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ORIGINAL RESEARCH

Real-life effectiveness of FLOT in resectable gastric cancer: existing challenges

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Abstract

Background: Gastric cancer has a high mortality rate. Therapeutic management must be multidisciplinary to offer the patient the best, personalized strategy.

Patients and methods: We performed an observational study to evaluate the pathological response, survival and nutritional status in patients with resectable gastric cancer and candidates for perioperative chemotherapy with the fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) regimen *versus* other regimens. The primary endpoints were pathological response rate, care continuity rate and survival outcomes. A total of 96 patients attending the Hospital "Policlinico San Matteo" in Pavia (Italy) between January 2012 and August 2022 were selected for the study.

Results: Regarding pathological response rates, the best rate (TRG-0) was recorded in the FLOT group with a percentage of 6.2% compared with 4.7% in the NO-FLOT arm (p=0.052). The highest failure rate to complete the post-operative phase was 75% in the NO-FLOT group and only 25% in the FLOT group (p=0.007). Survival outcomes were better in the FLOT group with a median disease-free survival of 30 *versus* 22.2 months (p=0.586).

Conclusions: Despite the limitations, the results obtained were consistent with the medical literature and confirmed the effectiveness of the FLOT chemotherapy in real life. Nevertheless, some questions remain: the application in elderly patients, the addition of immunotherapy in patients with microsatellite instability or with high PD-L1 levels, comparison with chemoradiotherapy in junctional cancers and real cure rates. The FLOT regimen has revolutionized the treatment of resectable gastric cancer, but caution is needed before considering it an absolute standard of care.

Keywords: effectiveness, FLOT regimen, perioperative treatment, real-life studies, resectable gastric cancer.

Citation

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Introduction

According to the most updated epidemiological data provided by the Global Cancer Observatory, gastric cancer ranks sixth in incidence and fifth in mortality in the general world population, including all age groups and both sexes.[1] Regarding aetiology, gastric cancer, like most malignant tumours, has a multifactorial origin in which dietary, environmental, infectious and genetic factors are involved.[2]

The World Health Organization's histopathological classification divides gastric cancer into two main types: adenocarcinomas, which account for 95% of all diagnoses, and other histological forms, which make up 5% of cases.[3] In the pathological anatomy of gastric cancer, four classifications are very important: the Lauren classification, the Ming classification, The Cancer Genome Atlas classification, and finally the HER2 and PDL1 scores.[4–8] The gold standard for the diagnosis of gastric cancer is esophagogastroduodenoscopy whilst staging is performed with a chest-abdomen CT scan with contrast medium.[9]

Therapeutic management of gastric cancer must be multidisciplinary to offer the patient the best, personalized strategy.[10] Gastric cancer occurs in a limited form in only 20% of cases and, in this setting, surgery remains the only potentially curative weapon.[11] In 80% of cases, gastric cancer is locally advanced or metastatic. The treatment of locally advanced forms has been revolutionized thanks to the advent of the fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) chemotherapy regimen, which has been shown to significantly increase the overall survival (OS) of patients. The FLOT regimen consists of a triplet of chemotherapy drugs: fluorouracil, oxaliplatin and docetaxel. The treatment protocol includes two phases: a neoadjuvant or pre-operative phase and an adjuvant or post-operative phase. Each phase involves the administration of four cycles of FLOT every 2 weeks. The most frequent adverse events are asthenia, haematological toxicity, gastrointestinal disorders and peripheral neuropathy.[12] In the relapsed and metastatic setting, it is essential to first understand whether a patient is fit for active oncological treatment or whether they are a candidate for the best supportive therapy.[13]

Rationale and study objectives

The treatment of gastric cancer is multimodal and involves both medical therapy and surgical therapy. This concept is especially valid for resectable forms of gastric cancer where the combination of the two therapies is a systematic approach. The scientific rationale of our study is based on this concept, comparing the FLOT chemotherapy regimen *versus* other chemotherapy regimens adopted in resectable gastric cancer.

In the oncology field, it is usual to simplify the TNM staging of malignant tumours into three classes of oncological disease: limited disease, locally advanced disease and metastatic disease. The TNM staging of gastric cancer is rather complex and escapes simplification into these categories because, even if confined to the parietal stratification of the organ, gastric cancer tends to cause early involvement of the lymphatic structures.[14]

For the purposes of our study, we will focus on resectable stages of gastric cancer for which perioperative chemotherapy is also planned. Over the years, several clinical studies have been performed demonstrating the efficacy of the multimodal perioperative strategy.[15–18]

Regardless of the pharmacological composition, perioperative chemotherapy treatment has become the standard of care in most Western countries. In 2019, the German study by Al-Batran et al.[12] further revolutionized the landscape in this disease setting by introducing the FLOT chemotherapy regimen, which led to an increased OS of patients, from 35 months in the control arm (the standard epirubicin–cisplatin–fluorouracil/epirubicin–cisplatin–capecitabine) to 50 months in the experimental arm with the FLOT scheme.

Before FLOT, perioperative chemotherapy regimens used in the treatment of resectable gastric cancer consisted mainly of fluorouracil in combination with other drugs such as docetaxel, platinum compounds and epirubicin (i.e. folinate–fluorouracil–oxaliplatin (FOLFOX), oxaliplatin–capecitabine (XELOX), cisplatin–fluorouracil, epirubicin–cisplatin–fluorouracil, epirubicin–cisplatin–capecitabine). Nevertheless, these regimens showed moderate objective response rates with a reduced impact on OS. This fact justified the very high rates of oncological recurrence and high mortality of gastric cancer even in the potentially surgical setting. In addition, there was a non-negligible spectrum of adverse events such as cardiac toxicity with epirubicin.[15–18] Therefore, the significant relevance of the FLOT objective response rate and OS, together with the safety profile, established the FLOT regimen as the standard medical treatment for resectable gastric cancer.[12] In patients considered unfit for the FLOT regimen, a chemotherapy doublet consisting of fluoropyrimidine in association with a platinum compound, generally oxaliplatin, is used.[19]

From these premises, arises our hypothesis: to demonstrate the real-life effectiveness of FLOT by comparing it with traditional chemotherapy regimens and discovering its strengths and weaknesses.

Patients and methods

Study design

This is a retrospective single-centre observational study aimed at evaluating the pathological response, survival and nutritional status in patients with resectable gastric cancer and candidates for perioperative chemotherapy with the FLOT regimen *versus* other regimens. The general aim of the study is to provide our real-world data of oncological practice of gastric cancer treatment to particularly validate the effectiveness of the FLOT regimen compared to alternative schemes. Following the publication of the clinical trial by Al-Batran et al.,[12] there is a need to produce scientific evidence, based on the real-world studies to demonstrate the effectiveness in clinical practice of the recently introduced chemotherapy regimen.

Ethics approval and informed consent

Since the study is a retrospective observational real-life study, according to current legislation in Italy, it does not require specific approval by an Ethics Committee.

The particular regulatory reference is the National Law of 30 November 2021, which regulates "Measures aimed at facilitating and supporting the implementation of non-profit clinical trials and observational studies and the consequent legal transfer of the trials results".

Endpoints

The primary endpoints of the study were the evaluation of pathological response rates through the tumour regression grade (TRG), care continuity rates (completion rates of the pre-operative and post-operative phases) and survival outcomes DFS and OS (disease-free survival and overall survival, respectively) compared between patients undergoing the FLOT regimen and patients undergoing other chemotherapy regimens.

The secondary endpoints are the assessment of nutritional status and the toxicity profile, both in general and in comparison between the two treatment groups.

Patient enrolment

A total of 96 patients with resectable gastric cancer and candidates for perioperative chemotherapy treatment attending the Medical Oncology Unit of the Hospital "Policlinico San Matteo" in Pavia (Italy), between January 2012 and August 2022, were selected. Patient data were obtained from the medical records and outpatient reports available at our hospital, and the selection of patients took place according to the inclusion and exclusion criteria reported below.

Inclusion criteria

Histological diagnosis of gastric or gastro-oesophageal junction adenocarcinoma, TNM stages I–III and having received neoadjuvant chemotherapy treatment.

Exclusion criteria

Other histological diagnoses, TNM stage IV and having undergone a gastrectomy.

For this study, it was essential to select the population to be subjected to analysis. In this sense, the exclusion criteria were as important as the inclusion criteria. Excluding non-adenocarcinomatous histologies, patients with metastatic disease and those who had already undergone gastrectomy allowed the elimination of biases that would have affected the final results. The study is aimed at the treatment of resectable gastric cancer susceptible to all three phases of the treatment plan: neoadjuvant chemotherapy, surgery and adjuvant chemotherapy.

Informed consent statement

According to Italian State hospitals denomination as providers of healthcare and scientific research, all patients who sign the informed consent for any hospital service are informed that their health data can be used for the purposes of scientific research. Patients' health data were used according to current legislation, in particular, according to the orders of the Privacy Guarantor, which strictly ensures the protection of health data.

Statistical analysis

The statistical analysis of the collected data was performed with Excel (Microsoft Office) and with the SPSS programme. Continuous variables are presented as mean, median, minimum value, maximum value and standard deviation whilst categorical variables are presented as absolute frequencies and percentages. Survival outcomes were analysed using the log-rank test for the comparison of subgroups and graphically represented by Kaplan–Meier curves. The statistical significance of the results obtained was set using the standard cut-off of a p value equal to or less than 0.05.

Of the 96 patients originally selected, data from 75 were used for statistical analysis for the primary endpoints; data for 21 patients were eliminated because they did not meet the inclusion and exclusion criteria or because they deliberately discontinued the treatment plan. Regarding the secondary endpoints and in particular nutritional status, the sample size was further reduced to 42 patients; 54 patients were excluded because they did not have nutritional screening at diagnosis. Given the enrolment period, the primary and secondary endpoints of the study were calculated in December 2022.

Results

Of the 96 patients selected, 21 were excluded from the statistical analysis for various reasons: 10 patients progressed during neoadjuvant chemotherapy, 5 did not continue the therapeutic plan due to clinical deterioration, 4 patients continued the care plan in another centre, 1 patient at the time of the analysis had not yet completed the neoadjuvant phase and 1 patient died during treatment. Statistical analysis was therefore conducted on a total sample of 75 patients. Data were first analysed in terms of five important variables: sex, age, cancer location, Lauren histological classification and TNM stage at diagnosis (Table 1).

The patients were divided into the two arms of the study: the group that received the perioperative FLOT chemotherapy regimen and the group that received other chemotherapy regimens. Specifically, these regimens were those used in current clinical practice before the introduction of the FLOT regimen and concern four essential compositions: XELOX, FOLFOX, docetaxel–cisplatin–fluorouracil and cisplatin–fluorouracil. Considering the

Table 1. Patient clinical characteristics.

Clinical characteristics	*n* (%)
Sex	52 (69.3%)
Male	23 (30.7%)
Female	
Age	
<65 years	38 (50.7%)
≥65 years	37 (49.3%)
Cancer location	
Gastro-oesophageal junction	27 (36.0%)
Stomach	48 (64.0%)
Lauren classification	
Intestinal	29 (38.7%)
Diffuse	29 (38.7%)
Mixed	9 (12.0%)
Unknown	8 (10.6%)
TNM stage	
I	0
II	29 (38.7%)
III	46 (61.3%)

75 patients whose data were used for statistical analysis, 42.7% (*n*=32) received the FLOT regimen, whereas 57.3% (*n*=43) received one of the other regimens (Figure 1).

The primary endpoints of the study were pathological response rates, care continuity rates and survival outcomes. Pathological response rates were defined using the TRG. The TRG system, created by Mandard et al.[20] and approved by the American Joint Commitee on Cancer (AJCC), divides the pathological response of a cancer to a preoperative treatment into five score classes: TRG-0, which indicates a complete pathological response; TRG-1, which corresponds to a moderate response; TRG-2, which indicates a minimal response; TRG-3, which corresponds to a poor response; and TRG-4, which indicates the absence of pathological response.[21] In the sample used for statistical analysis, 17.3% of patients lacked TRG data. In the FLOT group, 6.2% of patients obtained TRG-0, 3.1% TRG-1, 43.8% TRG-2, 37.5% TRG-3 and 3.1% TRG-4. Conversely, in the non-FLOT group, 4.7% obtained TRG-0, 4.7% TRG-1, 16.3% TRG-2, 48.8% TRG-3 and no patient had TRG-4 (*p*=0.052) (Figure 2).

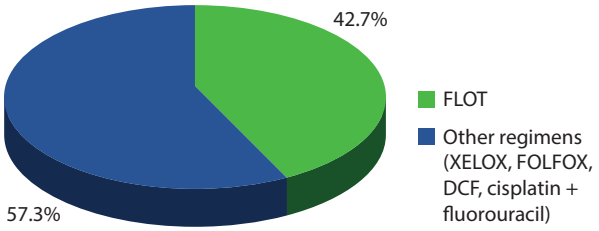
The care continuity rates express the patient's progression along the treatment plan, which includes a preoperative chemotherapy phase, a surgical phase and a post-operative chemotherapy phase. These rates specifically refer to the phases of medical treatment and were measured in percentage rates. The preoperative chemotherapy phase was completed by 70 patients, whereas 5 did not reach the conclusion. Of these 70 patients, 42.9% completed the pre-operative phase in the FLOT group, whereas 57.1% completed it in the non-FLOT group. Of the 5 patients who did not complete the preoperative phase, 40% belonged to the FLOT group and 60% to the non-FLOT group (*p*=1). Regarding the completion of the postoperative phase, 38 patients completed the treatment, whereas 12 did not complete the chemotherapy. Of the 38 patients analysed, 60.5% were in the FLOT group, whereas 39.5% were in the non-FLOT group. Amongst the 12 patients who did not complete the post-operative phase, 25% belonged to the FLOT group and 75% to the non-FLOT group (*p*=0.007). The care continuity rates are an innovative parameter in oncology research. In resectable diseases, such as gastric cancer, it is not only important to analyse patient survival at the end of the treatment plan but also how patients face the treatment plan. In our case, the results obtained demonstrate how the completion rates of neoadjuvant and adjuvant chemotherapy are better in those who received the FLOT regimen. Such data invites the oncology community to understand how essential it is to select a pharmacological regimen capable of allowing the patient to progress easily in their treatment plan.

The survival outcomes analysed in our study were DFS and OS. DFS is the time from treatment to disease recurrence (or patient death) and is typically used in the adjuvant setting to determine whether a given treatment is effective in preventing relapse.[22] DFS occurred at a median of 30.0 months and 22.2 months in the FLOT and non-FLOT groups, respectively (*p*=0.586) (Figure 3).

OS is defined as the time, expressed in months, between the start of treatment and the patient's death, from any cause.[23] The median OS was 42.5 months in the non-FLOT group, whereas it was not reached in the FLOT group (*p*=0.040) (Figure 4).

The secondary endpoints of the study were the evaluation of nutritional status and the toxicity profile. The nutritional status of the patients was assessed by calculating the body mass index (BMI) and the Nutritional Risk Index (NRI).[24,25] Overall, 17.3% had an unknown BMI, 1.3% had underweight (a single patient), 38.7% had normal weight, 37.3% had overweight and 5.3% had grade I obesity. The distribution of BMI was rather homogeneous amongst the five essential variables (sex, age, site of the tumour, histological classification and TNM stage). The only difference concerned the sex division because men

Figure 1. Treatment groups.



DCF, docetaxel, cisplatin and 5-fluorouracil; FOLFOX, folinate–fluorouracil–oxaliplatin; XELOX, oxaliplatin–capecitabine.

had a higher percentage of overweight whilst women had a higher percentage of patients with normal weight. Correlating BMI with the study's primary endpoints, no statistical significance was observed between patients' BMI and pathological response according to the TRG, although it is interesting to note that 50% of patients with overweight achieved a poor response with a TRG-3. There was statistical significance between the patients' BMI and the care continuity rates, with *p* values of 0.004 and 0.013, respectively, for the conclusion of the preoperative phase and the conclusion of the post-operative phase. These associations establish that patients with normal weight and overweight completed the entire treatment plan. Further, there was statistical significance (p=0.000) between patient BMI and survival outcomes; the mean OS was 9.9, 66.4, 62.0 and 23.7 months, respectively, in the group of patients with underweight, normal weight, overweight and obesity. This association suggests that the average OS is higher in patients with normal weight and overweight and has a tendency to be reduced in the 'extreme' weight groups (with underweight and obesity).

NRI was calculated with the formula (1.519 × serum albumin in g/L + 0.417 × [current weight/usual weight × 100]). Based on this formula, we identified a patient's malnutrition risk in the presence of an NRI <97.5. To analyse the NRI, we had to restrict the sample to 42 patients, specifically to those who, at diagnosis, had carried out a complete medical evaluation, including a nutritional one; statistical analysis divided the patients into two further groups: patients with malnourishment (45.2%) and patients properly nourished (54.8%). Similarly to the BMI, NRI was also correlated with the clinical characteristics of patients and the rate of malnutrition was greater in elderly patients than in younger patients. When correlating the NRI with the primary endpoints of the study, no statistically significant associations were observed.

The toxicity profile was evaluated by first summarizing the adverse effects with regards to gastroenterological and haematological toxicity for both treatment groups. The most common gastrointestinal toxicities recorded were nausea, loss of appetite, diarrhoea, dysgeusia and constipation, whereas the haematological toxicities were anaemia, leuko-neutropenia and thrombocytopenia. Since these are polychemotherapy regimens and have the consequent possibility leading to a very wide and diversified range of adverse effects, even beyond gastroenterological and haematological effects, for the purposes of this study, dose-limiting toxicity was used as an objective measure of toxicity. This is a measure borrowed from phase I clinical trials but appropriately revised and adjusted for the purposes of conventional clinical practice. In this sense, dose-limiting toxicity can be defined as

Figure 2. TRG rates between treatment groups.

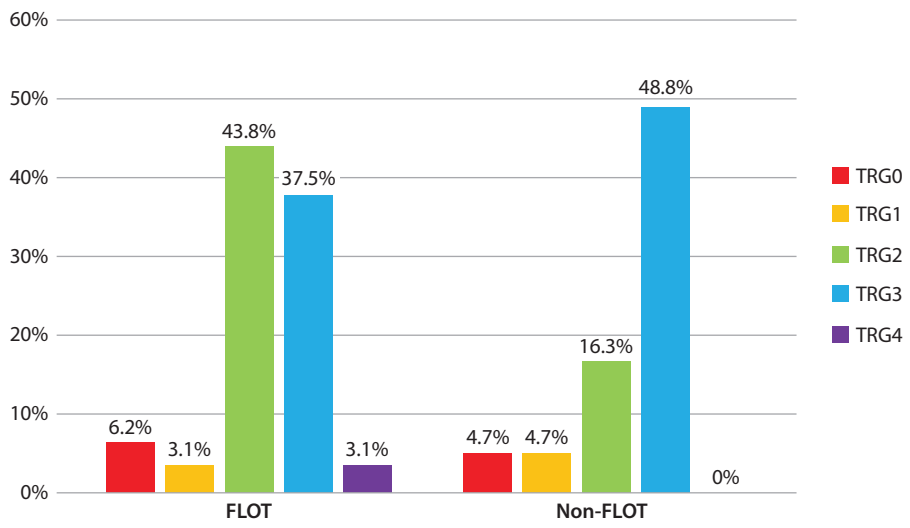


Figure 3. Disease-free survival between treatment groups.

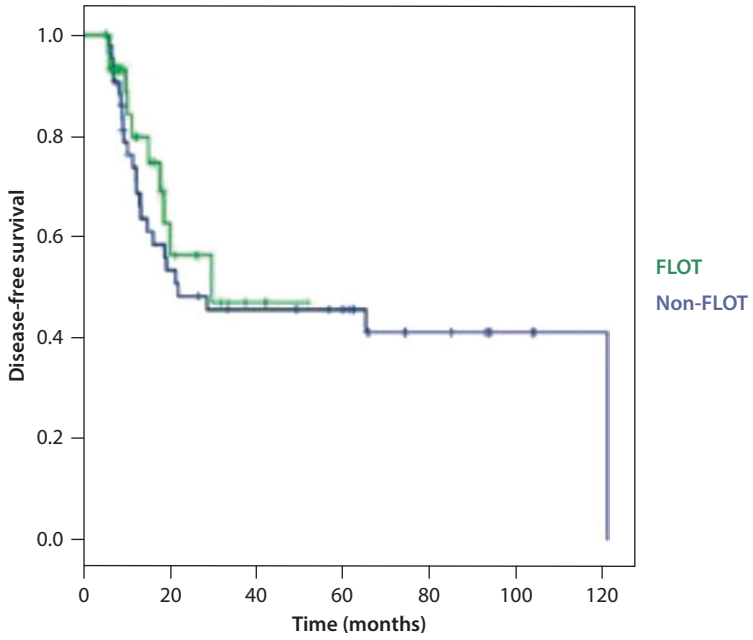
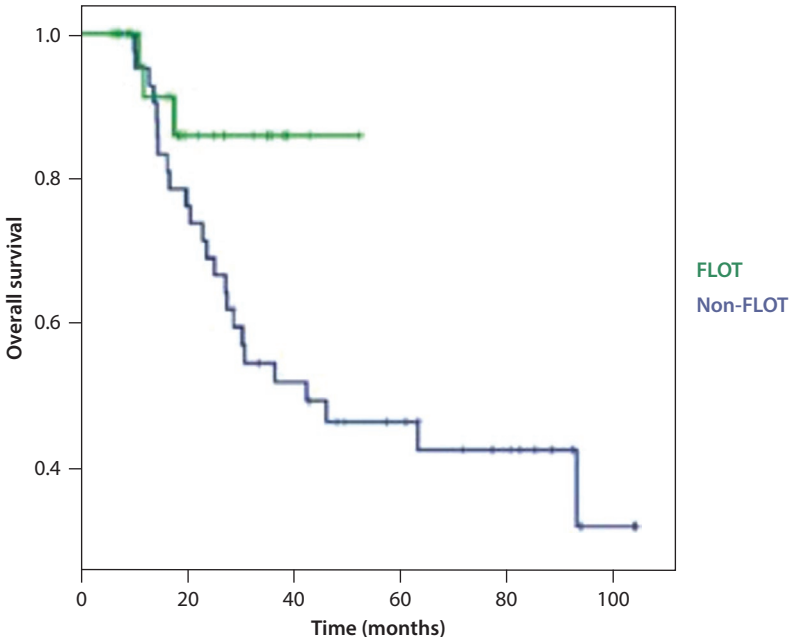


Figure 4. Overall survival between treatment groups.



a toxicity of any nature but of moderate-severe intensity such as to prevent further administration of the drug at the same dose level.[26] Statistical analysis showed that 62 patients did not present any dose-limiting toxicity, whereas 13 patients did; of these 13 patients, 69.2% were in the non-FLOT group, whereas 30.8% were part of the FLOT group (p=0.377).

Discussion

Therapeutic management of resectable gastric cancer has changed considerably in the last 3 years. The study by Al-Batran et al. documented the greater efficacy of the FLOT regimen compared with the previous standard

of treatment in terms of objective responses and patient survival outcomes.[12]

The application of a new treatment in clinical practice leads us to consider a new parameter: the effectiveness or "efficacy in the real life."[27] Hence, the importance of real-world studies like ours, whose aim is precisely to validate the recently developed FLOT chemotherapy regimen in resectable gastric cancer, thus providing a judgment of effectiveness.

Our study firstly presents four important limitations: the single-centre retrospective nature, the small sample size, the different duration of follow-up between the two treatment groups and the analytical complexity of the nutritional parameters. However, in the final processing of the results, we decided to base our work on the principles of methodological rigour to draw serious conclusions.

Of the 96 patients originally selected, data from 75 were admitted to statistical analysis. The primary endpoints of the study were therefore obtained from the sample of 75 patients by planning a comparative analysis between the FLOT group (42.7%) and the non-FLOT group (57.3%). Regarding secondary endpoints and in particular nutritional status, the sample size was further reduced to 42 patients to include those who had a nutritional assessment at diagnosis.

First, the epidemiology of our sample, in terms of incidence by sex and age, is in line with the general epidemiology of this cancer.[28] Analysing in detail the results of our study, all primary and secondary endpoints were better in the group of patients treated with the FLOT regimen. Although statistical significance was not always reached, the results obtained are in line with those of Al-Batran et al.[29] and others.[30–33]

Despite the declared limitations, our study allows us to draw some important conclusions: the pathological response rates, the care continuity rates and the survival outcomes were better in the group of patients treated with the FLOT regimen than in the comparison group. Nutritional status and overall toxicity profile were equally better in the FLOT group.

Therefore, our real-world, retrospective and monocentric experience demonstrates the effectiveness of the FLOT regimen in the treatment of patients with resectable gastric cancer and candidates for perioperative chemotherapy. Given this impact on clinical practice, we must be careful when applying the FLOT chemotherapy in particular categories of patients, for example, the elderly population. Although this category of patients in the study by Al-Batran et al.[12] constituted approximately a quarter of the overall population with a survival advantage similar to that reported in younger individuals, the toxicity profile in elderly patients continues to represent a real clinical problem. In this sense, our experience, in line with the data available in the literature, emphasizes the importance of carefully selecting patients to be candidates for the FLOT regimen.[34] Furthermore, scientific evidence suggests that patients with high levels of expression of PD-L1 or with high microsatellite instability can benefit from the addition of immunotherapy to perioperative chemotherapy treatment.[35] It also remains to be established whether the perioperative FLOT regimen can be considered superior to preoperative chemoradiotherapy (CROSS strategy) in cancers of the oesophagus-gastric junction.[36] There is also evidence demonstrating, more generally, a good response to preoperative chemoradiotherapy in patients with resectable gastric cancer and high lymph node involvement.[37]

Recently, the ESOPEC trial demonstrated that, in distal and junctional oesophageal adenocarcinomas, FLOT perioperative chemotherapy is superior to CROSS neoadjuvant chemoradiotherapy.[38] Another consideration, of a prognostic nature, concerns the fact that the FLOT regimen, whilst applying the cardinal principles of perioperative medical treatment and radical surgery, guarantees a cure rate of approximately 50% and this final result, understandably, is still far from being considered satisfactory.[39]

Conclusion

The FLOT regimen has certainly revolutionized the treatment of resectable gastric cancer; its effectiveness is confirmed but the problems exposed above invite us to be careful before considering it an absolute standard of care. In addition to the strictly oncological contents, the present study, in line with other scientific works, can represent a starting point for developing the area of nutritional care in the oncology field, recognizing an increasingly important role for nutrition, not only on an aetiological level but also as a factor modulating treatment tolerance, quality of life and patient prognosis.

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References

1. International Agency for Research on Cancer (IARC). Global Cancer Observatory. https://gco.iarc.fr/. Accessed February 3, 2025.
2. Yusefi AR, Bagheri Lankarani K, Bastani P, Radinmanesh M, Kavosi Z. Risk factors for gastric cancer: a systematic review. *Asian Pac J Cancer Prev*. 2018;19(3):591–603. https://doi.org/10.22034/APJCP.2018.19.3.591
3. Bosman FT, Carneiro F, Hruban RH, Theise ND. *WHO Classification of Tumours of the Digestive System*. Lyon: IARC Publications; 2010. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Digestive-System-2010
4. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand*. 1965:64:31–49. https://doi.org/10.1111/apm.1965.64.1.31
5. Ming SC. Gastric carcinoma: a pathobiological classification. *Cancer*. 1977;39(6):2475–2485. https://doi.org/10.1002/1097-0142(197706)39:6<2475::aid-cncr2820390626>3.0.co;2-l
6. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513(7517):202–209. https://doi.org/10.1038/nature13480

7. Giampieri R, Maccaroni E, Mandolesi A, et al. Mismatch repair deficiency may affect clinical outcome through immune response activation in metastatic gastric cancer patients receiving first-line chemotherapy. *Gastric Cancer*. 2017;20(1):156–163. https://doi.org/10.1007/s10120-016-0594-4
8. Costache S, Sajin M, Wedden S, D'Arrigo C. A consolidated working classification of gastric cancer for histopathologists (review). *Biomed Rep*. 2023;19(3):58. https://doi.org/10.3892/br.2023.1640
9. National Comprehensive Cancer Network. Gastric Cancer Guidelines 2024. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1434. Accessed February 3, 2025.
10. Misleh JG, Santoro P, Strasser JF, Bennett JJ. Multidisciplinary management of gastric cancer. *Surg Oncol Clin N Am*. 2013;22(2):247–264. https://doi.org/10.1016/j.soc.2012.12.013
11. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA Cancer J Clin*. 2021;71(3):264–279. https://doi.org/10.3322/caac.21657
12. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948–1957. https://doi.org/10.1016/S0140-6736(18)32557-1
13. Rogers JE, Ajani JA. Recent advances in the management of gastric adenocarcinoma patients. *Fac Rev*. 2023;12:2. https://doi.org/10.12703/r/12-2
14. Di Leo A, Marrelli D, Roviello F, et al. Lymph node involvement in gastric cancer for different tumor sites and T stage: Italian Research Group for Gastric Cancer (IRGGC) experience. *J Gastrointest Surg*. 2007;11(9):1146–1153. https://doi.org/10.1007/s11605-006-0062-2
15. Wu AW, Xu GW, Wang HY, Ji JF, Tang JL. Neoadjuvant chemotherapy versus none for resectable gastric cancer. *Cochrane Database Syst Rev*. 2007;(2):CD005047. https://doi.org/10.1002/14651858.CD005047.pub2
16. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11–20. https://doi.org/10.1056/NEJMoa055531
17. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med*. 2008;358(1):36–46. https://doi.org/10.1056/NEJMoa073149
18. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29(13):1715–1721. https://doi.org/10.1200/JCO.2010.33.0597
19. Mary F, Zaanan A, Boige V, et al. Perioperative chemotherapy with FOLFOX in resectable gas-troesophageal adenocarcinoma in real life practice: an AGEO multicenter retrospective study. *Dig Liver Dis*. 2016;48(12):1498–1502. https://doi.org/10.1016/j.dld.2016.07.022
20. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73(11):2680–2686. https://doi.org/10.1002/1097-0142(19940601)73:11<2680::AID-CNCR2820731105>3.0.CO;2-C
21. Thies S, Langer R. Tumor regression grading of gastrointestinal carcinomas after neoadjuvant treatment. *Front Oncol*. 2013;3:262. https://doi.org/10.3389/fonc.2013.00262
22. National Cancer Institute. DFS Definition 2022. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/dfs. Accessed February 3, 2025.
23. National Cancer Institute. OS Definition 2022. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/os. Accessed February 3, 2025.
24. Gadzik J. "How much should I weigh?" Quetelet's equation, upper weight limits, and BMI prime. *Conn Med*. 2006;70(2):81–88.
25. Adejumo OL, Koelling TM, Hummel SL. Nutritional Risk Index predicts mortality in hospitalized advanced heart failure patients. *J Heart Lung Transplant*. 2015;34(11):1385–1389. https://doi.org/10.1016/j.healun.2015.05.027
26. Lee SM, Ursino M, Cheung YK, Zohar S. Dose-finding designs for cumulative toxicities using multiple constraints. *Biostatistics*. 2019;20(1):17–29. https://doi.org/10.1093/biostatistics/kxx059
27. Boissel JP, Cogny F, Marko N, Boissel FH. From clinical trial efficacy to real-life effectiveness: why conventional metrics do not work. *Drugs Real World Outcomes*. 2019;6(3):125–132. https://doi.org/10.1007/s40801-019-0159-z
28. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol*. 2019;14(1):26–38. https://doi.org/10.5114/pg.2018.80001
29. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol*. 2016;17(12):1697–1708. https://doi.org/10.1016/S1470-2045(16)30531-9

30. Giommoni E, De Vita F, Pecora I, et al. Perioperative FLOT in resectable gastric cancer: Italian real-world data from the RealFLOT study. *J Clin Oncol*. 2020;38(Suppl. 4). https://doi.org/10.1200/JCO.2020.38.4_suppl.300
31. Glatz T, Verst R, Kuvendjiska J, et al. Pattern of recurrence and patient survival after perioperative chemotherapy with 5-FU, leucovorin, oxaliplatin and docetaxel (FLOT) for locally advanced esophagogastric adenocarcinoma in patients treated outside clinical trials. *J Clin Med*. 2020;9(8):2654. https://doi.org/10.3390/jcm9082654
32. Huemer F, Hecht S, Scharinger B, et al. Body composition dynamics and impact on clinical outcome in gastric and gastro-esophageal junction cancer patients undergoing perioperative chemotherapy with the FLOT protocol. *J Cancer Res Clin Oncol*. 2023;149(7):3051–3064. https://doi.org/10.1007/s00432-022-04096-w
33. Sakin A, Sahin S, Sakin A, Aldemir MN, Bayram I, Kotan C. The effect of obesity on response to neoadjuvant therapy in locally advanced gastric cancer. *Asian Pac J Cancer Prev*. 2020;21(9):2723–2731. https://doi.org/10.31557/APJCP.2020.21.9.2723
34. Adenis A, Samalin E, Mazard T, Portales F, Mourregot A, Ychou M. Does the FLOT regimen a new standard of perioperative chemotherapy for localized gastric cancer? *Bull Cancer*. 2020;107(1):54–60. https://doi.org/10.1016/j.bulcan.2019.12.005
35. Al-Batran SE, Lorenzen S, Thuss-Patience PC, et al. Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. *J Clin Oncol*. 2022;40(Suppl. 16). https://doi.org/10.1200/JCO.2022.40.16_suppl.4003
36. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074–2084. https://doi.org/10.1056/NEJMoa1112088
37. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: a randomized, phase III trial of perioperative ECF chemotherapy with or without preoperative chemoradiation for resectable gastric cancer: interim Results from an international, intergroup trial of the AGITG, TROG, EORTC and CCTG. *Ann Surg Oncol*. 2017;24(8):2252–2258. https://doi.org/10.1245/s10434-017-5830-6
38. Hoeppner J, Brunner T, Lordick F, et al. Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial). *J Clin Oncol*. 2024;42(Suppl. 17). https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA1
39. Spolverato G, Ejaz A, Kim Y, et al. Rates and patterns of recurrence after curative intent resection for gastric cancer: a United States multiinstitutional analysis. *J Am Coll Surg*. 2014;219(4):664–675. https://doi.org/10.1016/j.jamcollsurg.2014.03.062