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Efficacy of Perioperative FLOT Therapy in Locally Advanced Gastric Cancer and the Associated Prognostic Factors

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ABSTRACT Objective: Perioperative 5-fluorouracil, oxaliplatin, and docetaxel (FLOT) chemotherapy is the gold standard treatment for locally advanced gastric cancer (LAGC). The present study aimed to evaluate the efficacy and safety of perioperative FLOT and the prognostic role of the associated clinicopathological factors. **Material and Methods:** A retrospective analysis was conducted with 48 patients having gastric adenocarcinoma (stage cT2-4 and/or cN+ M0) who received perioperative FLOT (four preoperative and four postoperative 2-week cycles) and underwent surgery for LAGC. The clinical and demographic characteristics of the patients, pretreatment laboratory values, and histological features were recorded. Univariate and multivariate Cox regression analyses were conducted. **Results:** The median age of the patients was 59.5 years (age range, 28-73 years). R0 resection was possible in 86% of the patients who underwent surgery. The objective response rate was 58.3%, the median disease-free survival was 25.4 months (95% CI, 13.2-37.6), and the median overall survival (OS) was 42.9 months (95% CI,-/-). The 2-year OS was 69.1%. It was revealed that ≥ pN2 disease, a positive surgical margin (SM), the presence of perineural invasion (PNI), a poor pathological response to neoadjuvant therapy, and the use of an adjuvant chemotherapy regimen other than FLOT exerted a negative effect on survival. In the multivariate analysis, PNI and SM were revealed as independent factors. **Conclusion:** The study presents real-life data that demonstrate the effectiveness and feasibility of perioperative FLOT. The presence of PNI and positive SM were revealed to be the negative prognostic parameters for survival.

Keywords: Chemotherapy; gastric cancer; perioperative treatment

Gastric cancer is one of the most common types of cancer. However, despite a significant decrease in the incidence of this cancer over the past two decades, it remains a leading cause of cancer-related deaths worldwide.[1] Improved treatment strategies are, therefore, necessary as the prognosis for these patients remains poor. Gastric cancer is frequently diagnosed at an advanced stage due to the lack of specific, early symptoms associated with this disease. The low screening rates associated with this cancer in Türkiye, where gastric cancer is not included in the screening program, is another reason for its late diagnosis. Surgery is the main treatment modality used for treating gastric cancer in the early stages, while locally advanced and/or node-positive gastric cancer requires a multidisciplinary treatment approach.[2,3] Unfortunately, despite significant advances in surgical techniques and systemic therapy, local recurrence and distant metastases remain the leading causes of death among patients with gastric cancer. Therefore, perioperative chemotherapy is considered the standard treatment for locally advanced gastric cancer (LAGC) and gastroesophageal junction (GEJ) adenocarcinoma. The FLOT regimen has demonstrated the greatest survival benefit in randomized clinical trials, although other regimens might have to be used

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in daily practice depending on the patient characteristics and side effects.[4] Neoadjuvant therapy increases the R0 resection rate by decreasing the tumor stage, preventing local recurrence and micrometastasis, and extending long-term survival. However, the specific indications for this treatment, the optimal regimen and the number of cycles, and the effectiveness of its use in combination with radiotherapy or immunotherapy remain debatable to date.[5]

Tumor-associated inflammation is significant in various stages of tumor development, such as DNA damage, angiogenesis, proliferation, invasion, and metastasis.[6] Inflammation-based indices calculated from peripheral complete blood counts (CBC) are used to predict survival and relapse in cancer patients. The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) are reportedly associated with prognosis in certain malignant tumors.[7] The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is an inflammation and nutrition-based score that has been confirmed as a prognostic and predictive factor for survival in various cancers.[8,9] Non-invasive and easily accessible prognostic and predictive factors are important and necessary in clinical practice.

In the above context, the present study aimed to evaluate the reliability and real-life effectiveness of perioperative FLOT in terms of survival outcomes for patients with LAGC. In addition, the clinicopathological factors that affect survival and the relationship between survival and the inflammatory indices calculated based on routine blood tests were investigated.

MATERIAL AND METHODS

A retrospective analysis was conducted with forty-eight patients who were diagnosed with LAGC and had received perioperative FLOT chemotherapy at the Medical Oncology Department of Gülhane Training and Research Hospital between July 2017 and July 2022. All of these patients had histologically confirmed gastric or GEJ adenocarcinoma. The patients with clinical stage cT2 or higher, nodal positive stage (cN+) or both, and no evidence of distant metastasis according to the thorax and abdominal computed tomography were included in the study. All included patients were aged between 18 and 75 years and had a good performance status, according to the Eastern Clinical Oncology Group (ECOG PS≤2). The patients with an insufficient follow-up time were excluded from the study. The FLOT regimen comprised the intravenous administration of docetaxel at a dosage of 50 mg/m^2 on Day 1, oxaliplatin at a dose of 85 mg/m^2 on Day 1, leucovorin at 200 mg/m^2 on Day 1, and 5-fluorouracil as a 24-hour infusion of 2,600 mg/m^2 dosage on Day 1. The regimen was applied every two weeks for four cycles prior to as well as after the surgery. The response to chemotherapy was determined based on the College of American Pathologists Tumor Regression Grading system, which defines the following classification: Grade 0: No viable cancer cells (complete response); Grade 1: Single cells or small groups of cancer cells (moderate response); Grade 2: Residual cancer cells with marked tumor regression although greater than a single cell or rare groups of small cancer cells (minimal response); Grade 3: Minimal or no tumor death or widespread residual cancer (poor response). All subsequent analyses were conducted after categorizing the patients into three groups-complete response (Grade 0), partial response (Grade 1 and Grade 2), and poor or no response (Grade 3).

The demographic and clinical characteristics of the patients, along with their pretreatment laboratory values (including CBC and albumin level) clinical stage, histological characteristics, treatment response, side effects, progression, and death times were obtained from patient files and hospital software systems. The pan-immune-inflammation value (PIV) was calculated as follows: neutrophil count (10^9/L)×platelet count (10^9/L)×monocyte count (10^9/L)/lymphocyte count (10^9/L). The Score HALP was calculated as follows: [hemoglobin (g/L)×albumin (g/L)×lymphocytes (/L)]/platelets (/L). The NLR was calculated as follows: neutrophils/lymphocytes. The SII was defined as follows: SII=Platelet×neutrophil/lymphocyte. The data were divided into high and low values based on the median values of PIV, HALP, NLR, and SII (547.6 for PIV, 25.6 for HALP, 3.0 for NLR, and 807.6 for SII). Values below the median were classified as low, while those above the median were classified as high values. The primary

endpoint used in the present study was the real-life efficacy of perioperative FLOT treatment and the impact of the clinicopathological and treatment-related factors on the overall survival (OS) of patients. The secondary endpoint was the effect of systemic inflammatory scores, such as SII, NLR, PIV, and HALP score, on survival.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee by the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all living individual participants included in the study. This study was approved by the Ethics Committee of Gülhane Training and Research Hospital, Ankara under number 2023/187 (date: August 31, 2023).

"Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). A descriptive analysis was performed, and categorical variables were presented as the number and percentage of patients. The Kaplan-Meier analysis was conducted to estimate the values of OS and disease-free survival (DFS), beginning from the date of diagnosis to the event (progression or death due to any cause). Survival was compared between the groups using the log-rank test. Only the factors with a p-value of <0.05 in the univariate analysis were considered significant. The Cox regression model was adopted in the subsequent multivariate analyses to identify the independent factors that could predict survival.

RESULTS

Table 1 lists the characteristics of the patients included in the present study. The median age of these patients was 59.5 years (age range: 28-73 years), and 62.5% of these patients were male. Twenty-nine patients (60.4%) had poorly differentiated adenocarcinoma, and among these, 45.8% had signet ring cell differentiation. Among all included patients, eleven patients (22.8%) had cardia tumors, thirty-five patients had non-cardia tumors, and two patients (4.2%) had diffuse-linitis plastica tumors. Five patients (10.4%) did not undergo surgery, and among these, three patients had disease progression as the reason, while two patients refused surgery. Surgery resulted in R0 resection in 86% of the patients, and D2 dissection was performed for 86% of the patients who underwent surgery. Three patients (6.3%) achieved complete pathological remission with neoadjuvant treatment. Twenty-five patients (52%) exhibited a partial response, while 15 patients (31.3%) exhibited poor or no response. After the surgery, 32 patients (66.7%) continued with the FLOT treatment, while 8 patients underwent chemoradiation, and among the latter, 6 patients received chemoradiation with FOLFOX while 2 patients received the paclitaxel+carboplatin regimen. Six patients received the FOLFIRI regimen due to a poor pathologic response to neoadjuvant FLOT. No adjuvant treatment was administered to two patients who refused surgery and the subsequent chemotherapy. In the cases of relapse, FOLFIRI was the most commonly preferred chemotherapy regimen for first-line metastatic therapy and accounted for 41.7% of the cases. Forty percent of the patients were eligible for metastatic second-line chemotherapy. Table 2 provides a summary of the treatment characteristics.

TABLE 1: Patient characteristics.

Variables	No. of patients (n=48)	%
Median age, years (minimum-maximum)	59.5 (28-73)	
Sex		
Male	30	62.5
Female	18	37.5
ECOG performance status		
0	27	56.3
1	21	43.8
Primary tumor location		
Cardia	11	22.8
Antrum	12	25.0
Corpus	20	41.7
Pilor	3	6.3
Diffuse, linitisplastica	2	4.2
Tumor grade and differanciation		
Well	2	4.2
Moderate	17	35.4
Poor	29	60.4
■ Signet ring cell differantiation	22	45.8
HER 2 status		
Positive	4	8.3
Negative	44	91.7

ECOG: Eastern Cooperative Oncology Group; HER 2: Human epidermal growth factor receptor 2.

TABLE 2: Treatment characteristics.

Variables	n	%
The median number of preoperative cycles (range)	4 (4-12)	
Dose reductions for preoperative cycles		
Yes	13	27.1
No	35	72.9
The median number of postoperative cycles (range)	4 (0-4)	
Operation		
Yes	43	89.6
No	5	10.4
Postoperative FLOT treatment		
Yes	32	66.7
No	16	33.3
Pathological response of neoadjuvant treatment		
Poor and no response	15	31.3
Partial response	25	52
Complete response	3	6.3
Missing	5	10.4
The median number of lymph nodes dissected	28 (6-58)	
The median number of positive lymph nodes	2 (0-30)	
<3 LN	23	47.9
≥3 LN	20	41.7
Missing	5	10.4
LVI		
Positive	31	64.6
Negative	10	20.8
Missing	7	14.6
PNI		
Positive	22	45.8
Negative	19	39.6
Missing	7	14.6
Surgical margin		
Positive	6	12.5
Negative	37	77.1
Missing	5	10.4
Adjuvant treatment		
FLOT	32	66.7
FOLFIRI	6	12.5
Chemoradiation	8	16.6
Missing	2	4.2

LVI: Lymphovascular invasion; PNI: Perineural invasion; FLOT: 5-fluorouracil, oxaliplatin, leucovorin, and docetaxel; FOLFIRI: 5-Fluorouracil, irinotecan, leucovorin.

SURVIVAL ANALYSIS

After a median follow-up of 25.8 months (IQR: 12.4–49.5), the median DFS was 25.4 months (95% CI, 13.2-37.6), while the median OS was 42.9 months (95% CI,-/-). The 2-year OS ratio was 69.1%, while the 5-year OS ratio was 46.7% (Figure 1). The univariate analysis revealed that having more than three positive lymph nodes, positive surgical margins, perineural invasion (PNI), a poor pathological response (pCR) to neoadjuvant therapy, and the use of an adjuvant chemotherapy regimen other than FLOT exerted negative effects on survival (Figure 2). In the multivariate Cox regression analysis, PNI and a positive surgical margin were revealed as significant independent poor prognostic factors. No significant correlation was noted among the HALP score, PIV, SII, NLR, and OS. Table 3 summarizes the factors affecting OS revealed in the present study.

SIDE EFFECTS

Anemia was revealed as the most frequent adverse event, recorded in 56.2% of the subjects, with only a mild-to-moderate degree. Neutropenia was the second most common hematological side effect that occurred in 20.9% of patients. Primary GCSF prophylaxis was used for 64.6% of the cases, and only one of these patients experienced febrile neutropenia. Nausea and diarrhea were the most common gastrointestinal toxicities noted. Table 4 provides a summary of all other hematological and non-hematological adverse events recorded among the patients in the present study.

DISCUSSION

This retrospective study aimed to determine the real-world effectiveness of perioperative chemotherapy using the FLOT regimen and identify the prognostic clinicopathologic factors that could influence the survival of patients with LAGC. The results revealed that the patients who underwent R0 resection, had less than three metastatic lymph nodes and no PNI, exhibited a complete or partial pCR to neoadjuvant therapy, as revealed in the pathological examination, and continued with the adjuvant FLOT therapy exhibited significantly superior OS. The multivariate analyses revealed R0 resection and the absence of PNI as the only significant independent prognostic factors for OS. The median survival of the patients in the study cohort was comparable to that reported in the literature.

The median DFS of the patients included in the present study was 25.4 months (95% CI, 13.2-37.6), while the median OS was 42.9 months (95% CI,-/-). The two-year OS rate was 69.1%, while the five-year

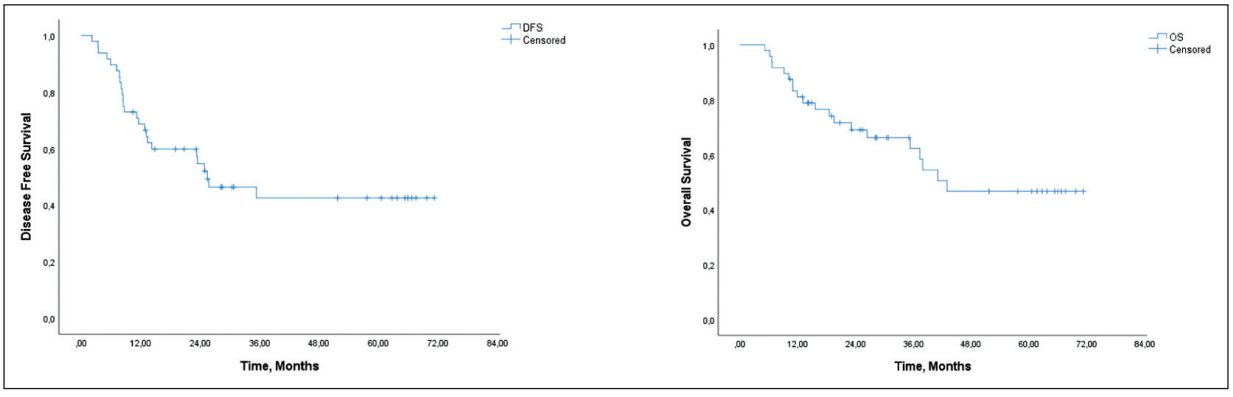

FIGURE 1: Kaplan-Meier estimates of disease free survival and overall survival.

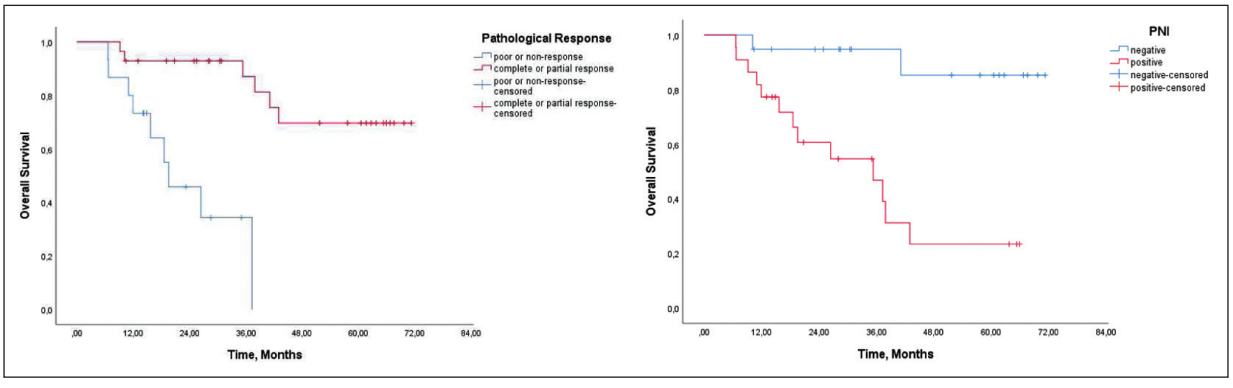

FIGURE 2: Kaplan-Meier of overall survival according to pathological response and perineural invasion status.

OS rate was 46.7%. In the past, two large phase-3 clinical trials, namely, the MAGIC and French FNCLCC/FFCD 9703 trials, have reported improved 5-year survival rates with the use of perioperative ECF/ECX (epirubicin, cisplatin, and fluorouracil/capecitabine) and CF (cisplatin and fluorouracil) chemotherapy compared to the use of surgery alone, leading to perioperative chemotherapy being considered the standard of care for resectable LAGC.[10,11] In a more recent German FLOT4 trial, Al-Batran et al. demonstrated that the FLOT regimen led to higher histopathological response rates and a longer OS compared to those achieved using the ECF/ECX regimen (50 months vs. 35 months).[4] The survival outcomes observed in our study are slightly inferior to those reported in the original FLOT 4 AIO study. This modest difference was attributed to the lower rate of complete pCR to neoadjuvant treatment noted in the present study compared to the FLOT4-AIO study (6.3% vs. 16%). This lower complete pCR rate recorded in the present study was attributed to the fact that treatment was administered to a group of patients who were not selected according to the disease stage and comorbidities, as is done in real-life clinical practice. In addition, even though dose reduction and dose delay were not preferred in the neoadjuvant setting, 27.1% of the patients in the present study failed to maintain dose intensity. Fatigue and hematological and gastrointestinal side effects require dose reductions and dose delays. Further, the proportion of patients who were eligible for the surgical resection of their tumors was 89.6% in the present study, with an R0 resection rate of 86%. In comparison, the surgery rate was 94%, and the R0 resection rate was 85% in the FLOT4-AIO study.[4]

In this study, FLOT could be continued postoperatively in just 66.6% of the patients. In 25% of the patients, the treatment plan had to be altered due to

TABLE 3: Univariate and multivariate analysis of predictors for overall survival.

	Univariate analysis		Multivariate analysis	
Variables	**Median OS (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age				
<65	37.8 (30.9-44.8)	0.215		
≥65	52.8 (40.6-65.0)			
Sex				
Male	42.9 (17.0-68.9)	0.425		
Female	49.7 (37.6-61.7)			
Differantiation				
Good-intermediate	49.4 (36.5-62.3)	0.500		
Poor-signet cell	37.8 (30.6-45.0)			
Localization				
Cardia	37.2 (4.5-70.0)	0.677		
Non-cardia	42.9 (36.8-42.9)			
No. of positive lymph nodes				
<3	**62.4 (53.6-71.3)**	**0.002**	1.821 (0.355-9.35)	0.473
≥3	**35.3 (7.7-62.8)**			
LVI				
Positive	42.9 (35.7-54.5)	0.159		
Negative	59.2 (40.1-78.4)			
PNI				
Positive	**35.3 (15.7-54.8)**	**0.001**	**5.38 (1.08-26.77)**	**0.039**
Negative	**65.1 (57.2-73.0)**			
Surgical margin				
Positive	**9.1 (2.8-15.4)**	**<0.001**	**7.61 (1.29-44.63)**	**0.024**
Negative	**54.9 (46.8-63.0)**			
Pathological response				
Complete or partial response	**59.4 (51.2-67.5)**	**<0.001**	0.29 (0.057-1.599)	0.152
Poor or No response	**19.5 (8.7-30.3)**			
Postop FLOT				
Yes	**55.1 (46.0-64.1)**	**<0.001**	0.47 (0.14-1.56)	0.221
No	**13.0 (0.1-26.0)**			
HALP score				
<25.6	41.1 (28.8-53.5)	0.154		
≥25.6	50.6 (40.9-60.3)			
PIV				
<547.9	46.4 (36.1-56.7)	0.634		
≥547.9	43.9 (31.8-56.0)			
SII				
<807.6	47.8 (37.7-57.9)	0.447		
≥807.6	43.1 (30.6-55.5)			
NLR				
<3.0	49.4 (39.7-59.1)	0.273		
≥3.0	43.0 (30.5-55.5)			

LVI: Lymphovascular invasion; PNI: Perineural invasion; HALP: Hemoglobin, albumin, lymphocyte, platelet; PIV: Pan immune inflammation value; SII: Systemic immune inflammation index; NLR: Neutrophil to lymphocyte ratio; FLOT: 5-fluorouracil, oxaliplatin, leucovorin, and docetaxel.

radiological or pathological progression. In the remaining 8.3% of patients, the triplet regimen was not continued in the postoperative period due to poor tolerability despite a good pCR.

In addition, the present study revealed that the perioperative survival results of FLOT were better than those of the alternative regimens such as FOLFOX and/or ECX/EOX, as reported in the litera-

TABLE 4: Side effects.

Side effects	Grade 1-2	Grade 3-4
Diarrhea	6 (12.5%)	2 (4.2%)
Nausea	8 (16.7%)	2(4.2%)
Vomiting	5 (10.4%)	-
Mucositis	5 (10.4%)	-
Fatigue	15 (31.2%)	-
Neuropathy	6 (12.5%)	2 (4.2%)
Anemia	**27 (56.2%)**	-
Neutropenia	**8 (16.7%)**	**2 (4.2%)**
Thrombocytopenia	5 (10.4%)	1 (2.1%)

ture.[12-14] Farrokhi et al. compared various neoadjuvant treatments and reported that the FLOT regimen led to an OS duration of 39 months, which was significantly better than the OS duration of 28 months achieved with DCF, 25 months achieved with FOLFOX, and 21 months achieved with ECF ($p<0.001$).[13] The response rates and survival outcomes observed in the present study were similar to the real-world data obtained using the FLOT perioperative regimen. In the Italian RealFLOT trial, Giommoni et al. demonstrated achieving an objective response rate of 45.6% and a disease control rate of 94.2%. In addition, a complete pCR was achieved in just 7.3% of the patients, which was lower than expected. The authors reported that DFS and OS were significantly higher in the cases of pCR ($p=0.009$ and $p=0.023$, respectively). DFS was also significantly greater in ypN-patients compared to the ypN+ patients ($p<0.001$).[15]

In addition, the present study revealed that age, sex, tumor localization and differentiation status, and the CBC-based inflammatory indices such as the NLR, SII, PIV, and HALP did not influence survival. Several studies have reported a positive association of low NLR and SII with the long-term survival of cancer patients, although the data for LAGC patients remain debatable.[16,17] Qiu et al. conducted a meta-analysis that revealed a significant association between a higher pretreatment SII and worse survival outcomes.[18] Erol et al. conducted a large retrospective analysis to evaluate the effectiveness of perioperative FLOT treatment in patients with LAGC and reported that NLR exerted a statistically significant effect on OS. In this analysis, the patients with an NLR value lower than 2.8 presented higher OS ($p=0.007$).[19] The HALP score is used as an inflammatory marker to reflect the nutritional status of the patient. In a retrospective analysis of 147 patients with metastatic gastric cancer, patients with high HALP scores presented significantly superior median OS.[20] In the present study, no associations of the NLR or other systemic inflammatory indices such as the PIV, SII, and HALP were noted with the survival of patients with LAGC who were receiving perioperative chemotherapy. This difference could be related to the small number of patients included in the present study.

The safety profile obtained in the present study was consistent with that reported in the literature.[15,19] However, the incidence of neutropenia was significantly lower (21%) compared to that reported in previous studies. In the FLOT AIO study, the incidence of grade ≥3 neutropenia was 52%. Moreover, in a real-world data study by Möhring et al., the rate of grade ≥ 3 neutropenia was found to be 59%.[4,14] This difference may be attributed to the more frequent use of GCSF for primary prophylaxis in the present study. No perioperative chemotherapy or operation-related mortality was noted.

It is noteworthy that the present study also had certain limitations. First, the study was limited by its retrospective nature and single-center design. In addition, the number of patients included in the study was small. Moreover, the follow-up period for patients was relatively short despite the widespread use of FLOT treatment in recent years. Although the present study is a perioperative treatment study, there are no available data on surgery-related morbidities or postoperative recovery time. Finally, the pathological data revealed no information regarding the MSI status or PDL-1 CPS.

CONCLUSION

The present study demonstrated the efficacy and safety of perioperative FLOT in the treatment of LAGC. The results revealed positive surgical margins and the presence of PNI as independent poor prognostic factors for OS. The inflammation indices

calculated based on peripheral blood parameters were revealed to have no significant effect on survival.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gül Sema Yıldıran Keskin, Musa Barış Aykan, Ahmet Fatih Köse;* ***Design:*** *Gül Sema Yıldıran Keskin, Musa Barış Aykan;* ***Control/Supervision:*** *Gül Sema Yıldıran Keskin, Nuri Karadurmuş;* ***Data Collection and/or Processing:*** *Gül Sema Yıldıran Keskin, İsmail Ertürk, Musa Barış Aykan, Ramazan Acar, Ayşegül Dumludağ, Alper Topal, Çağlar Köseoğlu, Ömer Faruk Kuzu, İsa Dede, Pelin Durmaz, Ahmet Fatih Köse;* ***Analysis and/or Interpretation:*** *Gül Sema Yıldıran Keskin, Alper Topal;* ***Literature Review:*** *Gül Sema Yıldıran Keskin, Musa Barış Aykan;* ***Writing the Article:*** *Gül Sema Yıldıran Keskin;* ***Critical Review:*** *Musa Barış Aykan, Alper Topal;* ***References and Fundings:*** *Gül Sema Yıldıran Keskin;* ***Materials:*** *Ayşegül Dumludağ, Çağlar Köseoğlu, Ömer Faruk Kuzu, Pelin Durmaz, İsa Dede.*

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