio; CI=Confidence interval; ECOG=Eastern Cooperative Oncology Group; CR=Complete response; PR=Partial response; SD=Stable disease

Grades 3 and 4 adverse events (i.e., neutropenia and mucositis) of chemotherapy regimens are presented in Supplementary Table 4. Patients treated with the FOLFOX regimen experienced the lowest rate of adverse events compared to the other groups; nevertheless, differences in the rate of neutropenia were not significant between the groups.

DISCUSSION

According to the findings of this retrospective cohort study, the FLOT chemotherapy regimen, as a perioperative treatment for elderly (>60 years) patients with resectable gastric carcinoma, can improve their OS (38 months) and result in an acceptable adverse event profile. Moreover, the DCF chemotherapy regimen was associated with a longer OS (33 months, 95% CI: 24.77–41.22) compared to ECF and FOLFOX regimens. The results of survival analysis and adjusted multivariate model showed no significant differences in the OS and PFS of patients treated with the DCF and FLOT regimens. Due to the high rate of censored cases in the FLOT regimen group, the survival function did not reach 0.45; therefore, SPSS could not represent the CI bounds for the median. This might be also the reason for the insignificant difference between the FLOT and DCF regimens. The FOLFOX regimen showed the lowest toxicity rate of all regimens.

In a recent study, the effects of perioperative chemotherapy on OS were confirmed in patients with resectable gastric cancer under real-life conditions,[28] and it was found to be the most appropriate treatment for these patients; however, selection of the most effective regimen with an acceptable adverse event profile is challenging.

So far, few studies have compared the outcome parameters of different chemotherapy regimens. In a randomized clinical trial, the OS was longer in the perioperative FLOT regimen compared to the perioperative ECF and ECX regimens for patients with resectable (locally advanced) gastric adenocarcinoma.[29] Moreover, according to a very recent network meta-analysis (NMA), perioperative Taxane-based (Docetaxel, Paclitaxel) chemotherapy (e.g., DCF and FLOT) regimens are superior to other treatment plans, such as surgery alone and adjuvant chemotherapy.[30] Another recent NMA indicated the priority of perioperative FLOT regimen over other treatments for resectable gastric cancer.[31]

Table 3: Cox-regression analysis of progression-free survival covariates

	Univariate analysis			Multivariable analysis		
	P	HR	95% CI	*P*	Adjusted HR	95% CI
Age	0.070	1.041	0.997–1.088	0.906	0.997	0.944–1.053
Pathology differentiation		0.006				
Well-differentiated	0.009			0.245		
Moderately differentiated	0.166	0.569	0.256–1.264	0.405	0.666	0.256–1.733
Poorly differentiated	0.108	1.912	0.868–4.213	0.308	1.585	0.653–3.848
Undifferentiated	0.497	0.590	0.129–2.705	0.680	0.712	0.142–3.570
Response		<0.001				
CR	0.003			0.019		
PR	0.007	2.417	1.266–4.614	0.112	2.008	0.850–4.741
SD	0.013	15.554	1.791–135.109	0.011	20.790	2.017–214.266
Familial gastric cancer history		0.016				
No						
Yes	0.019	2.109	1.132–3.972	0.359	1.420	0.671–3.004
Resection rate		<0.001				
R0						
R1	0.001	2.738	1.502–4.991	0.011	2.372	1.215–4.630

HR=Hazard ratio; CI=Confidence interval; SD=Stable disease; CR=Complete response; PR=Partial response

Table 4: Adjusted multivariable Cox regression analysis of chemotherapy regimens

Chemotherapy regimen	OS*			PFS†		
	HR	95% CI	*P*	HR	95% CI	*P*
ECF	1			1		
DCF	0.263	0.074–0.940	0.040	0.562	0.194–1.627	0.288
FOLFOX	0.506	0.161–1.590	0.244	0.607	0.232–1.587	0.308
FLOT	0.218	0.048–0.994	0.049	0.516	0.175–1.525	0.231

*Adjusted for: age, ECOG performance status, family history of gastric cancer, pathology differentiation, tumor site, response category, and resection rate; †Adjusted for: age, family history of gastric cancer, pathology differentiation, response category, and resection rate. Data reported in the table have resulted from adjusted model analysis. OS=Overall survival; PFS=Progression-free survival; ECF=Epirubicin, cisplatin, and 5-fluorouracil; FLOT=Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; FOLFOX=Oxaliplatin plus 5-fluorouracil and leucovorin, HR=Hazard ratio; CI=Confidence interval, ECOG=Eastern Cooperative Oncology Group

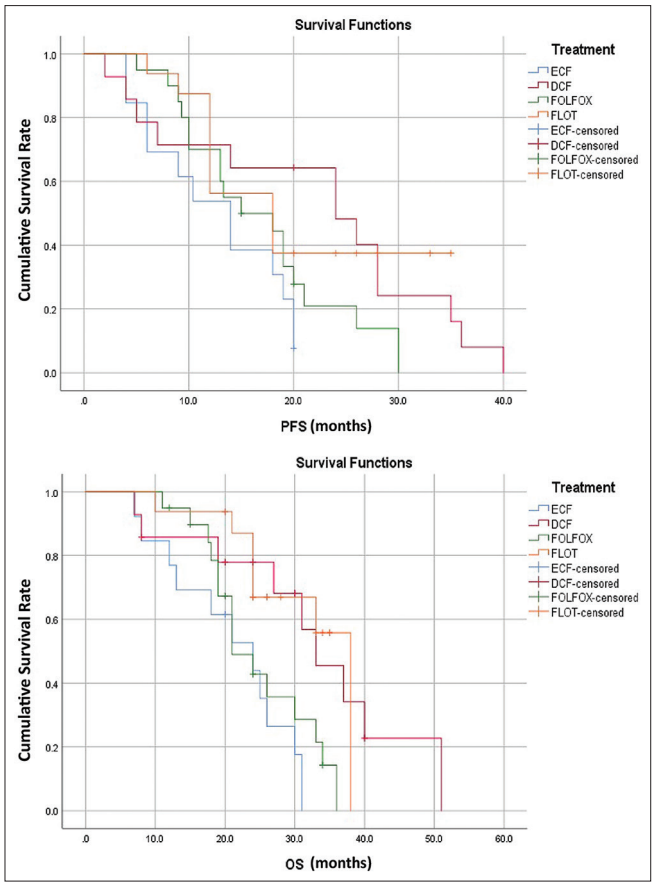

Figure 1: Kaplan–Meier plot of progression-free survival and overall survival. PFS = Progression-free survival; OS = Overall survival

Considering the chemotherapy regimens for elderly patients, a previous study found FOLFOX4 to be beneficial for elderly patients with advanced gastric carcinoma.[32] Cho *et al*. also found that mFOLFOX6 leads to the same outcomes in elderly and younger patients.[33] Similarly, the phase III FLOT4 trial described no significant differences in the HRs for death of patients aged <60 years and >70 years.[29] Moreover, phase III of the randomized FLOT4-AIO trial indicated the superiority of the FLOT regimen over ECF/ECX, even in older patients (≥70 years).[34] Nevertheless, research discussing the outcomes of chemotherapy regimens in elderly patients is quite limited. Besides, results from the CRITICS study revealed that the perioperative chemotherapy compliance of patients aged ≥70 years was significantly lower than that of younger patients.[35]

A Cochrane review revealed that resection with negative margins is a potent survival predictor. In addition, the results of multivariate analysis showed the significant effects of age, performance status, and tumor site on survival.[36] Our results confirmed that R0 resection has a significantly lower HR for death compared to R1 resection. Nevertheless, other predictors that were significant in the univariate analysis were insignificant in the multivariate analysis, possibly due to the smaller sample size.

The present study had some limitations. First, the participants were all selected from the Persian population; therefore, ethnicity may be a confounder in the outcome evaluation of different chemotherapy regimens. The limited follow-up period and total sample size were another limitations of this study.

Further large-scale randomized clinical trials (on different ethnicities and races), investigating different chemotherapy regimens in only the elderly population, are recommended to evaluate different aspects of perioperative chemotherapy for resectable gastric cancer (e.g., outcome parameters, tolerability, and effects of comorbidities) and identify the optimal treatment regimen.

CONCLUSION

In this study, the superiority of perioperative FLOT and DCF to other chemotherapy regimens was approved in patients with resectable gastric carcinoma, aged >60 years. Considering the significant increase in OS and the acceptable adverse event profile of patients treated with the FLOT regimen, it can be proposed that this chemotherapy regimen is the most appropriate option for elderly patients with resectable gastric cancer; however, further well-designed multi-center trials are needed to approve this finding.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Demographic and clinical features of included patients

		Chemotherapy regimen				
	Total (*n*=63), *n* (%)	ECF (*n*=13), *n* (%)	DCF (*n*=14), *n* (%)	FOLFOX (*n*=20), *n* (%)	FLOT (*n*=16), *n* (%)	*P*
Age (years) ±SD	68.15±6.69	66.07±6.44	68.46±5.10	72.05±6.91	66.31±5.00	0.015
Sex						
Male	48 (76.2)	8 (61.5)	11 (78.6)	18 (90)	11 (68.8)	0.243
Female	15 (23.8)	5 (38.5)	3 (21.4)	2 (10)	5 (31.3)	
ECOG*						
0	2 (3.2)	0	0	0	2 (12.5)	<0.001
1	20 (31.7)	3 (23.1)	2 (14.3)	3 (15)	12 (75)	
2	34 (54)	10 (76.9)	11 (78.6)	11 (55)	2 (12.5)	
3	7 (11.1)	0	1 (7.1)	6 (30)	0	
BMI						
<18	17 (27)	2 (15.4)	2 (14.3)	9 (45)	4 (25)	0.159
18–24	43 (68.3)	11 (84.6)	10 (71.4)	11 (55)	11 (68.8)	
>24	3 (4.8)	0	2 (14.3)	0	1 (6.3)	
Helicobacter pylori infection history	35 (55.6)	8 (61.5)	9 (64.3)	12 (60)	6 (37.5)	0.408
Smoking history	31 (49.2)	6 (46.2)	9 (64.3)	11 (55)	5 (31.3)	0.301
Familial gastric cancer history	16 (25.4)	6 (46.2)	3 (21.4)	6 (30)	1 (6.3)	0.094
Tumor site						
Cardia	30 (47.6)	7 (53.8)	5 (35.7)	9 (45)	9 (56.3)	0.675
Noncardia	23 (36.5)	5 (38.5)	6 (42.9)	6 (30)	6 (37.5)	
Total involvement	10 (15.9)	1 (7.7)	3 (21.4)	5 (25)	1 (6.3)	
Tumor size (cm)						
<4	24 (38.1)	7 (53.8)	6 (42.9)	7 (35)	4 (25)	0.432
>4	39 (61.9)	6 (46.2)	8 (57.1)	13 (65)	12 (75)	
Histological type						
Tubular	28 (44.4)	5 (38.5)	8 (57.1)	10 (50)	5 (31.3)	0.111
Diffuse	9 (14.3)	1 (7.7)	2 (14.3)	2 (10)	4 (25)	
Pathology differentiation						
Well-differentiated	11 (17.5)	1 (7.7)	1 (7.1)	6 (30)	3 (18.8)	0.627
Moderately differentiated	21 (33.3)	4 (30.8)	7 (50)	6 (30)	4 (25)	
Poorly differentiated	28 (44.4)	7 (53.8)	5 (35.7)	8 (40)	8 (50)	
Undifferentiated	3 (4.8)	1 (7.7)	1 (7.1)	0	1 (6.3)	
Depth of tumor invasion						
T1	4 (6.3)	0	1 (7.1)	2 (10)	1 (6.3)	0.591
T2	21 (33.3)	2 (15.4)	5 (35.7)	7 (35)	7 (43.8)	
T3	29 (46)	10 (76.9)	5 (35.7)	8 (40)	6 (37.5)	
T4	9 (14.3)	1 (7.7)	3 (21.4)	3 (15)	2 (12.5)	
Lymph node involvement						
N0	8 (12.7)	0	0	5 (25)	3 (18.8)	0.31
N1	23 (36.5)	5 (38.5)	6 (42.9)	8 (40)	4 (25)	
N2	25 (39.7)	7 (53.8)	5 (35.7)	6 (30)	7 (43.8)	
N3	7 (11.1)	1 (7.7)	3 (21.4)	1 (5)	2 (12.5)	
Metastatic						
No metastasis	57 (90.5)	12 (93.3)	13 (92.9)	19 (95)	13 (81.3)	0.532
Limited metastasis	6 (9.5)	1 (7.7)	1 (7.1)	1 (5)	3 (18.8)	
Site of metastasis						
Extra abdominal lymph node	5 (7.9)	1 (7.7)	1 (7.1)	1 (5)	2 (12.6)	0.588
Liver	1 (1.6)	0	1 (7.1)	0	0	
Tumor invasion						
Lymphatic	23 (36.5)	6 (46.2)	6 (42.9)	6 (30)	5 (31.3)	0.023
Vascular	8 (12.7)	0	5 (35.7)	1 (5)	2 (12.5)	
Perineural	5 (7.9)	3 (23.1)	0	2 (10)	0	
Peritoneal	1 (1.6)	0	1 (7.1)	0	0	

Contd...

Supplementary Table 1: Contd...

	Chemotherapy regimen					
	Total (*n*=63), *n* (%)	ECF (*n*=13), *n* (%)	DCF (*n*=14), *n* (%)	FOLFOX (*n*=20), *n* (%)	FLOT (*n*=16), *n* (%)	*P*
Surgery type						
Total gastrectomy	59 (93.7)	12 (92.3)	14 (100)	19 (95)	14 (87.5)	0.558
Partial gastrectomy	4 (6.3)	1 (7.7)	0	1 (5)	2 (12.5)	

*Eastern Cooperative Oncology Group. Reported data in the table are *n* (%). BMI=Body mass index; ECOG=Eastern cooperative oncology group; ECF=Epirubicin, cisplatin, and 5-fluorouracil; FLOT=Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; FOLFOX=Oxaliplatin plus 5-fluorouracil and leucovorin; DCF=Docetaxel, cisplatin, and 5-fluorouracil; SD=Standard deviation

Supplementary Table 2: Response to chemotherapy regimens

		Chemotherapy regimen				
	Total	ECF, *n* (%)	DCF, *n* (%)	FOLFOX, *n* (%)	FLOT, *n* (%)	*P*
Response						
CR	48 (76.2)	12 (92.3)	11 (78.6)	12 (60)	13 (81.3)	0.368
PR	14 (22.2)	1 (7.7)	3 (21.4)	7 (35)	3 (18.8)	
SD	1 (1.6)	0	0	1 (5)	0	
Resection rate						
R0	44 (69.8)	7 (53.8)	11 (78.6)	12 (60)	14 (87.5)	0.129
R1	19 (30.2)	6 (46.2)	3 (21.4)	8 (40)	2 (12.5)	
Hospitalization rate	31 (49.2)	11 (84.6)	9 (64.3)	4 (20)	7 (43.8)	0.002

ECF=Epirubicin, cisplatin, and 5-fluorouracil; FLOT=Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; FOLFOX=Oxaliplatin plus 5-fluorouracil and leucovorin; DCF=Docetaxel, cisplatin, and 5-fluorouraci; CR=Complete response; PR=Partial response; SD=Stable disease

Supplementary Table 3: 1- and 2-year overall survival and progression-free survival

Chemotherapy regimen	OS				PFS			
	1-year, *n* (%)	*P*	2-year, *n* (%)	*P*	1-year, *n* (%)	*P*	2-year, *n* (%)	*P*
ECF	84.6	0.420	46.2	0.068	53.8	0.241	0.0	0.001
DCF	78.6		64.3		71.4		57.1	
FOLFOX	95.0		40.0		70.0		15.0	
FLOT	93.8		81.3		87.5		31.3	

OS=Overall survival; PFS=Progression-free survival; ECF=Epirubicin, cisplatin, and 5-fluorouracil; FLOT=Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; FOLFOX=Oxaliplatin plus 5-fluorouracil and leucovorin; DCF=Docetaxel, cisplatin, and 5-fluorouraci

Supplementary Table 4: Chemotherapy Grade 3 and 4 adverse events based on common terminology criteria for adverse events criteria

	Chemotherapy regimen					
	Total (*n*=63), *n* (%)	ECF (*n*=13), *n* (%)	DCF (*n*=14), *n* (%)	FOLFOX (*n*=20), *n* (%)	FLOT (*n*=16), *n* (%)	*P*
Neutropenia	24 (38.1)	4 (30.8)	8 (57.1)	6 (30)	6 (37.5)	0.398
Mucositis	18 (28.6)	6 (46.2)	7 (50)	1 (5)	4 (25)	0.007

FLOT=Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; FOLFOX=Oxaliplatin plus 5-fluorouracil and leucovorin; DCF=Docetaxel, cisplatin, and 5-fluorouracil; ECF=Epirubicin, cisplatin, and 5-fluorouracil