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Comparision of Perioperative Fluoropyrimidine, Docetaxel and Oxaliplatin Regimen with Adjuvant Fluoropyrimidine and Oxaliplatine Regimen in Operable Gastric Cancer Patients

Ameliyata Uygun Mide Kanseri Hastalarında Perioperatif Floropirimidin, Docetaxel ve Oksaliplatin Rejiminin Adjuvan Floropirimidin ve Oksaliplatin Rejimi ile Karşılaştırılması

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Abstract

Amaç Bu çalışma, perioperatif 5-Florourasil (5-FU), oksaliplatin ve docetaxel (FLOT) kemoterapi rejimleri postoperatif adjuvan oral kapesitabin ve oksaliplatin/5-FU ve oksaliplatin (CAPEOX/FOLFOX) kemoterapi rejimleriyle karşılaştırılması amacıyla planlanmıştır.

Gereç ve Yöntem Bu tek merkezli, retrospektif çalışmaya en az T2 veya daha fazla invaziv mide kanseri olan ve pozitif lenf nodu(ları) olan veya olmayan 59 hasta (17 kadın ve 42 erkek) dahil edildi. Tüm hastalara D2 lenf nodu diseksiyonu ile birlikte total veya subtotal ((sub) total) mide rezeksiyonu uygulandı. Araştırma bulgularını istatistiksel olarak analiz etmek için Sosyal Bilimler İstatistik Paketi (IBM SPSS) 26.0 programı kullanıldı.

Bulgular 30 hastadan oluşan perioperatif FLOT tedavi grubu, adjuvan CAPEOX/FOLFOX tedavi grubuna (29 hasta) göre tanı sırasında önemli ölçüde daha ileri klinik nodal (cN) evre ($p<.005$), daha fazla komorbidite ($p=.025$) ve daha kötü Doğu Kooperatif Onkoloji Grubu (ECOG) performansı ($p=.007$) gösterdi. Medyan genel anket (mOS) ve medyan ilerleme serbest anket (mPFS)'nin adjuvan tedavi grubunun lehine istatistiksel olarak anlamlı (sırasıyla 21'e karşı 14 ay, $p=.018$ ve 17'ye karşı 8,5 ay $p=.009$) daha yüksek olduğu bulundu.

Sonuç Gerçek yaşam verilerine göre, kanseri mümkün olan en kısa sürede ortadan kaldırmak için ilk tedavi seçeneği olarak cerrahiyi seçen daha genç ve daha erken evre hastaların daha uzun mOS ve mPFS'lerinin olduğu görülmüştür.

Anahtar Kelimeler Adjuvan, kanser, gastrik, neoadjuvan, tedavi

Özet

Aim *As no study has compared perioperative 5-Fluorouracil (5-FU), oxaliplatin, and docetaxel (FLOT) chemotherapy regimens with postoperative adjuvant oral capecitabine and oxaliplatin/5-FU and oxaliplatin (CAPEOX/FOLFOX) chemotherapy regimens, the goal of this study was to compare them in terms of median and overall survival of operable gastric cancers.*

Material and Method *This single-center, retrospective study recruited 59 subjects (17 females and 42 males) with at least T2 or more invasive gastric cancers with or without positive lymph node(s). All the patients underwent total or subtotal ((sub) total) gastric resection with D2 lymph node dissection. The Statistical Package for the Social Sciences (IBM SPSS) 26.0 program was used to statistically analyze the research findings.*

Results *The peri-operative FLOT treatment group with 30 patients displayed significantly more advanced clinical nodal (cN) stage ($p<0.005$), more comorbidities ($p=0.025$), and worse Eastern Cooperative Oncology Group (ECOG) performance ($p=0.007$) during diagnosis than the adjuvant CAPEOX/FOLFOX treatment group (29 patients). The median overall survival (mOS) and median progression free survival (mPFS) were found to be statistically significant (21 vs. 14 months, $p=0.018$ and 17 versus 8.5 months $p=0.009$, respectively) higher in favor of the adjuvant treatment group.*

Conclusion *According to real-life data, younger and earlier stage patients who chose surgery as the first treatment option to eliminate cancer as soon as possible had longer mOS and mPFS.*

Keywords *Adjuvant, cancer, gastric, neoadjuvant, treatment*

INTRODUCTION

Gastric cancer stands as the fifth most prevalent cancer among all malign tumors and the third leading cause of cancer-related deaths throughout the global boundaries.[1] Early stage gastric cancers are defined as tumors limited to the mucosa or submucosa without lymph node metastases, while locally- advanced stage gastric cancers are defined as those invading at least the muscular layer and/or metastasizing to the regional lymph node(s). Since the possibility of cure is low with surgery alone owing to the low rate of early diagnosis, perioperative or adjuvant treatment modalities, such as chemotherapy or chemoradiotherapy, should be added according to the current treatment guidelines.[2] (Sub) Total gastrectomy with D2 lymph node dissection, in which at least 15-16 lymph nodes must be removed, is currently the standard procedure for gastric cancer surgeries due to its lower recurrence and cancer-related mortality rates when compared with D1 lymph node dissection.[3] D1 lymph node dissection is a gastric resection, which involves the regional (peri-gastric) lymphatics, whereas D2 lymph node dissection includes D1 plus all nodes along the celiac axis (left gastric, common hepatic, celiac, and splenic arteries.[3-6]

In the Medical Research Council's Adjuvant Gastric Infusional Chemotherapy (MAGIC) study conducted in 2005, patients with resectable gastric cancer were randomized into two arms to compare three cycles of pre-operative 5-FU, epirubicin, and cisplatin (ECF) combination chemotherapy regimen, followed by surgery and then three cycles of postoperative ECF, with surgery alone. At the last stage of the study, statistically significant tumor shrinkage and improved 5-year OS from %23 to %36 were observed in the patients in the chemotherapy arm compared to those in the surgery alone arm.[7] In the phase 3 Adjuvant Capecitabine and Oxaliplatin for Gastric Cancer After D2 Gastrectomy (CLASSIC) trial, stage 2-3B patients with D2 lymph node dissection were randomized to postoperative adjuvant CAPEOX combination regimen or surgery alone arm. According to this study, the 5-year disease free survey (DFS) rate and 5-year OS rates were found to be statistically significant in the chemotherapy arm (%68-%53 and %78-%68, respectively).[8-9] In addition, neoadjuvant chemotherapy with the FOLFOX regimen has been found to improve survival rates without increasing adverse events. Beyond that, greater R0 resection rates have been obtained by employing neoadjuvant chemotherapies.[10-11] On the other hand, the Chemotherapy Versus Chemoradiotherapy After Surgery And Preoperative Chemotherapy For Resectable Gastric Cancer (CRITICS) trial did not show any benefit of adding radiotherapy to postoperative adjuvant chemotherapy when compared with perioperative chemotherapy in terms of PFS and OS.[12] Moreover, recent FLOT studies have shown that taxane-based treatments are more effective than epirubicin-based chemotherapies in neoadjuvant settings for resectable gastric cancer.[13] Therefore, instead of epirubicin, docetaxel-based regimens have been most widely prescribed, especially in the neoadjuvant settings of resectable gastric cancer, which invades at least the muscularis propria or has regional gastric lymphatic metastasis according to the 2.2022 version of the National Comprehensive Cancer Network (NCCN) guidelines.

Surgery is the main strategy for locoregional gastric cancer, although it is insufficient as a cure alone.[2] The benefits of both neoadjuvant and adjuvant chemotherapy have been demonstrated in patients with D2 lymph node-dissected gastric cancers. Since, to our knowledge, these treatment strategies have not been compared with each other, we aimed to compare FLOT chemotherapy regimens with postoperative adjuvant FOLFOX/CAPEOX chemotherapy regimens in terms of mPFS and mOS in patients with resectable gastric cancer who underwent D2 lymph node dissection.

MATERIALS and METHODS

Study Design and Eligibility of Patients

This single-center, retrospective study recruited 59 subjects, including 17 females and 42 males, with all patients having histologically or radiologically proven at least T2

or more invasive gastric cancers with or without positive lymph node(s) according to the American Joint Committee on Cancer, 8th edition Tumor, lymph node, and metastasis (TNM) Staging Classifications for Carcinoma of the Stomach. Patient selection was conducted between 01 January 2017 and January 31, 2020. The patients were sampled through convenient sampling tecnique and enrolled after obtaining their written informed consent based on Helsinki Decleration Principles and the study was approved by Malatya Training and Research Hospital Human Ethics Committee. The flow chart of the study is shown in Figure 1.

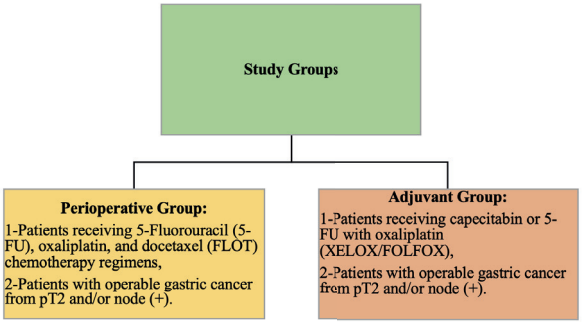

Figure 1: The flow chart of the study

All patients had adequate hematological, renal, and liver functions according to their blood tests, which were repeated before each chemotherapy cycle. Patients aged ≥ 18 years with ECOG performance status ≤ 3 were included in the study. The exclusion criteria were clinical T1 (cT1 N0) stage disease; presence of distant metastases including peritoneal spread; medically inoperable situations due to comorbidities; irresectable status due to infiltration to the root of the mesentery or para-aortic lymph node(s); patients with missing data; and insufficient hematological, renal, and liver functions at diagnosis.

Patients were staged according to their endoscopic ultrasound (EUS), computed tomography (CT), and/or magnetic resonance (MRI) findings at diagnosis. Positron emission tomography (PET-CT) was used as an optional approach when confounding findings were present in the CT or MRI findings.

The primary endpoint was to defined mPFS, which is determined as the length of time from the date of the surgery to the development of local and/or distant recurrence(s) in the adjuvant group while in the perioperative group, it was determined as the length of time from the first cycle of chemotherapy to the development of local and/or distant recurrence(s). Our secondary endpoint was to determine mOS, which was defined as the length of time from the date of the first choice of treatment (either surgery in the adjuvant group or chemotherapy in the perioperative group) to death due to any reason.

Chemotherapy Options, Surgical Procedures and Assessment of Responses

In the perioperative group, 30 patients received 2-4 cycles of neoadjuvant docetaxel 50 mg/m2 on day 1, leucovorin (LV) 200 mg/m2 on day 1, oxaliplatin 85 mg/m2 on day 1, and 5-FU 2600 mg/m2 on days 1-2 cycled every 14 days FLOT of the treatment regimen after being subjected to an adequate endoscopic biopsy that showed a pathological diagnosis of gastric cancer. Two weeks after the end of neoadjuvant chemotherapy, radiologic response rates were evaluated using thorax-abdominal CT in line with the response evaluation criteria in solid tumors (RECIST) 1.1, followed by (sub)total surgery with either laparoscopic or open procedures applied to the patients. The remaining 2-4 chemotherapy cycles were provided to patients 4-6 weeks after surgery with the aim of achieving a total of 6-8 cycles.

In the adjuvant group, 29 patients received 5-FU 2800 mg/m2 on days 1-2 with oxaliplatin 100 mg/m2 on day 1, and LV 400 mg/m2 on day 1 cycled every 14 days FOLFOX or oxaliplatin 130 mg/m2 on day 1 with capecitabine 2000 mg/m2 on day 1-14, cycled every 21 days CAPEOX for a total of 6-8 cycles throughout the postoperative adjuvant treatment period. In the adjuvant group, CAPEOX or FOLFOX chemotherapy was applied 4-6 weeks after sur-

gery in an attempt to achieve a total of 6-8 cycles. Severe adverse events were classified using the Common Terminology Criteria for Adverse Events (CTCAE) version [4].

Assessment of Pathological Specimens

Pathological response rates were determined in surgical specimens using the Becker and/or Mandard Scoring Systems after completion of neoadjuvant treatment settings.[14] The pathological depth of invasion was assessed with pathological metastatic regional lymph nodes (pT and pN stages) after surgery using the TNM 8th edition. Lauren's classification was used to define tumor types as intestinal, diffuse, or unclassified. Tumor localization, grade, postoperative margin status, and the presence or absence of lymphatic and vascular invasion were assessed in this study. Treatment response to neoadjuvant chemotherapy is described as follows: complete response means no viable cancer cells, including lymph nodes, are visible. Near-complete response was defined as the presence of a single or rare group of cancer cells. Partial response is the existence of residual cancer cells with evident tumor regression, but more than single cells or small groups of cancer cells. Poor or no response is defined as extensive residual cancer with no evident tumor regression in postoperative pathology specimens.[15]

Human epidermal growth factor-2 (HER-2) expression in tumors was assessed using immunohistochemistry. Two positive results were assessed as equivocal findings in surgery or biopsy specimens, for which the fluorescence in-situ hybridization (FISH) method was used.[16]

Finally, R0 resection indicates no evidence of tumor, R1 resection indicates the presence of microscopic residuale tumor at the resection margin, and R2 resection indicates macroscopic evidence of tumors beyond the resection margin.[17]

Statistical Analyses

Data are presented as median (min-max), mean±standard deviation, and numbers as percentages. Conformity to the normal distribution was assessed using the Shapiro-Wilk test. The Mann-Whitney U test, independent samples t-test, Pearson's chi-square test, Yatesin's corrected chi-square test, Fisher's exact and chi-square tests, and Kruskal-Wallis test were used in statistical analyses wherever appropriate. The Conover test was used for Kruskal-Wallis analysis in multiple comparisons. Survival analyses were performed using the Kaplan-Meier test. Statistical significance was set at <.05 The IBM SPSS Statistics program version 26.0 was used for the analysis.

In this study, the frequency and percentage values of the patients were given according to the general characteristics. Pearson's chi-square test was used to examine the clinical features of the patients according to the perioperative and adjuvant groups. Adjustments were made using Fisher's exact if the probability of in-group expected values less than 5 was less than %20. In the analysis, $\alpha=0.05$ was determined as the critical decision value. IBM SPSS Statistics version 26.00 was used.

Data Collection

In this study, our hospital management was consulted with the ethics committee report and access to the database was provided for data collection. Data were derived from the medical history of patients, radiological assessments, and pathology reports found in patient files.

RESULTS

A total of 59 patients, including 17 women (%28.8) and 42 men (%71.2), with a mean age of 63 years, were included in this study. The mPFS of the patients involved in this study was 13 months, and the mOS was 18 months. The descriptive statistics for the other sociodemographic variables of the data-set are presented in Table 1.

Table 1. Descriptive Properties of Patients		
Descriptive Properties of Patients		*n (%)
Age	65 and younger	37 (62.7)
	>65	22 (37.3)
Gender	Female	17 (28.8)
	Male	42 (71.2)
Lymphovascular Invasion (LVI)	Positive	50 (84.7)
	Negative	9 (15.3)
Perineural Invasion (PNI)	Positive	49 (83.1)
	Negative	10 (16.9)
T Stage at the Diagnosis	T1	0 (0)
	T2	3 (5.1)
	T3	27 (45.8)
	T4	29 (49.2)
N Stage at the Diagnosis	N0	8 (13.6)
	N1	15 (25.4)
	N2	18 (30.5)
	N3	18 (30.5)
Grade	1	1 (1.7)
	2	17 (28.8)
	3	41 (69.5)
Cerbb2 (HER-2) Status	Negative	50 (84.7)
	Positive	9 (15.3)
Lauren	İntestinal	46 (78.0)
	Diffuse	11(18.6)
	Mixt	2 (3.4)
Histology	Adenocancer	53 (89.8)
	Squamous cell ca	2 (3.4)
	Mucinous ca	3 (5.1)
	Adenosquamous ca	1 (1.7)
Chemotherapy Type Patients Received	Perioperative	30 (50.8)
	Only Adjuvant	29 (49.2)
Tumor Localization	Cardia	16 (27.1)
	Fundus	7 (11.9)
	Corpus	20 (33.9)
	Antrum	9 (15.3)
Tumor Regression Score After Neoadjuvant Chemotherapy	Pylorus	5 (8.5)
	Diffuse	2 (3.4)
	Complete Response	1 (3.3)
	Near Complete Response	6 (20.0)
	Partial Response	11 (36.7)
	Poor or No Response	12 (40.0)
Pathologic Response After Neoadjuvant Chemotherapy	Patients With Complete Response to Partial Response	18 (60.0)
	Patients With Poor or No Response	12 (40.0)
Surgical Margin	Positive	10 (16.9)
	Negative	49 (83.1)
Postoperative Chemotherapy Agents	FLOT	24 (43.6)
	FOLFOX	15 (27.3)
	CAPEOX	16 (29.1)
RT	Received	16 (27.1)
	Not Received	43 (72.9)
Reason For Receiving RT	Positive Surgical Margin	7 (43.8)
	N2 or N3 Lymph Node Metastasis	6 (37.5)
	Both N2-N3 Lymph Node metastasis and Positive surgical margin	3 (18.8)
Surgery Style	Subtotal Gastrectomy	9 (15.3)
	Total Gastrectomy	50 (84.7)
T Stage on Post-op Surgical Specimen After Neoadjuvant Chemotherapy	T	7 (23.3)
	T1	4 (13.3)
	T2	13 (43.3)
	T3	6 (20.0)
	T4	0 (0)
N Stage on Post-op Surgical Specimen After Neoadjuvant Chemotherapy	N0	12 (40.0)
	N1	9 (30.0)
	N2	6 (20.0)
	N3	3 (10.0)
Local or Distant Relaps Status During Follow-up	Relapsed	41 (69.5)
	Not Relapsed	18 (30.5)
Latest Status	Alive	26 (44.1)
	Exitus	33 (55.9)
ECOG Performance Status at the Time of Diagnosis	ECOG 0	29 (49.2)
	ECOG 1	13 (22.0)
	ECOG 2	12 (20.3)
	ECOG Between 2-3	5 (8.5)
Toxicity During Chemotherapy Periods	Developed	22 (37.3)
	Not Developed	37 (62.7)
Dose Reduction During Chemotherapy Periods	Applied	20 (33.9)
	Not Applied	39 (66.1)
Chemotherapy Interrupted or Stopped	Yes	46 (78.0)
	No	13 (22.0)
Comorbidity at the Time of Diagnosis	Existed	26 (44.1)
*n: Total Number of Patients		

The median age of the patients in the adjuvant group was significantly lower than that in the perioperative group (57 and 65 years, respectively; p=0.011). The perioperative treatment group had a significantly more locally advanced clinical nodal (cN) stage than the adjuvant treatment group at diagnosis (p=0.008), there was no statistically significant difference between the two groups in terms of cT stage (p=0.231). Furthermore, the ECOG performance status of patients was significantly better in the adjuvant therapy group. The toxicities developed during the chemotherapy process, the necessity for chemotherapy dose reduction, and the presence of comorbidities at the time of diagnosis were also found to be statistically significantly lower. Finally, the mPFS was calculated as 8.5 in the perioperative group and 17.0 months in the adjuvant group, which was statistically significant (p=0.009). Similarly, the mOS was significantly higher in the adjuvant treatment group than in the perioperative treatment group (21 and 14 months, respectively, p=0.018). These findings are summarized in Table 2. Neutropenia was the most common toxicity detected in 23 (%39) patients, followed by leukopenia detected in 6 (%10.1) patients. Other toxicities that developed during chemotherapy are summarized in Table 3.

Table 2. Variables Between Perioperative And Adjuvant Group

Variables Between Perioperative And Adjuvant Group		Treatment Type		X2**	p
		Perioperative (FLOT)	Adjuvant (CAPEOX/FOLFOX)		
		n (%)	n (%)		
N Stage at Diagnosis	N0	0 (0)	8 (27.6)	11.25	0.008*
	N1	7 (23.3)	8 (27.6)		
	N2	13 (43.3)	5 (17.2)		
	N3	10 (33.3)	8 (27.6)		
	Negative	23 (76.7)	26 (89.7)		
ECOG Performance	ECOG 0	9 (30.0)	20 (69.0)	13.54	0.007*
	ECOG 1	7 (23.3)	6 (20.7)		
	ECOG 2	9 (30.0)	3 (10.3)		
	ECOG between 2-3	5 (16.7)	0 (0.0)		
ECOG Performance Good or Mild	Good (ECOG 0,1)	16 (53.3)	26 (89.7)	14.28	0.005*
	Mild (ECOG 2 and between 2-3)	14 (46.7)	3 (10.3)		
Toxicity During Chemotherapy	Developed	18 (60.0)	4 (13.8)	16.85	0.001*
	Not Developed	12 (40.0)	25 (86.2)		
Chemotherapy Dose Reduction	Applied	16 (53.3)	4 (13.8)	14.44	0.003*
	Not Applied	14 (46.7)	25 (86.2)		
Comorbidity at Diagnosis	Existed	18 (60.0)	8 (27.6)	5.63	0.025*
	Not Existed	12 (40.0)	21 (72.4)		

**Chi-square analysis was performed. *Denotes a significant difference at the 0.05 level.

Table 3. Toxicities During Chemotherapy

Toxicities During Chemotherapy	*n (%)
Neutropenia	23 (52.3)
Leukopenia	6 (13.6)
Liver Functional Disorder	4 (9.1)
Diarrhea	3 (6.8)
Neuropathy	2 (4.5)
Fatigue	2 (4.5)
Nausea-Vomiting	2 (4.5)
Allergic Reactions	1 (2.3)
Hand-Foot Syndrom	1 (2.3)

*n: Total Number of Patients

DISCUSSION

Studies have confirmed statistically significant increases in surveys with multimodal treatments for locoregional gastric cancers. In the phase 3 CLASSIC trial, locoregional gastric cancers with stage 2 or 3 B were randomized into two groups: those receiving postoperative CAPEOX or surgery only. Three-year mDFS improved significantly in the chemotherapy arm compared with the surgery-only arm (%74 and %59, respectively, p<0.001).[18] Since the phase 3 Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial showed no survival benefit of adding postoperative radiotherapy to chemotherapy compared with chemotherapy alone in patients with D2

lymph node resection, postoperative radiotherapy was no longer recommended except in patients with positive surgical margins.[19] Furthermore, the superiority of the FLOT chemotherapy schedule over ECF chemotherapy in terms of mPFS and mOS has changed the main perioperative treatment method to FLOT or FOLFOX chemotherapy (mOS was detected at 50 and 35 months in the FLOT and ECF groups, respectively). HR = 0.77; %95 CI, 0.63-0.94).[13]

In our study, 30 (%51) patients who received perioperative FLOT chemotherapy were compared with 29 (%49) patients who received postoperative adjuvant FOLFOX or CAPEOX chemotherapy in terms of surveillance. Their mean age was higher (65 vs. 57 years, p=0.011), and the development of treatment-related toxicity (p=0.001), presence of comorbidities (p=0.025), the requirement of chemotherapy dose reduction was increasingly frequent among these patients (p=0.003), and the ECOG performance status was worse (p=0.007) in the perioperative FLOT chemotherapy group in this study. In addition, the cN stage in the perioperative underdiagnosis group was significantly more advanced than that in the adjuvant FOLFOX/CAPEOX treatment group (p=0.008). These findings are summarized in Table 2.

Studies have shown that the age of the patient has a significant impact on the clinician's choice of treatment. For instance, older patients prefer to undergo surgery and are subjected to perioperative chemotherapy less frequently than younger patients.[12] However, the median age was significantly higher in the perioperative FLOT group. This may be accrued to the fact that clinicians in this study might avoid surgery in older patients in the first place, especially when these patients had a more advanced stage of the disease. In this situation, patients are first administered neoadjuvant chemotherapy to downstage tumors to decrease the rate of surgical morbidities and increase the rate of R0 resection.[13]

Several studies have demonstrated that older patients are less fit and more susceptible to treatment-related toxicity. 19-21 According to these studies, mPFS and mOS were not negatively affected in older patients. However, both values were significantly lower in the perioperative FLOT treatment group in our study (17 versus 8.5 months, p=0.009 and 21 vs. 14 months, p=0.018, respectively). From our perspective, the fact that patients included in prospective studies, even older ones, are more fit than those who are confronted by clinicians in real life should be considered when interpreting these results.

In a study conducted by Al-Batran et al., patients aged ≥ 65 years with locally advanced or metastatic esophagogastric cancer were randomly segregated to receive FLOT or FLO (without docetaxel). The toxicity in the FLOT group was higher, and the quality of life was negatively affected. In addition, docetaxel did not increase the response rate of patients aged > 70 years. Hence, the benefit of adding docetaxel to perioperative treatment settings in older patients remains unclear. Generally, perioperative treatment should not be abandoned in older patients, although there is yet no clarity regarding the treatment that should be chosen.[12-13, 21]

CONCLUSION

In conclusion, the adjuvant FOLFOX/CAPEOX treatment group, who preferred surgery initially with the goal of getting rid of cancer as soon as possible, had significantly fewer comorbidities, had lower (c) N-stage, experienced fewer chemotherapy toxicities, and had longer mPFS and mOS than the perioperative FLOT chemotherapy group in the real-life data in this study. The small number of patients, retrospective nature of the study, lack of laparoscopy and the bias arising from the preference of surgeons for surgery in the first place in younger and relatively earlier stage patients can be considered the most important limiting factors for this study.

Ethics Approval

The Ethical approve of this study was obtained from Malatya Training and Research Hospital (Number no: E-23536505-604.02).

Peer Review

This study was externally and internally peer-reviewed.

Authorship Contrubutions

Concept and Design: A.Y., H.E., Z.E., Data Collection and Processing: A.Y., N.K.B., Analysis and Interpretation: G.K., Writing: A.Y., D.T.

Conflict of Interest

No conflict of interest regarding the publication of this article was declared by the authors.

Informed Consent

The patients were sampled through convenient sampling tecnique and enrolled after obtaining their written informed consent based on Helsinki Decleration Principles.

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