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Tumor Response with Neoadjuvant FLOT vs. FOLOFX6 in Gastric Cancer

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ABSTRACT

Background: Gastric cancer is considered the second leading cause of cancer-related mortality, which is ranked as the fourth most common malignancy in terms of diagnosis. For resectable gastric cancer, neoadjuvant chemotherapy has been showed to be well-tolerated and effective, with enhanced mean overall survival (OS) and progression-free survival (PFS). The aim of our study was to assess and compare the effectiveness and safety of two commonly used perioperative chemotherapy regimens, FOLFOX6 and FLOT, for resectable and locally-advanced-gastric adenocarcinoma.

Method: A prospective cohort analytical study was conducted on 65 patients (19 females and 46 males who received perioperative chemotherapy and underwent gastric adenocarcinoma resection. Cases were parted into two groups: group-I, 35 cases who received FOLFOX6 chemotherapy regimens preoperatively and group-II, 30 cases who received FLOT chemotherapy regimens peri-operatively. All the patients were evaluated and followed-up throughout the study period to carry out the study was obtained before starting the study.

Results: Most patients had a partial response (PR) of (68.57% and 80%) in the FOLFOX6 and FLOT groups, respectively. In terms of overall response rate, the FOLFOX6 group had an overall response rate of (74.29%) compared to (83.33%) for the FLOT group. Regarding the disease control rate, the FOLFOX6 group had a disease control rate of (88.57%) compared to (96.67%) in the FLOT group. In terms of resection rate, the majority of patients had a complete remission (R0) (80% and 86.67%) in the FOLFOX6 and the FLOT groups, respectively. Moreover, most patients in the FOLFOX6 group suffered from neutropenia (8.57%). At the same time, most patients in the FLOT group had neutropenia (13.33%).

Conclusion: The overall response rate of the perioperative FLOT regimen was greater than that of the FOLFOX6 regimen in cases with resectable and locally advanced gastric adenocarcinoma, although there was no significant. The FLOT regimen was considerably more likely than the other regimens to have adverse effects such as neutropenia and anemia. The study does not show the superiority of one regimen over the other, and both can be used for now. In the future, we will study the need for a larger number of included patient studies to confirm the effectiveness of various TNT regimens.

Keywords: adenocarcinoma, perioperative regimen, neoadjuvant chemotherapy, gastric cancer, FOLFOX6

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INTRODUCTION

Although there has been a nationwide drop in more than fifty years, gastric cancer(GC) is regarded as the fourth most frequently diagnosed cancer and the second major cause of cancer-related deaths (1). According to a study conducted in Basrah province, cancer is the seventh most diagnosed cancer (2). Although the frequency of stomach cancer has decreased in the United States over the last several decades, the incidence of gastric cancer has also grown at the same time (3). Gastric adenocarcinomas are divided into two types: intestinal (well-differentiated) and diffuse (undifferentiated)(4), each with a histopathologic appearance, etiology, and genomic profile. The only curative therapeutic approach for gastric cancer is surgical excision with sufficient lymph node dissection. Perioperative treatment has been shown to enhance patient survival. Patients with unresectable regionally progressed or metastatic disease might only be administered life-prolonging palliative therapy regimens, which is unfortunate (5).

Nutritional factors such as salty food (6), N-nitroso substance utilization (7), cigarettes, lack of vitamins A and C in the diet, eating large quantities of barbecued foods, deficiency of frozen food, and polluted water supply have all been associated with a higher risk of gastric cancer (8). Furthermore, Adenocarcinomas of the lower esophagus, proximal stomach, and gastroesophageal junction are linked to an increased body mass index (BMI), high caloric intake, gastroesophageal reflux, and smoking. Rubber production, tin mining, mineral processing, and coal mining activities are all high-risk occupations (8,9). Helicobacter pylori infection has a 46 percent to 63 percent associated risk (10), whereas Epstein-Barr virus infection is believed to be 5 % to 10% worldwide. Previous stomach surgery and radiation exposure have also been considered as risk factors (11).

Group A blood is related to approximately 20% more stomach cancer cases than other blood groups, O, B, or AB, and is especially connected with the diffuse type (12). Pernicious anemia, an autoimmune chronic-atrophic-gastritis, increases the risk of intestinal-type stomach cancer up to six times. Gastric polyps, hypertrophic gastropathy, and peptic ulcer disease have all been linked to a higher risk of gastric cancer (13).

A 1st-degree relative's history of stomach cancer is linked to a two- to three-fold significantly increased risk of stomach cancer (14). H. pylori infection is much more common in relatives of patients with stomach cancer than in the general population, and premalignant histological alterations in the gastric epithelium are more extensive in these individuals (15).

Annually, approximately 990,000 people are diagnosed with GC globally, with approximately 738,000 deaths (16). GC is the fourth most frequent cancer and the second leading cause of cancer-related mortality (1). In terms of sex and regional variation, the incidence of GC varies. Men are two to three times as likely as women to become affected (16). Geographically, the incidence of this condition is extremely diverse. According to statistics, more than half of all new patients occur in developing nations. South and Central America, Eastern-Europe, and East-Asia are among the areas with an increased chance of GC development (China and Japan). Australia, New Zealand, Southern Asia, North and East Africa, and North America are among the low-risk regions (17).

The proximal GC rate was greater than the distal GC rate. This pattern could be described by improved hygiene, healthier food preservation, and increased consumption of fresh fruits and vegetables, as well as the eradication of Helicobacter pylori. All these measures resulted in a lower H. pylori infection rate, which is associated more with distal GC (18).

The goals of neoadjuvant chemotherapy are to prevent local or systemic recurrence, achieve better survival by downstaging the malignancy, promote pathological responsiveness, and enable eventual surgery, in addition to evaluating responsiveness and tolerance to chemotherapeutics. However, Individuals with locally advanced stomach cancer have poor prognosis, underscoring the need for innovative therapeutic options (19). The median survival time of patients who received neoadjuvant chemotherapy was 15–40 months in such trials, which was considerably better than that of participants who had just undergone surgery (20). Preoperative treatment has been demonstrated to have a beneficial effect on the survival of patients with surgically resectable GC (21). The MAGIC study (a Phase III, randomized, controlled trial) compared patients who received three rounds of epirubicin, cisplatin, and fluorouracil (ECF) as chemotherapeutics before and after the surgical procedure with those who underwent surgery alone in 2006 and discovered that perioperative chemotherapeutic agents had a considerably higher overall survival (OS) rate than the surgical intervention group alone (36 percent vs. 23 percent) (22). In another multicenter randomized controlled trial conducted in Paris (FNCLCC ACCORD 07-FFCD 9703), the use of 5-FU and cisplatin in comparison with surgery alone resulted in OS rates

of 38 percent and 24 percent, respectively (P=0.02), and disease-free survival rates of 34 percent and 19 percent, respectively (P=0.003) (23). Moreover, according to the findings of Phase II/III multicenter randomized controlled trials (FLOT4-AIO), the FLOT regimen was considerably superior to the ECF/ECX regimen of the MAGIC trial (24).

International clinical practice guidelines recommend that GC patients with clinical T1, N0 neoplasms should undergo surgery, with adjunctive treatment only if the histopathologic stage appears to require it, while patients with T3-4 or N+ neoplasms must be managed with a perioperative approach, which currently involves an anthracycline-free treatment regimen like the FLOT schedule (25,26). Although the latest research recommends the adoption of a perioperative strategy in the context of T2, the selection of a suitable management for T2 remains highly debatable. However, to reduce postoperative mortality and morbidity and enhance perioperative care for such patients, all patients should be monitored at specialized institutes with a high volume and experience in GC therapy (27).

The FOLFOX6 chemotherapy, which consists of 5-fluorouracil, leucovorin, as well as oxaliplatin, has been demonstrated to be a tolerated and successful perioperative treatment for resectable gastric cancer, with mean progression-free survival (PFS) and overall survival (OS) improvements of up to 22 months and 29 months, respectively (28). This study was performed on this topic. In comparison to the old FOLFOX6 regimen (200 mg/m^2 leucovorin with 2.6 m2 5-fluorouracil), the perioperative delivery of a modified FOLFOX66 regimen, including a greater dosage of leucovorin (400 mg/m^2) and 5-fluorouracil (2.8 g/m^2), ultimately resulted in a 50% cancer regression rate in 42.9 percent of cases, indicating the effectiveness of FOLFOX6 while having a favorable toxicity profile (29) According to the studies mentioned, FOLFOX6 regimens have been efficacious and well-tolerated in the perioperative setting for the management of resectable malignant tumors.

Modern combined regimens, such as 5-fluorouracil, docetaxel, oxaliplatin, as well as leucovorin (FLOT regimen), have, however, shown benefits over surgery alone, boosting 3-year overall survival to 58.7% in FLOT regimen patients compared to 30.9 percent in those who only underwent surgery (30). FLOT-AIO clinical trials have also shown that FLOT regimens are superior to ECF regimens (31).

The Study Aim

The goal of this study was to assess and compare the effectiveness and safety of two commonly used perioperative chemotherapy regimens, FOLFOX6 and FLOT, as preoperative tools in locally advanced and resectable Gastric Adenocarcinoma to identify the most effective chemo-therapy protocol with the least risk.

METHODS

Study Design

A prospective cohort analytical study was conducted at the Basrah Oncology and Hematology Center from January 2021 to May 2022 on 65 patients (19 females and 46 males who underwent Gastric Adenocarcinoma resection and received perioperational chemotherapy. All cases were followed-up and evaluated throughout the work period at the Oncology Center, which is a tertiary referral center designated for oncology patients and affiliated with the Al-Sader Teaching Hospital.

Study Population

Patients with newly diagnosed gastric adenocarcinoma who were scheduled for neoadjuvant chemotherapy were parted into the following groups:

- Group I: Thirty-five cases who received FOL-FOX6 chemotherapy regimens perioperatively.
- Group II: thirty patients who received FLOT chemotherapy regimens peri-operatively.

Inclusion Criteria

- Age between 55-80 years old.
- All patients who planned for neoadjuvant as locally advanced or resectable gastric adenocarcinoma.
- Patients with no concurrent active malignancy.

Exclusion Criteria

- Poor performance status 3 and 4.
- Stage four Gastric adenocarcinoma.
- Medically unfit for surgery.

Official Endorsement

The agreement of the Basrah Directorate of Health to conduct the study was obtained before starting the

study. All participants signed a consent form for all aspects of the study before they agreed to participate in the survey.

Chemotherapy Regimens

The complete blood count, renal function, and liver function were evaluated before each chemotherapy session. In conditions where toxicity was observed (grade 3-4), the dosage was reduced by 20% of the total calculated dose for the patients.

- FOLFOX6 regimen (28): it includes.
- Oxaliplatin (85 mg/m^2, day 1).
- Leucoverin (400 mg/m^2, day 1)
- Fluouracil (400 mg/m^2 intravenous push, day 1).
- Fluouracil (1200 mg/m^2 continuous infusion over 24 h, days 1-2).
- FLOT regimen (35): it includes.
- Docetaxel (50 mg/m^2, day 1).
- Oxaliplatin (85 mg/m^2, day 1).
- Leucoverin (200 mg/m^2, day 1).
- Fluouracil (2600 mg/m^2 continuous infusion over 24 h, day 1).

Patient Follow-up and Evaluation

Histopathological studies and computed tomography (CT) were used to assess and measure the tumor response rate during the follow-up period (6-8 weeks) after chemotherapy administration according to the RECIST)Response Evaluation Criteria in Solid Tumours).

Response Evaluation Criteria in Solid Tumours

These criteria were established to measure the tumor response depending upon the reduction in tumor size and were categorized into:

- Complete responses (CR): disappearance of the tumor lesion for at least four weeks.
- Partial responses (PR): decrease in the longest diameter of the tumor lesion by >30% that was lasting for at least four weeks.
- Progressive diseases (PD): increase in the longest diameter of a target tumor lesion by 20% or appearance of a new lesion on imaging findings.
- Stable diseases (SD): Patients who did not meet the criteria for progressive disease or partial response.

The overall response rate (ORR) was calculated and measured by the summation of the CR and PR. Additionally, the disease control rate (DCR) was calculated as the summation of complete response (CR), partial response (PR), and stable disease (SD).

Chemotherapy Adverse Events

Side effects were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 (32), which includes:

- Hematological adverse effects: anemia, thrombocytopenia, and neutropenia.
- Gastrointestinal adverse effects: nausea, vomiting, diarrhea, and mucositis.

Survival Rates Evaluation

This study measured important issues that illustrate the overall response and outcome of a specific regimen to a patient's health condition, including:

- Progression-free survival rate (PFS): the period during and post treatment until disease progression.
- Overall response rate (ORR): the proportion of people in a study or treatment group who have a partial or complete response to treatment within a certain period.

Pathological Response

Regarding the resection rate this study included both:

- R0 resection: indicates a microscopically margin-negative resection;
- R1 resection: indicates the removal of all macroscopic diseases, but microscopic margins are positive for tumors.

Data Collection

The study relied on a specially designed list of information collection, which was composed of socio-demographic, clinical, and histopathological aspects. Furthermore, data were collected and analyzed.

Statistical Analysis

Version-26 of the Statistical Package for the Social Sciences (SPSS Inc.) was used. Categorical data are presented as numbers and percentages. The Independent Sample T-test (for normally distributed data) was used to assess continuous data and to express the differences between the groups. Graphical

representations have been included to illustrate therapeutic responses. Clustered simple and stacked bar charts were used to compare treatment responses, overall response rates, and disease control rates between the FOLFOX6 and FLOT groups. Statistical significance was set at $p < 0.05$.

RESULTS

This study included 65 cases (19 females and 46 males) who were divided into two groups. FOLFOX6 group (n=35) with a mean age of 58.21±10.61 and a FLOT group (n=30) with a mean age of 53.61±21.28, (P=0.09). There were no signifi-cant differences in the BMI (P=0.062). Most of the participants had normal weight. The majority of the FOLFOX6 and FLOT groups had an ECOG score of zero 24(68.57%) and 17(56.6%), respectively. Regarding smoking, most of the participants for the FOLFOX6 and FLOT groups were smokers 26(74.29%) and 19(63.33%), respec-tively. Additionally, no significant differences in family history of carcinoma were observed between the group (P=0.36) (*table 1*).

Regarding tumor characters, the study showed no significant differences among the FOLFOX6 and FLOT groups in terms of differentiation (p=0.097). The study showed no significant differences in terms of the tumor site (p=0.072). More than half of the FLOT group had a proximal tumor (66.67%) compared to (33.33%) with a distal tumor. The majority of patients underwent a total gastrectomy (85.71% and 90%) in the FOLFOX6 and FLOT groups, respectively. There were no significant differences in the resection rates (P=0.056) (*table 2*).

Regarding treatment, most patients had a partial response (PR) of (68.57% and 80%) in the FOLFOX6 and FLOT groups, respectively (P=0.24). The study also didn't show any significant differences among the arms in terms of overall response rate (P=0.64), where the FOLFOX6 group had an overall response rate of (74.29%) compared to (83.33%) for the FLOT group. Additionally, no significant differences were

Table 1 - General socio-demographical data analysis regarding the studied groups.

Variables	FOLFOX6	FLOT	P-value
	No. (%)		
Age	58.21±10.61	53.61±21.28	0.09
Gender			
Male	26 (74.29)	20 (66.67)	0.059
Female	9 (25.71)	10 (33.33)	
BMI			
Underweight	12 (34.29)	9 (30.00)	0.062
Normal weight	17 (48.57)	15 (50.00)	
Overweight and obese	6 (17.14)	6 (20.00)	
ECOG			
Zero	24 (68.57)	17 (56.6)	0.057
One	8 (22.86)	10 (33.4)	
Two	3 (8.57)	3 (10.00)	
Smoking	26 (74.29)	19 (63.33)	0.24
Family history of carcinoma	7 (20.00)	5 (16.67)	0.36

Table 2 - Tumor characteristics analysis regarding the studied groups.

Variables	FOLFOX6	FLOT	P-value
	No. (%)		
Differentiation			
Well-differentiated	19 (54.29)	16 (53.33)	0.097
Poor differentiation	16 (45.71)	14 (46.67)	
Tumor site			
Proximal	25 (71.43)	20 (66.67)	0.072
Distal	10 (28.57)	10 (33.33)	
Type of surgery			
Total gastrectomy	30 (85.71)	27 (90.00)	0.078
Partial gastrectomy	5 (14.29)	3 (10.00)	
Resection rate			
R0	28 (80.00)	26 (86.67)	0.056
R1	7 (20.00)	4 (13.33)	

Table 3 - Treatment characteristics analysis regarding the studied groups.

Variables	FOLFOX6 (n=35)	FLOT (n=30)	P-value
	No. (%)		
Response rate			
Partial response	24 (68.57)	24 (80.00)	0.24
Complete response	1 (2.86)	1 (3.33)	
Stable disease	6 (17.14)	3 (10.00)	
Progressive disease	4 (11.43)	2 (6.67)	
Overall response rate	26 (74.29)	25 (83.33)	0.64
Disease control rate	31 (88.57)	29 (96.67)	0.42

observed in disease control rate (P=0.42) (*table 3*).

A comparative graphical representation of treat-ment response categories (complete, partial, stable disease, and progressive disease) between patients receiving FOLFOX6 and FLOT chemotherapy regimens is shown (*fig. 1*). The overall response and disease control rates were higher in the FLOT arm, although the differences were not significant (*fig. 2*).

Regarding adverse effects, there were no significant differences between the arms (p≥0.05). Most patients in the FOLFOX6 group suffered from neutro-penia 3(8.57%), whereas most patients in the FLOT group had neutropenia 4(13.33%) (*table 4*).

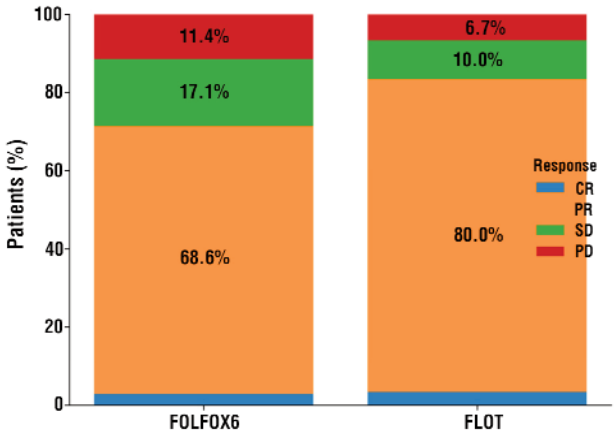

Figure 1 - Therapeutic response patterns among patients treated with FOLFOX6 and FLOT regimens

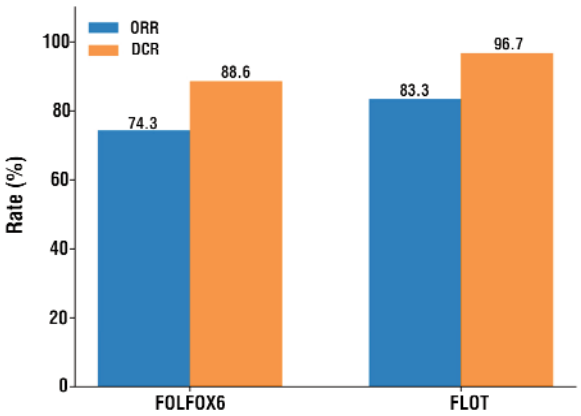

Figure 2 - Overall response rate and disease control rate patterns among patients treated with FOLFOX6 and FLOT regimens.

DISCUSSION

Gastric cancer is the second leading reason of malignancy-related deaths globally, despite its reduced incidence. China accounts for more than 40% of the global annual cancer incidence, making it the country with the highest incidence of stomach cancer (33).

More than 80% of patients with confirmed stomach cancer have advanced disease because of the absence of specific symptoms in the early stages (34). Using advanced diagnostic technologies, such as EUS and improved CT, surgeons may monitor preoperative staging more precisely as tools and experience progress (35). The majority of advanced gastric cancer patients treated with surgery alone are unable to effectively undergo R0 resection and relapse, with significant recurrence and death rates, despite advancements in sufficient lymph node dissection (36).

Similar to the research of Lou et al., (37) which shows that males had a greater incidence than women, the present study revealed that there were overall more men than women and more elderly patients (more than 50 years) than youthful patients (up to or less than 50 years). Additionally, there are maximal sex

Table 4 - Grade III and IV adverse effects analysis regarding the studied groups.

Variables	FOLFOX6	FLOT	P-value
	No. (%)		
Toxic effect			
Nausea	1 (2.86)	3 (10.0)	0.08
Vomiting	1 (2.86)	1 (3.33)	0.64
Mucositis	2 (5.71)	2 (6.67)	0.71
Diarrhea	2 (5.71)	2 (6.67)	0.091
Neutropenia	3 (8.57)	4 (13.33)	0.057
Thrombocytopenia	0	1 (3.33)	0.056
Anemia	1 (2.86)	1 (3.33)	0.41

disparities as people age. Additionally, as noted in the Globocan 2012 study, males develop stomach cancer at a rate that is twice as high as females (38). According to Radkiewicz et al. (39), men have a higher chance of developing stomach cancer, a large percentage of cancers are explained by characteristics connected to men, and men have a worse prognosis across the spectrum of cancers.

In this prospective study, we investigated two administered chemotherapy protocols, FOLFOX6 and FLOT, for the peri-operative treatment of gastric cancer cases with resectable tumors for the first time in the Iraqi population.

Several previous studies have demonstrated the superior effect of the FLOT regimen on overall survival compared to other regimens such as ECF-based pre-operative chemotherapy(40). Nevertheless, in our analysis, the median progression survival time was 20 months, which is lower than the median survival in other published studies (41). This is due to differences in the sample size and sociodemographic factors of the studied population. Additionally, the majority of Iraqi patients with stomach cancer were found to have advanced tumors at the time of diagnosis (stage III and stage IV), which is directly related to their short survival times, according to a study by Shahid et al. in 2017 (42).

The present study showed that the R0 resection rate was greater with the FLOT regimen (90%) than the of FOLFOX6 (82 %). The resection rate for the FLOT regimen was greater than the resection rate given by Schulz C et al. research, which was 86 % in 50 patients (43), and comparable to Wang K. et al. 's retrospective analysis with a 91 % resection rate in 40 enrolled patients (44).

Side effects and toxicity of the chemotherapy protocols were the secondary endpoints of the study. Notably, oxaliplatin-based chemotherapy protocols, such as FLOT and FOLFOX6, have a lower rate of side effects than other regimens. Additionally, oxaliplatin-based protocols maintain their overall efficacy at the same or higher level.

The Meta-analysis performed by Huang J et al. to compare the efficacy and safety of oxaliplatin-based and cisplatin-based therapy in advanced gastric cancer (45) clearly demonstrated this issue and showed that there was no difference in the efficacy between the two chemotherapy regimens (46). With the exception of neurotoxicity, the oxaliplatin-based regimen was linked with fewer harmful effects, and in this work, we focused on the differences in terms of side effects between FLOT and FOLFOX6 rather than comparing them with other chemotherapy protocols.

In this study, in terms of hematological toxicity of chemotherapy regimens, the FLOT regimen was noticeably more likely to cause side effects, including neutropenia (13.33%) and anemia (3.33%), than the other regimens. The documented hematological toxicity, in particularly neutropenia, in our investigation was consistent with earlier published toxicity rates for the FLOT regimen by Farrokhi et al., which were 37% for neutropenia and 18% for anemia, 6.3%, which were much higher than those of FOLFOX6 in the aforementioned study (47).

Regarding gastrointestinal side effects, the present study demonstrated that the FLOT protocol had more side effects in terms of diarrhea, mucositis, nausea, and vomiting. The significant gastrointestinal side effects of the FLOT regimen have been well studied by previous studies (48, 49), and this is another challenging point facing physicians when choosing the FLOT regimen as suitable chemotherapy prior to gastric cancer surgery.

Limitation

This work has some limitations. First, the relatively small sample size may have limited the statistical power to detect significant differences between FOLFOX6 and FLOT regimens. Second, the study was conducted at a limited number of centers, which may affect the generalizability of the findings to a broader population. Third, the follow-up period was short, restricting the assessment of long-term outcomes such as OS, PFS, and recurrence rates. Additionally, the non-randomized cohort design may have introduced a selection bias and potential confounding factors that could influence treatment outcomes. Variability in patient characters, tumor stage, and treatment tolerance may also have affected the observed responses and adverse events. Therefore, larger multi-center randomized studies with extended follow-up are recommended to validate these findings and to establish clearer comparative evidence regarding the efficacy and safety of peri-operative FOLFOX6 and FLOT regimens in gastric adenocarcinoma.

CONCLUSIONS

In terms of progression free survival, neither peri-operative FLOT nor FOLFOX6 regimens were statistically different. In this regard, both regimens could be considered the best therapy options for cases with resectable gastric cancer.

Conflicts of Interest

The authors declare no conflict of interest regarding this article.

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Ethical Approval

The Medical Ethical Committee of The Basrah Oncology Center, Basrah Health Directorate this study (no. 79 on 4/9/2021).

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