GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 9 (354) Сентябрь 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 7-8 (352-353) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 9 (354) 2024

PERIOPERATIVE FLOT CHEMOTHERAPY FOR GASTRIC CANCER: A RETROSPECTIVE SINGLE-CENTER COHORT TRIAL

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Abstract.

Aim: To analyze the short- and long-term outcomes of surgical treatment of patients with gastric cancer who received perioperative chemotherapy (PCT) FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel).

Materials and methods: A retrospective cohort study included 146 patients who received surgical treatment at the Faculty Surgery Clinic of Sechenov University for gastric cancer (GC) and/or EGJC Sievert Type II–III in the period from January 2018 to December 2022. The main group consisted of 28 patients who received PCT FLOT; there were 118 patients operated "up front" in control group. Patients in both groups did not statistically differ in average age (p=0.110), ASA (p=0.541) and ECOG (p=0.12) status, localization (p=0.063), depth of invasion (p=0.099) and histological structure of tumor (p=0.787).

Results: In 92.9% of the patients in the main group and in 94.9% of the control group, R0 resection margins (p=0.750) were achieved. The number of dissected lymph nodes was statistically significantly higher in the main group (average 26 vs 21; p=0.010). There was no difference in intraoperative blood loss (p=0.294) and time of hospital stay (p=0.992); the average duration of surgery in the main group was 319 minutes, compared to 250 minutes in the control group (p<0.001). In the early postoperative period, the total number of complications (CD I–IV) was higher in the main group (p=0.031), however, there was no difference in the number of minor (CD I–II; p=0.094) and significant (CD III–V; p=0.142) complications. Postoperative mortality in the first 30 days after the surgical treatment was 3.6% and 2.5% in the main and control groups, respectively (p=0.764). The overall 6-month survival rate in the control group was 95.9% vs 90.9% in the main group, and the 12-month survival rate was 88.8% vs 75.7%, respectively. The reccurence-free 6-month survival rate in the control group was 96%, in the main group – 100%; the reccurence-free 12-month survival rate in the control group was 92.1%, in the PCT group – 93.3%.

Conclusion: PCT FLOT in the treatment of GC does not increase the level of intraoperative blood loss, the number of postoperative complications and the duration of hospital stay. The 6-month and one-year survival rates did not differ in the two groups. Considering that the majority of patients in the PCT group belonged to the cN+ category, with an initially less favorable treatment prognosis, it can be assumed that comparable survival results were achieved thanks to PCT.

Key words. Gastric cancer, esophagogastric junction cancer, perioperative chemotherapy, FLOT regimen, gastrectomy.

Introduction.

Gastric cancer (GC) ranks 4th in cancer incidence and 5th in mortality among all oncological diseases in the world [1]. In the Russian Federation 28,806 new cases of this disease were registered in 2021 [2]. The optimal method for treating locally advanced GC (MEGC) is a combination of perioperative chemotherapy (CT) and radical surgery [3]. Current studies have demonstrated that the FLOT treatment protocol is the most effective in improving oncological outcomes [4-6]. The use of this drug treatment regimen as adjuvant and neoadjuvant polychemotherapy (NCT) in patients with MEGC allowed to increase the median survival to 50 months and did not affect the level of adverse events caused by drug toxicity [4].

When studying the effect of NCT on the tumor process, several mechanisms capable of improving survival rates were demonstrated: a decrease in the number of viable tumor cells in the main tumor site and in regional lymph nodes (LN), early impact on potential distant micrometastases, and a decrease in the risk of vascular and perineural invasion [7,8].

At the same time, there is an opposite point of view regarding the relevance of performing NCT in patients with GC. Supporters of surgical treatment report a potential increase in the risk of intra- and postoperative complications due to edema and increased tissue bleeding, apparent adhesions in the area of the main vessels, as well as a decrease in the reparative properties of the body after NCT.

The aim of the study - a comparative assessment of the level of intra- and postoperative complications, overall survival (OS) and relapse-free survival (RFS) in radical surgeries for gastric adenocarcinoma and esophagogastric junction cancer (EGJC) depending on previous drug treatment.

Materials and Methods.

A retrospective single-center cohort study included 146 patients who underwent radical surgical treatment at the Burdenko Faculty Surgery Clinic of Sechenov University for gastric cancer (GC) and/or EGJC Sievert Type II–III in the period from January 2018 to December 2022.

The inclusion criteria were: age 18–75 years, voluntary informed consent for treatment, verified gastric cancer and/or EGJC Sievert type II–III (I–III stage according to TNM 8 – cT1b-4 cN0-3), general status of the cancer patient ECOG 0–3, absence of decompensated complications of the tumor process.

Exclusion criteria: M1 status (according to TNM 8), EGJC Sievert type I, early GC (Tis, T1a). Primary endpoints of the study: number of deaths, total number of postoperative complications (Clavien–Dindo classification – CD), number of patients with "positive" tumor resection margins (R1), OS and RFS.

Secondary endpoints of the study: the number of minor (CD I–II) and major (CD III–V) postoperative complications, surgery time, blood loss volume, hospital stay (bed days), repeated surgical interventions within 30 days after the surgery, tumor pathomorphism according to A. Mandard, response to

chemotherapy (RECIST), overall and relapse-free 6- / 12-month survival.

All the interventions performed on patients in this study met the ethical standards of the institutional and/or national research committee and were conducted in accordance with the 1964 Helsinki Declaration (revised in 2008) and its later amendments or comparable ethical standards. The authors declare no financial support for the study and preparation of the article.

The main group (the database was maintained prospectively) consisted of patients who received NCT with FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel) regimen at the preoperative stage (n=28). In case of a suspicion of tumor spread beyond the stomach wall, the presence of free fluid in the abdomen, or peritoneal carcinomatosis, diagnostic laparoscopy was performed with aspiration of peritoneal lavage to assess the spread of the tumor process. The depth of tumor invasion was determined based on the results of endosonography and multislice computed tomography of the abdominal organs with intravenous contrast. Before the operation, 4 courses were administered, with a 2-week interval between them, followed by a control examination to assess the clinical pathomorphosis and exclude progression of the disease. The depth of tumor invasion met the criteria: cT_{1b} in 1 (3.6%) patient, cT_2 in 12 (42.9%) patients, cT_3 in 9 (32.1%), and cT_4 in 6 (21.4%) patients. The criterion for regional lymph node involvement was an increase in their size to 8 mm or more along the short axis and/or changed architectonics (according to the data of multislice computed tomography with contrast enhancement and endosonography) [9]. In the main group, affected regional lymph nodes (cN+) were clinically diagnosed in 18 (64.3%) patients.

The general condition of patients in the main group was assessed according to the ECOG (Eastern Cooperative Oncology Group) scale. The main integral indicator for assessing the comorbidity of patients was the patient's physical status according to ASA (American Association of Anesthesiologists) classification.

Based on the electronic database, a control group was retrospectively formed for comparative analysis of immediate results of surgical treatment. It included patients operated without previous antitumor drug treatment (n=118) (Table 1).

The surgery in the main group was performed 6–8 weeks after the completion of chemotherapy. The effectiveness of NCT was analyzed according to RECIST 1.1 criteria. In case of suspected disease progression or multidirectional dynamics of response to chemotherapy, diagnostic laparoscopy was performed. The decision on the scope of surgical intervention, reconstruction method, and the surgical approach were made at a multidisciplinary oncological council, based upon current clinical guidelines for the treatment of gastric cancer [3,9,10]. The frequency and structure of postoperative complications were assessed according to the Clavien–Dindo scale. The degree of therapeutic pathomorphism of the tumor after NCT was assessed according to the A. Mandard scale. Statistical processing was performed using STATA (17.1, StataCorp LLC, College Station, TX). Depending on the type of data and the normality of distribution, various criteria were used to compare two samples: Pearson's $\chi 2$ criterion, Student's t-test, regression analysis methods and multivariate statistical evaluation methods. A reliably significant difference was considered to be $p<0.05$.

Results.

Patients in the main and control groups did not differ statistically significantly in the severity of concomitant diseases (according to the ASA scale; p=0.541), as well as in the ECOG status (p=0.12). In 4 patients (14.3%) of the main group, EGJC was diagnosed; in the control group there were 14 such patients

Table 1. *Clinical characteristics of patients in the main and control groups.*

Indicator	**Main group, n=28**	**Control group, n=118**	***p*-value***
Average age, years	62±8,68	59±11,85	0,110
Age, n (%)			
<60 years	13 (29,7)	35 (46,4)	0,103
60–75 years	15 (70,3)	83 (53,6)	
ASA classification, n (%)			
I/II/III	9 (32,2)/14 (50,0)/5 (17,9)	38(32,2)/48(40,7)/32(27,1)	0,541
ECOG scale, n (%)			
0/1/2/3	5 (17,9)/14 (50,0)/9 (32,1)/0(0)	45(38,1)/48(40,7)/22(18,6)/3(2,5)	0,120
Tumor localization, n (%)			
EGJC	4 (14,3)	14 (11,9)	0,063
Distal third	8 (28,6)	48 (40,7)	
Middle third	9 (32,1)	48 (40,7)	
Proximal third	2 (7,1)	3 (2,5)	
Total damage	5 (17,9)	5 (4,2)	
Depth of invasion (cT), n (%)			
T_{1b} / T_2 / T_3 / T_4	1 (3,6) / 12 (42,9)/ 9 (32,1)/ 6 (21,4)	28 (23,7)/ 43 (36,4)/ 32 (27,1)/ 15 (12,7)	0,099
Regional lymph nodes (cN), n (%)			
cN_0 / cN_+	10 (35,7) / 18 (64,3)	107 (90,7) / 11 (9,3)	<0,001
Histological structure of the tumor, n (%)			
G1 / G2/ G3/ G4	1 (3,6) / 8 (28,6)/ 9 (32,1)/ 1 (3,6)	10 (8,5) / 23 (19,5)/ 43 (36,4)/ 4 (3,4)	0,787
"signet-ring" cells	9 (32,1)	38 (32,2)	

**indicates the observed value regarding the probability of rejecting the hypothesis of equality of distributions for the considered indicators between respondents in the main and control groups.*

(11.9%). In the other cases, the tumor was localized in different parts of the stomach, however, no significant differences in the distribution of tumor localization between patients in the main and control groups were found (p=0.063).

According to RECIST 1.1 criteria, 24 (85.8%) patients had a partial response, and 2 (7.1%) had stabilization of their condition. Two (7.1%) patients had disease progression manifested by an increase in the size of the primary tumor.

The rate of minimally invasive surgeries (laparoscopic or robot-assisted) in the main group was 25.0%; in the control group - 27.1% (p = 0.974). The control and main groups did not statistically differ in the resection volume of interventions (p = 0.154). In the main group, D2 lymph node dissection was performed in all the study cases. In the control group, D1 lymph node dissection was performed in 22 (18.6%) patients.

Patients from both groups who underwent distal gastrectomy more often underwent reconstruction according to Billroth II. After gastrectomy, the most common method of restoring continuity of the gastrointestinal tract was the Roux-en-Y method. It was used in 62.5% of the patients in the main group and in 85.1% of the control group (p=0.089). The structure of the volume of surgical interventions is presented in Table 2.

R_0 resection margins were achieved in 92.9% of the patients in the main group and in 94.9% of the control group. The number of lymph node dissections was statistically significantly higher in the group of patients who received NCT (the average was 26 in the main group versus 21 in the control group; p=0.010; median values were 24 versus 20); Table 3.

The degree of therapeutic pathomorphosis in the tumor and lymph nodes during histological examination was assessed in 23 patients of the main group. Response to treatment was diagnosed in 22 patients: 6 (26.1%) patients had grade II regression according to the A. Mandard scale, 9 (39.1%) had grade III, and 7 (30.4%) had grade IV.

There were no differences in intraoperative blood loss (p=0.294) and time of hospital stay (p=0.992) between the two groups of patients. However, the average duration of surgery in the main group was 319 min, which is significantly longer than in the control group - 250 min; p<0.001. In the early postoperative period, I–V grade complications according to Clavien-Dindo were diagnosed in 9 (32.1%) patients of the main group and in 28 (17.8%) of the control group; p=0.091; 4 (14.3%) and 10 (8.5%) patients had minor complications (CD I–II); 5 (17.9%) and 10 (8.5%) patients had major complications (CD III–V); postoperative mortality in the first 30 days after the surgical treatment was 3.6% and 2.5% in the main and control groups, respectively; p=0.764.

In order to obtain more reliable results from the comparative study of the groups of patients based on the most significant indicators from the clinical and oncological points of view (postoperative complications, the presence of a "positive" resection margin R1, relapse and/or progression of gastric cancer), we conducted quasi-randomization via matching procedure with the selection of the nearest neighbours.

The following characteristics of observation similarities were used in the matching procedure: age, invasion depth, clinical

Table 2. *Characteristics of operations performed in the main and control groups.*

Indicator	**Main group, n=28**	**Control group, n=118**	***p-value****
Approach, n (%)			
Open procedure	21 (75,0)	86 (72,9)	0,974
Laparoscopic procedure	5 (17,9)	23 (19,5)	
Robot-assisted	2 (7,1)	9 (7,6)	
Types of surgeries, n (%)			
Gastrectomy	16 (57,1)	47 (39,8)	0,154
Distal resection	10 (35,7)	66 (55,9)	
Proximal resection	2 (7,2)	5 (4,3)	
Reconstruction after gastrectomy, n (%)			
Roux-en-Y	10 (62,5)	40 (85,1)	0,054
Double tract reconstruction	2 (12,5)	3 (6,4)	0,434
Esophagojejunal anastomosis by Gilyarovich-Shalimov	3 (18,8)	1 (2,1)	0,019
Jejunogastroplasty by Zakharov	1 (6,3)	3 (6,4)	0,985
Reconstructions after distal gastrectomy, n (%)			
Billroth I	1 (10,0)	27 (40,9)	0,059
Roux-en-Y	7 (70,0)	27 (40,9)	0,085
Hoffmeister-Fensterer modification	2 (20,0)	12 (18,2)	0,890
Lymphadenectomy, n (%)			
D_1 / D_2	0 (0) / 28 (100)	22 (18,6) / 96 (81,4)	0,013
Average number of lymph node dissections, n±CO	26±8,6	21±8,4	0,010
Median number of lymph node dissections, n (min–max)	24 (15–47)	20 (3–48)	
Positive resection margins, n (%)			
R_0 / R_1	26 (92,9) / 2 (7,1)	112 (94,9) / 6 (5,1)	0,667

**indicates the observed value regarding the probability of rejecting the hypothesis of equality of distributions for the considered indicators between respondents in the main and control groups.*

Table 3. *Short-term results of surgical treatment.*

Indicator	**Main group, n=28**	**Control group, n=118**	***p-value****
I–V grade complications by Clavien–Dindo, n (%)	9 (32,1)	21 (17,8)	0,091
I–II grade complications (minor) by Clavien–Dindo, n (%)	4 (14,3)	10 (8,5)	0,348
III–V grade complications (major) by Clavien–Dindo, n (%)	5 (17,9)	10 (8,5)	0,142
Lethal outcome, n (%)	1 (3,6)	3 (2,5%)	0,764
Repeated surgery, n (%)	3 (10,7)	9 (7,6)	0,593
Surgery time, min., average [95% CI]	319 [286; 352]	250 [237; 264]	<0,001
Blood loss, ml, average [95% CI]	252 [199; 305]	226 [207; 245]	0,294
Hospital stay, days, average [95% CI]	17 [13; 20]	17 [16; 18]	0,992
NCT response (RECIST 1.1), n (%)(main group)			
CR/ PR /DP /SC*		0 / 24 (85,8)/ 2 (7,1)/ 2 (7,1)	
Degree of pathomorphosis according to A. Mandard, n (%) (main group)			
TRG1/ TRG2/ TRG3/ TRG4/ TRG5		0 / 6 (26,1)/ 9 (39,1)/ 7 (30,4)/ 1 (4,4)	

Note: *Here and further in Tables 4,5. CI – confidence interval; * CR - complete response; PR - partial response; DP - disease progression; SC –stabilization of the condition.*

Table 4. *Estimates of the average according to individual characteristics for the main and control groups, taking into account the selection of nearest neighbors by the matching procedure.*

Indicator	**Control group**		**Main group**		***p****
	Average	**95% CI**	**Average**	**95% CI**	
I–V grade complications by Clavien–Dindo	0,162	[0,101; 0,223]	0,500	[0,274; 0,726]	0,031
Minor complications by Clavien-Dindo (grade I–II)	0,107	[0,052; 0,162]	0,369	[0,124; 0,615]	0,094
Major complications by Clavien-Dindo (grade III–V)	0,079	[0,034; 0,124]	0,304	[0,064; 0,545]	0,142
Presence of relapse or worsening (progression)	0,267	[0,158; 0,376]	0,194	[0,013; 0,374]	0,560
Positive resection margin R_1	0,083	[0,017; 0,149]	0,116	[-0,074; 0,307]	0,750

** Indicates the significance level of the tested hypothesis regarding the equality of the mean values of the corresponding indicator.*

signs of regional lymph node involvement and histological structure of the tumor.

The matching quality can be represented graphically using distributions before and after the selection of matching pairs: parametric distribution density (Figure 1a), nonparametric distribution (box plot; Figure 1b). The procedure for selecting a control group based on the "similarity degree" with patients in the main group (the closest 2 and 3 neighbours) allows constructing a sample of patients that are maximally similar in terms of the listed parameters. There were 80 patients from control included in matching process.

When assessing the average values of the indicators (Table 4), no differences were noted between the groups in the incidence of relapse or disease progression (p=0.560) and the presence of a positive resection margin R1 (p=0.750).

The total number of postoperative complications (CD I–IV) was higher in the main group of patients (p=0.031). However, while considering minor (CD I–II) and significant (CD III–V) complications separately, we did not observe a statistically significant difference between their numbers (Table 4).

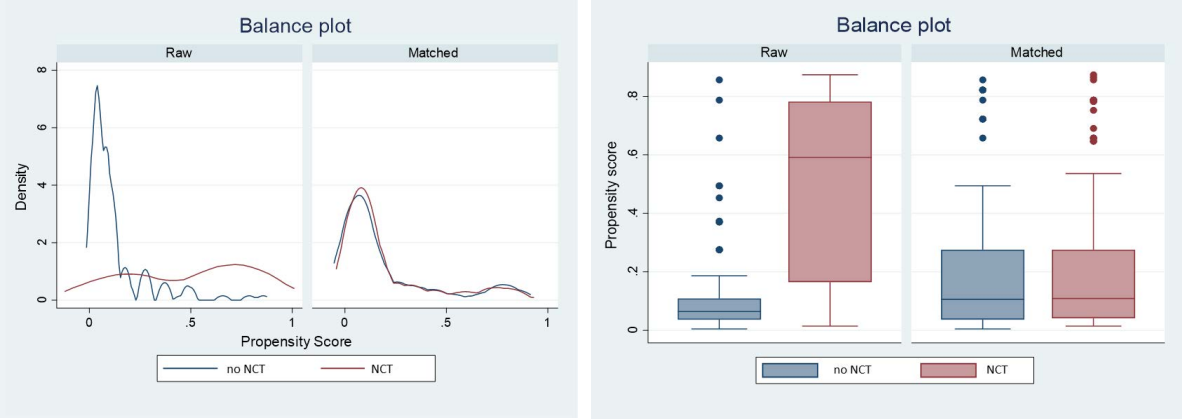
Among the key indicators of the effectiveness of cancer patients treatment are OS and RFS. Six-month OS in the control group was 95.9% versus 90.9% in the main group, 12-month OS was 88.8% versus 75.7%, respectively (Figure 2). Nonparametric survival models in the main and control groups did not differ statistically significantly.

The six-month RFS in the control group was 96%, in the main group – 100%; the 12-month RFS in the control group was 92.1%, in the group with NCT – 93.3% (Figure 3). Nonparametric RFS models in the main and control groups statistically significantly differed at 10% level. In the subsequent period, there was a significant decrease in both overall and relapse-free survival of patients in the main group, as compared with the control group. From our point of view, the absence of statistically significant differences in 6- and 12-month OS and RFS between the two groups of patients was due to the fact that the patients we referred for NCT had a priori clinical stage of the tumor process, and, accordingly, the survival prognosis was worse than those of the comparison group. And we cautiously assume that without NCT, the survival rates of patients included in the main group could have been even lower.

Discussion.

The advantages of performing NCT with FLOT regimen in GC and EGJC have been proven by a number of international studies. Moreover, this treatment regimen is prescribed in clinical guidelines [3,9,10]. Nevertheless, the surgical oncology community is still debating the increased risks of developing intra- and postoperative complications among patients who have undergone NCT.

The results we obtained indicate that the use of NCT with FLOT regimen does not increase the level of intraoperative



a **b**

Figure 1. *Distribution of characteristics for the main and control groups before and after matching pairs.* ***a -*** *balance plot Density;* ***b -*** *balance plot Propensity score.*

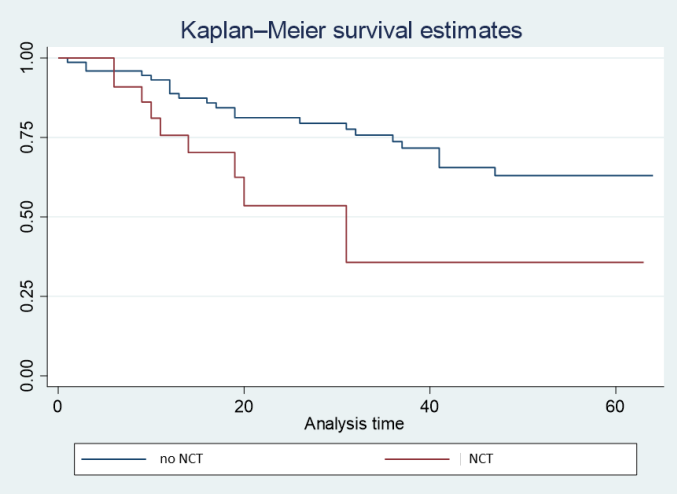


Figure 2. *Plot of survival function for the main and control groups (log-rank test: chi2 = 5.16; p-value=0.0232).*

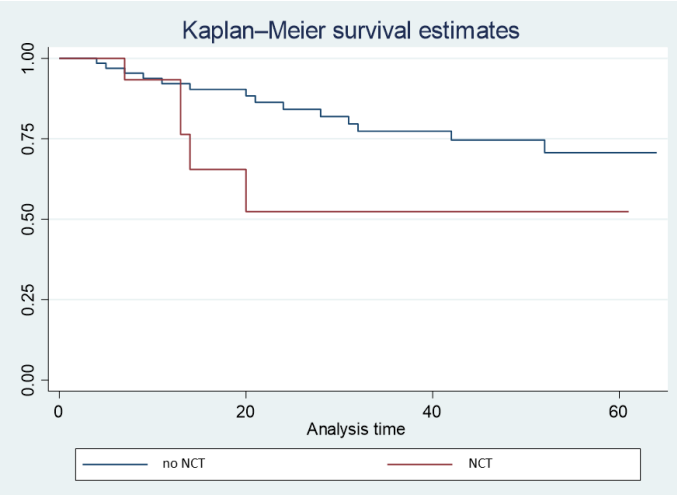


Figure 3. *Plot of the RFS function for the main and control groups (log-rank test: chi2 = 3.54; p-value=0.0601).*

blood loss (p=0.294) and the time of hospital stay (p=0.992). At the same time, the data recorded by R. Tu et al. [11] indicate a reduced risk of intraoperative bleeding (p<0.001) and a shorter surgery time (p<0.001), which does not contradict our thesis regarding the safety of NCT. However, in contrast to the work of R. Tu et al., we recorded that the average duration of the operation was significantly higher in the NCT group (319 versus 250 min.; p<0.001). From our point of view, this may be partly due to the development of inflammatory and cicatricial changes in tissues as a result of NCT.

The effect of NCT on the level of interstitial fibrosis is a controversial issue. There are studies describing changes in tissues after NCT, for example, Y. Gao et al. demonstrate adhesions and fibrosis, edema and microhemorrhages in the thorax after neoadjuvant chemoimmunotherapy in patients with non-small cell lung cancer [12]. The work of H. Yang et al. describes changes in surrounding tissues observed intraoperatively in patients with gastric adenocarcinoma. The authors distinguish several degrees of fibrosis, edema and effusion in the paragastric tissue, metastatically affected LNs and the primary tumor [13]. According to L. Marano et al., fibrosis caused by neoadjuvant chemotherapy is especially pronounced in the peripancreatic and retroperitoneal areas. Their review states that in case of sclerosis and fibrosis of tissues caused by chemotherapy, surgeons have to perform lymphadenectomy more thoroughly. Since peripheral metastatic nodes can be difficult to palpate during surgery, the number of dissected LNs varies greatly depending on the surgeon's skills [14]. Our results support the data of a meta-analysis conducted by J. Yu et al., who found that neoadjuvant chemotherapy followed by surgery is associated with a longer surgery time (p < 0.0001) as compared with surgical treatment at stage I [15].

In our study, the rate of postoperative mortality in the first 30 days after surgery was 3.6% in the main group and 2.5% in the control group; p=0.764. German colleagues S. Al-Batran et al. obtained similar results in their study, recording 2% and 4% 30-day mortality, respectively [4]. In addition, the study by I. Avdyukhin et al. showed 0% 30-day mortality, which proves the safety and reliability of NCT [16].

In our work, we did not obtain a statistically significant difference between the number of minor (CD I–II) and significant (CD III–V) complications in the studied groups of patients. The data obtained by H. Bozkurt et al., where the complications were detected in 53.8% of cases in the main group and 39.4% in the control group; p=0.186 [17], are consistent with our results. The estimates given in the article by V. Skoropada et al. [18] also confirm an insignificant difference in the number of complications, 38% (n=13) in the main group and 32% (n=11) in the control group. In addition, in the study conducted by A. Avgustinovich et al., no complications were observed in patients [5].

Despite the positive results obtained by us and confirmed by other studies, there are still disagreements regarding the relevance of using the FLOT regimen. Thus, colleagues from Korea led by Y. Kang point out a high percentage of grade 3 and 4 neutropenia, which raises concerns about significant hematotoxicity [19]. At the same time, less than 1/2 of the patients participating in this study (46%) fully received the prescribed cycles [19]. For comparison, we can provide the data obtained in the study of I. Avdyukhin et al., indicating controlled toxicity, as well as a low degree and number of adverse events (56%) [16]. The results of colleagues give reason to believe that drug and nutritional support of patients undergoing NCT plays an important role. It is worth mentioning that the somatic status of patients before the start of the surgical stage of treatment largely depends on the competence and alertness of chemotherapists who carried out preoperative drug antitumor treatment.

Conclusion.

NCT-FLOT in the treatment of GC and EGJC does not increase the level of intraoperative blood loss, the number of postoperative complications and the duration of hospital stay. A statistically significant increase in the surgery time in the main group of patients is most likely associated with intraoperative technical difficulties caused by cicatricial and inflammatory tissue changes due to NCT. Six-month and one-year survival in the main and control groups do not have statistically significant differences. Considering that most patients in the NCT group belonged to the cN+ category, and, therefore, had a less favourable prognosis for life expectancy, it can be assumed that comparable survival rates were achieved precisely due to the use of NCT. At the same time, according to many randomized studies and meta-analyses devoted to the issue of using NCT-FLOT in GC, this method reliably increases the median RFS and overall life expectancy. The results of conducting NCT-FLOT in patients among domestic population require further study and balanced assessment.

Disclosure of interests: The authors declare no obvious or potential conflicts of interest related to the publication of this article.

Source of funding: The authors declare no external funding for the research and publication of the article.

Compliance with ethical principles: The study protocol was approved by the local ethics committee of Sechenov First Moscow State Medical University (Sechenov University). The approval and the protocol procedure were obtained according to the principles of the Helsinki Convention.

Informed consent for publication: Patients signed a voluntary informed consent form for the publication of their medical information.

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