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The role of neoadjuvant systemic and regional chemotherapy in the treatment of gastric cancer: single tertiary level center experience of the last decade

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Abstract

Background: Gastric cancer is a significant global health challenge with high incidence and mortality rates in certain regions. Despite advancements in diagnostic and therapeutic approaches, the prognosis for advanced gastric cancer remains poor. This study evaluates the impact of neoadjuvant chemotherapy and hyperthermic intraperitoneal chemoperfusion (HIPEC) on outcomes in patients with gastric cancer treated at a single center.

Methods: A retrospective analysis of 343 gastric cancer patients treated between 2015 and 2023 was conducted. Patients were stratified based on chemotherapy protocols (CX or FLOT) and the use of HIPEC. Short-term outcomes, including complications and hospital stay, and long-term outcomes, such as overall survival, were assessed.

Results: FLOT-based neoadjuvant chemotherapy improved survival, with a 5-year survival rate of 60%, compared to 40% with CX-based regimens and 31% in patients without neoadjuvant therapy. HIPEC, employed in selected patients with advanced disease, demonstrated promising early results, doubling the median survival compared to systemic chemotherapy alone. Neither neodjuvant systemic nor regional chemotherapy does not appear to increase the perioperative morbidity or mortality.

Conclusions: Neoadjuvant chemotherapy should be an essential component of the multimodal treatment of gastric cancer, while prophylactic HIPEC represent promising strategy for improving survival in locally advanced gastric cancer in selected patients.

Introduction

Gastric cancer was the fifth most common malignant tumor in the world in 2020 with approximately 1.1 million new cases, and is the fourth leading cause of cancer death, with around 800000 deaths [1, 2].

Over the past decades, the incidence and mortality due to stomach cancer have substantially declined in many countries [1, 2]. This trend could be linked to improved lifestyle factors, early diagnosis of *H. pylori* infection, and timely eradication of this bacterium [2]. However, gastric cancer incidence and mortality correlate with increasing age (aging population) and are relatively rare in persons of both genders younger than 45 years. [1–3].

There is also a considerable geographic variation in gastric cancer incidence with the highest

rates in Eastern Asia (22.4 per 100000 people), followed by Central and Eastern Europe (11.3 per 100000 people), and South America, Polynesia and Western Asia (equally about 8.6 per 100000 people) [1, 2].

Although Lithuania is a part of the geographic region with high gastric cancer incidence, early diagnosis of this disease remains a challenge in our country due to the absence of a dedicated screening program. Consequently, gastric cancer is most commonly diagnosed at advanced stages, necessitating complex multi-modal treatment approaches. Despite advancements in diagnostic techniques, the early detection

rate of gastric cancer remains low, likely due to the lack of specific clinical signs [4]. In Lithuania, the standard diagnostic criteria for gastric cancer include endoscopy and histological verification of biopsy samples. It is important to note that endoscopy is not used as a screening method but is instead performed for other indications, such as anemia of unknown origin, symptoms of gastritis, and gastroesophageal reflux disease (GERD), unexplained weight loss, etc.

Chemotherapy plays a crucial role in the treatment of gastric cancer, particularly in advanced stages. It is used as neoadjuvant therapy to shrink tumors before surgery. From the surgeon's perspective, the main objective was to improve the R0 resection rate. However, an analysis of clinical data reveals that the effects of neoadjuvant chemotherapy are similar to those of adjuvant chemotherapy, as both improve survival by eradicating micrometastases [5].Adjuvant chemotherapy is used to eliminate residual cancer cells after surgery, or as palliative treatment to control disease progression and improve quality of life in metastatic cases. Combining chemotherapy with other modalities, such as targeted therapy or immunotherapy, can further enhance treatment efficacy, however, the radical surgery so far remains the key component of the curative treatment of gastric cancer [6, 7].

Another important aspect is the emphasis on patient-centered treatment, where patients are given the opportunity to participate in the selection of treatment strategies. Advances in medical research today enable the possibility of tailoring drug treatments to individual patients in the future, based on their unique cellular and molecular profiles, extent of the disease at the time of diagnosis. Employment of intra-peritoneal chemotherapy for the preventation or treatment of peritoenal carcinomatosis is one of the areas for application of personalized medicine in the treatment of gastric cancer. Peritoneal metastasis (PM) have an incidence of 10–20% in patients with gastric cancer, and even up to 40% in patients with UICC Stage III gastric cancer. In order to minimize the locoregional recurrences after surgical treatment of locally advance gastric cancer, the protocols for normothermic (NIPEC) and hyperthermic intraperitoneal chemotherapy (HIPEC) were devised and are widely used in Asia and less frequently in the United States and Europe [8].

A multidisciplinary approach for planning of the gastric cancer treatment is mandatory. According to the tumor size, its histological verification, regional lymph node involvement, the presence of distant metastases, and the patient’s general condition, the multidisciplinary team selects the optimal multimodal treatment strategy for gastric cancer [6]. In our study, we aimed to evaluate the impact of a comprehensive treatment approach, mainly introduction of more systematic neoadjuvant chemotherapy and intraoperative prophylactic heated intraperitoneal chemoperfusion (HIPEC) in selected cases, on the management of advanced gastric cancer.

Patients and methods

This was a retrospective, non-randomized, single-center cohort study. Data were collected at the Clinic of Surgery, Lithuanian University of Health Sciences Hospital, using a specially developed and maintained database from January 1, 2015, to December 31, 2023. All patients treated during this period at the

Hospital of the Lithuanian University of Health Sciences were included. In the period from 2015 to 2019 selected patients received neoadjuvant chemotherapy based on cisplatin and capecitabine (CX) regimen, from 2020 onwards neoadjuvant chemotherapy employing fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) was used. Prophylactic hyperthermic intraabdominal chemoperfusion (HIPEC) was also employed for treatment of selected patients with locally advanced disease and/or limited peritoneal carcinomatosis. All patients provided written informed consent, and the study was approved by the local ethics committee (No. BEC-MF-87). Diagnoses were preoperatively confirmed for all patients through pathological examination of gastroscopic biopsy samples.

Before surgery, chest, abdominal, and pelvic CT examinations were performed for all patients to determine the clinical diagnosis and rule out distant metastases. Serologic markers, including CEA, CA19-9, and CA 125, were also evaluated. Treatment tactics for each patient were discussed by a multidisciplinary team prior to surgery.

All operations were performed by four experienced upper gastrointestinal tract surgeons. Depending on tumor location, standard total gastrectomy (for adenocarcinomas involving the proximal third of the stomach) or subtotal gastrectomy (for adenocarcinomas of the distal and middle thirds of the stomach) was routinely performed, accompanied by D2 lymphadenectomy and Roux-en-Y reconstruction, in accordance with the Japanese Gastric Cancer Treatment Guidelines [9, 10]. Surgical procedures involved partial or total gastrectomy based on the feasibility of achieving an adequate proximal resection margin (≥ 6 cm). Pathological staging was classified according to the Japanese Classification of Gastric Carcinoma [11]. The same postoperative treatment protocols were applied to all patients. The operating surgeon determined the appropriate timing for initiating a soft diet and discharging patients, based on their individual conditions.

The study was divided into two parts: (1) the impact of neoadjuvant chemotherapy using the CX and FLOT protocols on the treatment of gastric cancer, (2) the first results of HIPEC on the treatment of locally advanced gastric cancer.

During the study period, 343 consecutive patients were included according to the following inclusion criteria: (1) histologically confirmed gastric adenocarcinoma; (2) diagnosis based on the UICC TNM staging classification; (3) curative D2 lymphadenectomy performed; (4) availability of a complete medical record; and (5) postoperative follow-up data.

The study population was divided into three groups based on the type of chemotherapy received:

Group 1: 108 patients who received neoadjuvant chemotherapy according to CX protocol.

Group 2: 187 patients who did not receive neoadjuvant chemotherapy.

Group 3: 48 patients who received neoadjuvant chemotherapy according to FLOT protocol.

Short-term outcome variables included operative time, the number of harvested lymph nodes, intraoperative and postoperative complications, and hospital length of stay. Long-term outcomes were evaluated based on disease-free survival time.

Additionally we have concisely analyzed our first cohort of 28 patients who underwent surgery with HIPEC. In this group all patients received 4 cycles of FLOT neoadjuvant chemotherapy as well as systemic treatment in the postoperative period.

Neoadjuvant and Adjuvant Treatments

Neoadjuvant chemotherapy was given in patients with clinically (CT scan) identified stage

≥ T2N1. In the CX regimen group patients received a combined intravenous cisplatin 80mg/m^2 once a day and capecitabin 1000mg/m2 orally twice a day. The same scheme of adjuvant chemotherapy was given in patients with pathologically identified stage ≥ II. Adjuvant chemotherapy was given 3–4 weeks after surgery. In FLOT regimen group chemotherapy was administered in 4 cycles. Each cycle lasted 14 days, and the regimen was repeated every two weeks. On Day 1 (Infusion Day) patients received docetaxel 50 mg/m² intravenously (IV) over 1 hour; oxaliplatin 85 mg/m² IV over 2 hours, starting immediately after docetaxel; leucovorin (folinic acid) 200 mg/m² IV over 2 hours, administered concurrently with oxaliplatin; 5-fluorouracil (5-FU) 2600 mg/m² continuous IV infusion over 24 hours, started immediately after leucovorin and oxaliplatin. Day 2 to Day 14 no chemotherapy is given, allowing for recovery and monitoring of side effects. Adjuvant chemotherapy based on the same scheme was given 3–4 weeks after surgery.

The main reasons why patients did not receive neoadjuvant chemotherapy were patient‘s refusal, gastric cancer complications (stenosis or bleeding). Surgical treatment was planned 4–6 weeks after neoadjuvant chemotherapy.

No patients died during neoadjuvant chemotherapy. All patients who underwent neoadjuvant treatment later proceeded to surgery.

Statistical analysis

Statistical analysis was performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, USA). The data are presented as mean ± Standard deviation or median and range. The cumulative survival was determined by the Kaplan-Meier method, and univariate comparisons between the groups were performed using the log-rank test. For comparison between groups, the Mann–Whitney test or Student’s t test were employed where appropriate. $P < 0.05$ was considered statistically significant.

Results

Data from 343 patients who were followed up postoperatively were analyzed. The distribution of patients across groups is shown in Table 1. There were no significant differences between the groups in terms of

gender, type of operation (open vs. laparoscopic), or postoperative complications (Table 2). However, a significant difference was observed between the groups regarding the use of postoperative (adjuvant) chemotherapy. Patient ages ranged from 33 to 92 years, with a mean age of 66.5 ± 15.05 years. Patients who received neoadjuvant chemotherapy were statistically significantly younger.

Survival analysis

The survival time was calculated from the date of operation until the date of death. This survival calculation was selected because there were no deaths during neoadjuvant chemotherapy. The median follow-up period in group 1 was 46 months (with an interval of 27–95 months), and in group 2 it was 64 months (with an interval of 12–96 months). The total 5-year survival rate in group 1 was 40%, while in group 2, it was 31%. When comparing these two groups based on treatment method, no significant difference was identified ($p = 0.217$) (Fig. 1). However, when calculating the total survival time between groups at different stages of illness, a statistically significant difference was found when comparing patients with stage II cancer ($p = 0.01$) (Fig. 2). The median survival time in group 1, was not calculated because more than 50% of the patients were alive until the end of the follow-up period. In group 2, the median survival time was 34.0 ± 17.4 months. No significant difference was identified between the groups with stage III and IV cancer. In stage III, group 1 had a median survival time of 40.0 ± 13.5 months, while group 2 had a median survival time of 21.0 ± 13.2 months ($p = 0.596$). When comparing stage IV patients, group 1 had a median survival time of 5.0 ± 2.8 months, while group 2 had a median survival time of 8.0 ± 0.8 months ($p = 0.144$).

In FLOT neoadjuvant treatment group (group 3) the median follow-up period 47 months (with an interval of 4–81 months), the mean overall survival rate during the follow-up time reached 58 ± 4 months, with 60% 5-year survival rate. Survival analysis stratifying data according to the stages of the diseases shows significantly better survival rates, especially in the more advanced stages of the disease when compared to CX chemotherapy group (table 3, Fig. 3). In the subgroup analysis, only stage IV patients had significantly shorter survival when compared to stage I-III.

First experience with HIPEC for management of locally advanced gastric cancer

In 2020 we started employing HIPEC as part of multimodal treatment of locally advanced cancer in selected patients. This treatment option was offered to younger patients (mean age 51 [range 21–69] in good physical status with mean BMI of 22 and only 1/3 of them having non-significant comorbidities like hypertension, dyslipidemia, diabetes. Majority of patients were male (18 of 28) and had stage 3a-4 disease as confirmed by preoperative CT. Prophylactic HIPEC was performed when no peritoneal carcinomatosis was detected during operation (16 patients [57%]) and curative HIPEC was offered to those who had limited peritoneal carcinomatosis (mean PCI 4 [1–11]) when radical surgery was still possible (12 patients [43%]). More than half of patients had T4 tumor with N3-4 nodal involvement, thus

9 patients (32%) underwent multivisceral surgery at the time of gastrectomy (e.g. distal pancreatectomy with splenectomy, colon resection, non-anatomical liver resection, etc.). On other hand in 16 patients (57%) had fully laparoscopic operation with application of minimally invasive HIPEC and in 1 patient (3,5%) pathology revealed R1 resection. Although the mean OR time was 6 hours, in our experience addition of HIPEC did not significantly increase the perioperative risks as Clavien-Dindo grade 3–4 complications were observed only in 3 patients (10%) and one postoperative death (3,5%) was recorded within 60 days of follow-up (due to COVID-19 pneumonia). The mean hospital stay was 11 days and only one patient required treatment in ICU (all the patients spent 1–2 nights in high dependence unit postoperatively for monitoring and initial treatment). In this selected population the mean survival is 23 (± 3) months with 50% of patients being alive at the last check-up (mean follow-up 33 months).

Discussion

Gastric cancer treatment strategies vary across different regions of the world. In many countries, these strategies are well described in national guidelines [12, 13]. Neoadjuvant chemotherapy is a treatment option for advanced stages of gastric cancer. However, the majority of available data on gastric cancer treatment originates from Eastern countries, including Japan, South Korea, and China. Several factors may contribute to the differences observed between Eastern and Western populations, including age and disease stage, tumor biology, socio-epidemiological factors, and ethnic characteristics. These variations can significantly impact the effectiveness and outcomes of neoadjuvant chemotherapy across populations. Thus, it is crucial to consider these factors when interpreting research findings and applying them to specific patient populations [14].

Brenkman et al. [15] stated that the majority of surgeons (84.4%) worldwide report the application of neoadjuvant chemotherapy or chemoradiation prior to gastrectomy. This study also reported that the percentage of surgeons in Europe (76.8%) using neoadjuvant therapy (2013–2014) is higher compared to the period of 2011–2012, where more than 60% of patients did not receive neoadjuvant therapy [16].

Our surgical clinic performs 70–80 radical procedures (total or subtotal gastrectomies) annually. Neoadjuvant chemotherapy was introduced as a routine procedure at our hospital at the beginning of 2017. From 1990s till early 2000 the changes of the gastric cancer treatment outcomes in our center were largely influenced by the improved preoperative assessment and modernization of the surgical techniques and technological advancements. Comparison of consecutive patient groups from 1994 – 2000 (Group I – 273 patients) and 2001 – 2007 (Group II – 284 patients) in our center showed that with the time the complication rates (9.5% vs. 3.9%, $p = 0.02$) and 30-day mortality (5.5% vs. 1.4%, $p = 0.02$) significantly decreased and the length of hospital stay shortened (22.6 ± 28.9 vs. 16.2 ± 17.01 days, $p = 0.001$). Analysis of 1-year and 5-year survival rates demonstrated that after year 2000 the survival also improved significantly (71.5% vs. 50.2% and 35.6% vs. 23.4%) [17].

A more recent study conducted in our hospital demonstrated that the advancement of surgical technologies and operative technique positively impacts the outcomes of the patients with gastric

cancer: laparoscopic gastrectomy is comparable to open surgery regarding postoperative morbidity, mortality, and long-term outcomes (including survival) [18]. Nevertheless, it results in a shorter hospital stay and may determine earlier initiation of adjuvant chemotherapy. Many other studies demonstrate that the outcomes of laparoscopic gastrectomies are non-inferior or even better than open surgery in terms of perioperative complications and even cancer specific survival [19, 20]Our first data also indicates that adding HIPEC to extended surgery in selected patients does not substantially increase perioperative morbidity and/or mortality but further extends the pool of patients with advanced disease in whom radical surgery is feasible. The early survival data of patients with advanced GC after HIPEC appears to be promising and at least doubles the OS of 11–12 months achieved by systemic chemotherapy alone. However, the data from large series shows that 25% of patients with stage III GC could achieve a 5 year survival and we are looking forward to repeat these results. There are some promising studies showing possible survival benefits of HIPEC in treatment of gastric cancer, however many data comes from Asia rather than Western world and the use of drug combinations and treatment regimens is highly variable. Furthermore, there is an ongoing research as to which patients would be the best candidates for this treatment since it is clear that PCI is a very poor prognostic indicator in gastric cancer thus we need other biological or clinical markers for patient stratification and prediction of response.

1. Martins at al.[21], in their systempatic review indicates that cytoreductive surgery and HIPEC seems to increase the survival of patients with gastric cancer with peritoneal carcinomatosis, more than treatment with cytoreductive surgery alone, decrease the risk of peritoneal recurrence and not be associated with more complications.

Our study results demonstrated significant differences in anatomical localization, operation type, and clinical stage between the groups. The anatomical localization of the lesion is closely related to the choice of surgical technique. The decision regarding the type of operation (total or subtotal gastrectomy) was based on the feasibility of achieving an adequately distant proximal resection margin (≥ 6 cm). In both types of operations, D2 lymphadenectomy was performed.

Postoperative morbidity was 14.6% in the neoadjuvant chemotherapy group and 27.5% in the adjuvant chemotherapy group, with no statistically significant difference ($p = 0.196$). However, the rate of esophagojejunal anastomotic leakage was significantly higher in the adjuvant chemotherapy group.

Huiyu Luo et al. [22], in their systematic review and meta-analysis, investigated postoperative morbidity and mortality in patients undergoing neoadjuvant chemotherapy (NAC) plus surgery compared to surgery alone. They concluded that NAC does not increase the risk of postoperative complications, including pulmonary complications, anastomotic leakage, surgical site infections, or postoperative mortality, when compared to surgery alone.

According to previous studies, neoadjuvant chemotherapy has been shown to reduce mortality in patients with gastric cancer. However, it is important to note that neoadjuvant chemotherapy does not significantly impact morbidity or perioperative complications in these patients [23, 24, 25]. Additionally,

neoadjuvant chemotherapy has been demonstrated to improve the R0 resection rate in cases of locally advanced gastric cancer [26], which is associated with better long-term outcomes for patients.

Based on our results, neoadjuvant chemotherapy appears to be most effective in the second stage of cancer, highlighting the importance of early diagnosis and timely intervention. Another significant factor influencing outcomes is patient age. Our findings indicate that patients who received neoadjuvant chemotherapy were statistically younger, which may be associated with lower morbidity rates and better overall health. This age-related factor could also contribute to improved survival outcomes.

The overall 5-year survival rate of patients who received CX-based neoadjuvant chemotherapy in our study was 40%, compared to 31% in those who did not receive it, with no statistically significant difference. These results are consistent with findings published in the literature.

In the MAGIC study [24], a 5-year survival rate of 36% was reported in the neoadjuvant group compared to 23% in the control group. Similarly, the FNCLCC and FFCD multicenter phase III trial [28] demonstrated that in patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal junction, or stomach, perioperative chemotherapy with fluorouracil plus cisplatin significantly increased the curative resection rate, disease-free survival, and overall survival (34% vs. 19%).

In the FLOT4-AIO trial, patients with locally advanced gastric or gastroesophageal junction adenocarcinoma received perioperative FLOT chemotherapy. The study reported a median overall survival of 50 months for the FLOT group, compared to 35 months for those treated with the ECF/ECX regimen (epirubicin, cisplatin, and 5-fluorouracil or capecitabine), indicating a significant survival benefit for the FLOT regimen [28].

A retrospective analysis further supported these findings, showing that patients treated with FLOT had a median overall survival of 57.8 months, compared to 28.9 months for those receiving 5-FU/platinum-based therapies. This study also noted a higher pathological tumor regression rate in the FLOT group, suggesting improved treatment efficacy [29].

Additionally, the RealFLOT study, an observational prospective analysis, examined the real-world application of the FLOT regimen. While detailed survival data from this study are limited, it provided insights into the regimen's tolerability and implementation in clinical practice [30].

Overall, these studies indicate that the FLOT regimen offers a survival advantage for patients with locally advanced gastric and gastroesophageal junction cancers, making it a preferred perioperative chemotherapy option in these cases and our small cohort of patients included into the study for the reference shows similar trends. However, a randomized study incorporating multivariate analysis would be required to confirm the superiority of neoadjuvant chemotherapy over other treatment strategies.

This study has several significant limitations. It is a retrospective study rather than a randomized clinical trial, where the treatment plan is determined by a multidisciplinary team.

The number of patients in each group is relatively small, which limited our ability to independently analyze each stage of cancer separately.

Conclusions

Advancements in surgical technologies and operative techniques, along with improved preoperative imaging, have primarily contributed to reductions in perioperative morbidity and mortality, shorter hospital stays, and improved quality of life. However, their impact on critical outcomes such as disease-free and overall survival appears to be modest.

Regional chemotherapy, delivered as heated or pressurized perfusion, has expanded the pool of patients eligible for more extensive surgery with curative intent. Nonetheless, systemic chemotherapy, in both neoadjuvant and adjuvant forms, as well as precision therapy, currently play a more significant role in influencing the long-term survival of patients with advanced gastric cancer. Continued research and advancements in these areas are anticipated to further improve patient outcomes.

Declarations

Author Contribution

1. made substantial contributions to the conception or design of the work: M.K, Ž.D, D.B. A.M, A.I, A.Š2. he acquisition, analysis, or interpretation of data: A.M, Ž.D. R.G, D.B, M.KAll authors reviewed the manuscript.

Tables

Table 1-3 are available in the Supplementary Files section.

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Figures

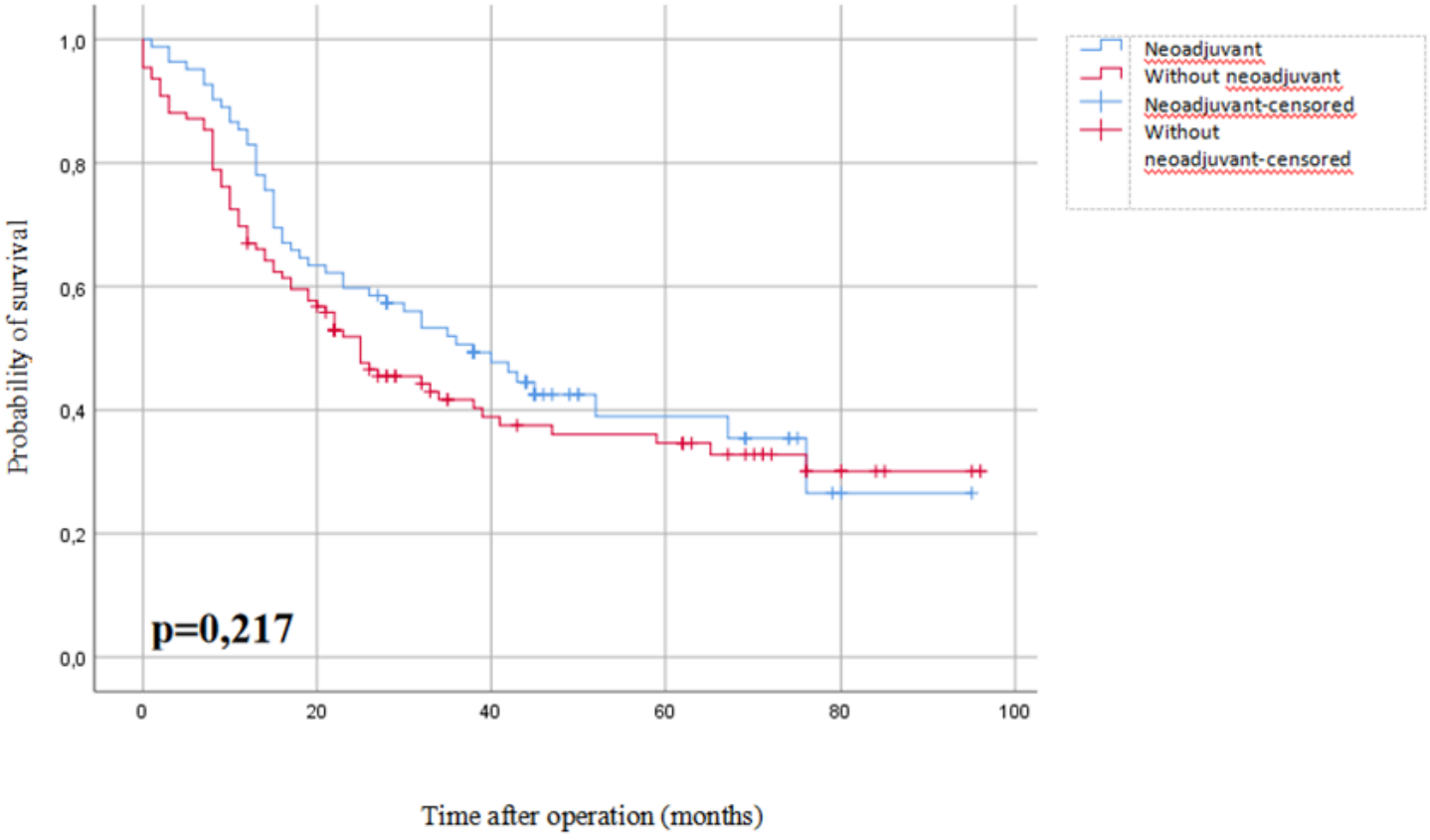


Figure 1

Kaplan–Meier estimator for total survival between the groups

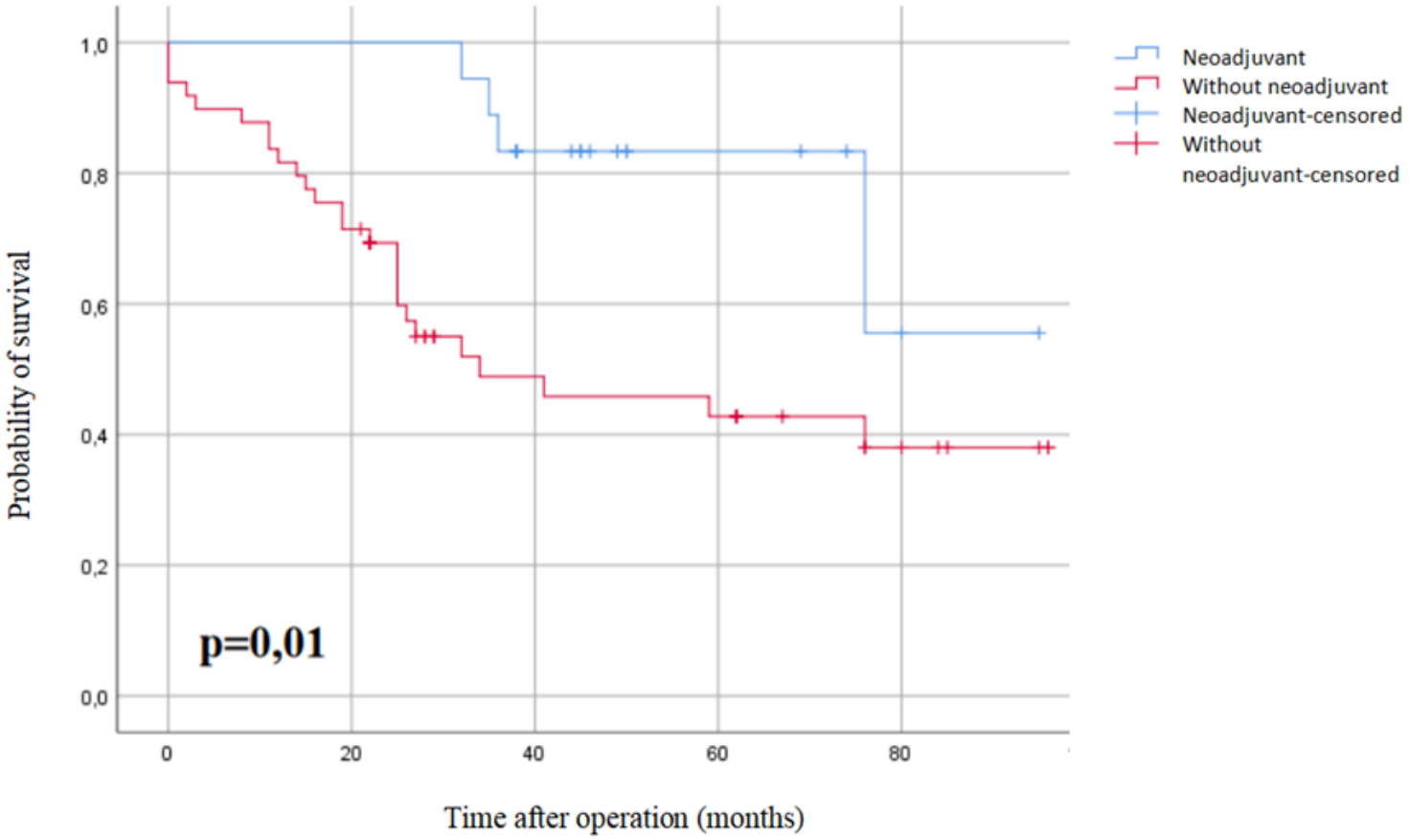


Figure 2

Kaplan–Meier estimator for II stage cancer between the groups.

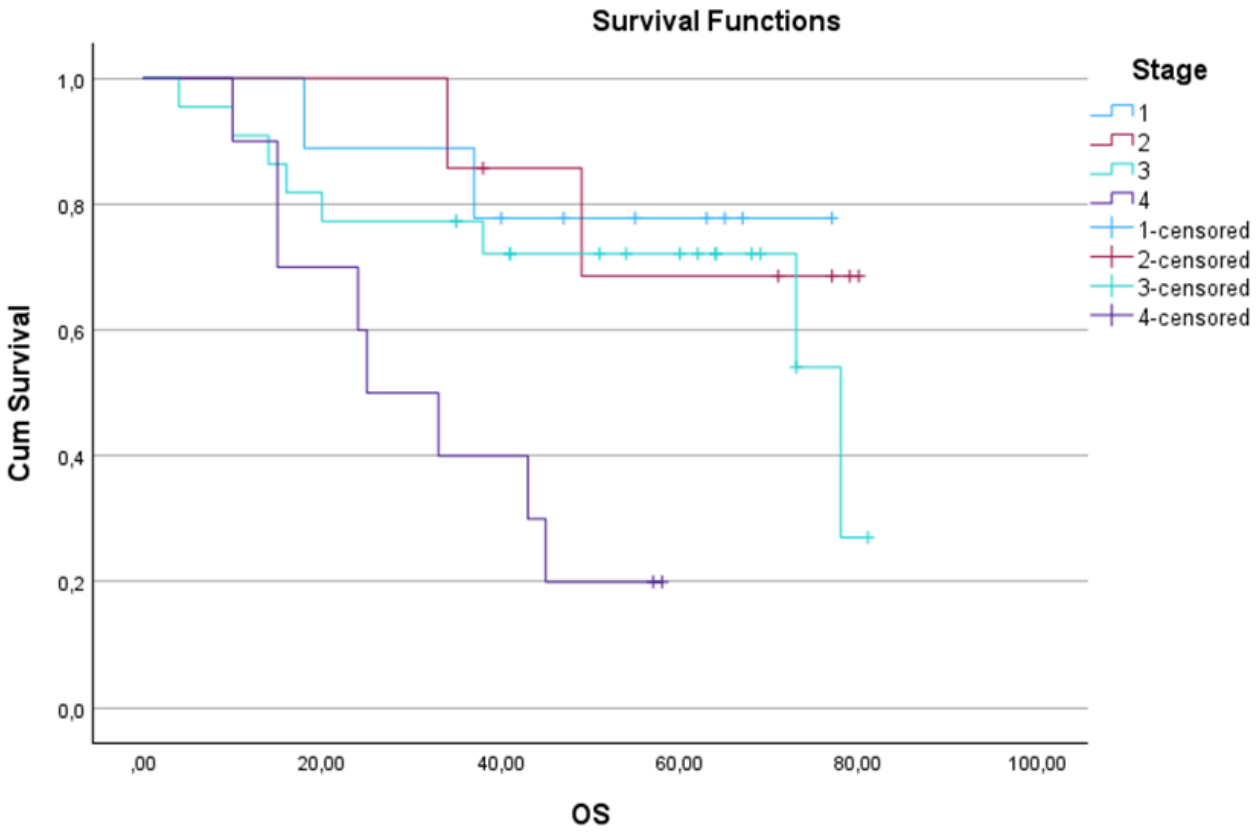


Figure 3

Legend not included with this version.

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