Evaluating the Role of Neoadjuvant and Adjuvant Chemotherapy in Gastric Cancer: A Retrospective Study and Future Directions

Birendra Kumar Sah (✉ rjsurgeon@hotmail.com)
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Zhen jia Yu
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Sheng Lu
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Yanan Zheng
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Zhenglun Zhu
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Jian Li
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Chen Li
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Min Yan
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Zhenggang Zhu
Ruijin Hospital Shanghai Jiao Tong University School of Medicine

Research Article

Keywords: gastric cancer, neoadjuvant chemotherapy, adjuvant chemotherapy

Posted Date: June 26th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3066551/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background

Different types of neoadjuvant chemotherapy regimens have been compared for gastric cancer, mostly in terms of radiological downgrading or pathological tumor regression; however, no large-scale multicenter randomized controlled trial (RCT) has conducted a head-to-head comparison of the overall survival rate between perioperative or neoadjuvant chemotherapy (NAC) and postoperative or adjuvant chemotherapy (AC). We explored whether the five-year overall survival rate was greater in patients who received perioperative chemotherapy plus surgery than in those who underwent surgery first and then underwent postoperative chemotherapy.

Methods

Altogether, 77 patients with a clinical diagnosis of cTNM stage III were included. Five-year overall survival (OS) rates were compared between patients who underwent neoadjuvant chemotherapy plus surgery (NAC) and those who underwent surgery first plus adjuvant chemotherapy (AC). Propensity score matching was used to adjust for disparity between the two groups. A Kaplan-Meier plot was created for survival analysis, and the log-rank method was used to compare the differences in OS.

Results

A total of 34 patients were in the NAC and 43 patients were in the AC group, respectively. There was no significant difference in age (median, 64 vs. 66 years), cTNM staging, or extent of gastrectomy between the two groups (p < 0.05). The median follow-up time was 58 months (range: 53–65 months). The five-year overall survival (OS) rates for patients in the NAC and AC groups were 61.8% and 73.5%, respectively. There was no significant difference between the two groups in the five-year overall survival rates (p > 0.05). There was no significant difference in the severity of postoperative complications between the two groups (p > 0.05).

Conclusions

There was no significant difference in the five-year overall survival rate between patients who underwent perioperative chemotherapy plus surgery and those who underwent surgery plus postoperative chemotherapy alone. A well-controlled prospective study is necessary to confirm whether perioperative chemotherapy is superior to postoperative chemotherapy in patients with GC.

Introduction
The treatment strategies for gastric cancer include surgery and adjuvant therapy. In terms of survival benefits, the extent of surgery is no longer the focus of new research, and there are clear suggestions that chemotherapy is beneficial for locally advanced disease. After the publication of results from the MAGIC trial by David Cunningham in 2006, a new trend started for research on neoadjuvant chemotherapy (1). However, it should be noted that the MAGIC trial was a comparison between a group of patients who underwent perioperative chemotherapy (preoperative and postoperative chemotherapy) plus surgery and a group of patients who underwent surgery only, that is, a group of patients who did not receive chemotherapy at all (1). In 2014, Sung Hoon Noh published the results of another famous trial, the CLASSIC trial, which compared a group of patients who underwent surgery only with a group of patients who underwent surgery and received postoperative chemotherapy (2). The 5-year overall survival rate of patients who received perioperative chemotherapy plus surgery was significantly higher than that of patients who underwent surgery alone in the MAGIC trial. The five-year OS was significantly higher in patients who underwent surgery and postoperative chemotherapy than in those who underwent surgery alone in the CLASSIC trial. Despite the demographic differences between the two trials, these results at the very least suggest that chemotherapy was beneficial for gastric cancer patients because the 5-year OS was increased in patients who received either perioperative chemotherapy or postoperative chemotherapy (1, 2). No large-scale multicenter RCT study has conducted a head-to-head comparison between perioperative chemotherapy and postoperative chemotherapy. Recently, a multicenter RCT from China, the RESOLVE trial, published their results in Lancet and compared perioperative chemotherapy with postoperative chemotherapy, but the patients in the two groups received different chemotherapy regimens (3). This study demonstrated that, in patients who underwent surgical treatment, the 3-year DFS was significantly better in patients who received perioperative chemotherapy with the SOX regimen than in those who received postoperative chemotherapy with the CAPOX regimen (59.4% vs. 51.1%). The 3-year DFS rate of patients who received postoperative chemotherapy with the SOX regimen was 56.5% (3). However, it is still unclear whether perioperative SOX is superior to postoperative SOX.

In addition, there are still blunt disagreements between Eastern and Western researchers regarding the indications for neoadjuvant chemotherapy (4–7). One reasonable argument is that the preoperative evaluation of the tumor (cT and cN) is not consistent with pathological pT and pN. In a large-scale Japanese study, more than 10% of stage I patients were misdiagnosed with late-stage disease (8). We explored whether the five-year overall survival rate was greater in patients who received perioperative chemotherapy plus surgery than in those who underwent surgery first and then postoperative chemotherapy.

**Methods**

Only patients with pathologically confirmed gastric cancer who were preoperatively diagnosed with cTNM stage III (cT3, T4, N1, N2, N3, and M0) and underwent radical surgery (total or partial gastrectomy with D2 lymphadenectomy) were included in this study. All patients were treated in 2018 at Ruijin Hospital, Shanghai Jiaotong University School of Medicine, which is a referral center for gastric cancer patients in China. Patients were divided into two groups: perioperative chemotherapy plus surgery (NAC) and surgery
first plus chemotherapy (AC). Due to the retrospective nature of the study, we excluded 403 patients for different reasons that may have adversely affected the analysis (Supplementary Table 1). Our previous study on elderly patients suggested that there was a difference in overall survival between patients who underwent total gastrectomy and those who underwent partial gastrectomy; therefore, we applied the propensity score matching method to eliminate the discrepancy between the two groups. Altogether, 172 cases were included in propensity score matching for cT staging, cN staging, and gastrectomy type. Among them, 98 were matched and approached for follow-up. Finally, only 77 patients were included in the final analysis, and 21 patients were excluded because of insufficient or unconfirmed data on survival time. Postoperative morbidity and mortality were recorded according to the Clavien-Dindo grading system (9). The overall survival (OS) time in this study was the time from the date of surgery to death from any cause. The data for relapse-free survival (RFS) were not accurately available and, thus, were not analyzed in this study.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 22.0 for Windows (SPSS, Inc., Chicago, Illinois). Nonparametric methods were used to analyze the data with an abnormal distribution. Continuous data were expressed as the median and range, and the Mann–Whitney U test was used for continuous data. The chi-square test and Fisher’s exact test were used to compare differences between the two groups, as appropriate. Survival data were presented as the length of overall survival (OS) in months. A Kaplan–Meier plot was created for survival analysis, and the log-rank method was used to compare OS rates. Cox regression analysis was used to identify risk factors for OS. Statistical significance was set than 0.05.

Results

In total, 77 patients were included in this study: 34 in the NAC group and 43 in the AC group. There were no significant differences in demographic variables between the two groups (p > 0.05), including the preoperative clinical staging of gastric cancer (cT stage and cN stage) and the extent of gastrectomy (Table 1). Patients received the established chemotherapy regimens; among 34 patients in the NAC group, 13 patients received SOX, 9 patients received EOX, 7 patients received FLOT, and 5 patients received SOX-A. Patients in both groups received postoperative chemotherapy for six months, and there was no significant difference in the completion of postoperative adjuvant chemotherapy between the two groups (p > 0.05). Details on the adverse effects of chemotherapy were not described because of the lack of accurate data owing to the retrospective nature of the current study. The median follow-up time was 58 months (range: 53–65 months). The estimated five-year overall survival (OS) rates for patients in the NAC and AC groups were 61.8% and 73.5%, respectively. There was no significant difference between the two groups in the five-year overall survival rates (p > 0.05). There was no significant difference in the severity grading of postoperative complications (Table 2) or the length of postoperative stay between the two groups (p > 0.05). One patient in the NAC group achieved pCR, and nine patients in the AC group achieved pTNM stage I (Table 3).
### Table 1
Demographic Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NAC</th>
<th>DS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>26(76.5)</td>
<td>26(60.5)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8(23.5)</td>
<td>17(39.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median(Range)</td>
<td>64(38–77)</td>
<td>66(44–86)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Median</td>
<td>22.42</td>
<td>22.18</td>
</tr>
<tr>
<td>Site of tumor</td>
<td>Proximal</td>
<td>8(23.5)</td>
<td>9(20.9)</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>11(32.4)</td>
<td>7(16.3)</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>15(44.1)</td>
<td>25(58.1)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0</td>
<td>2(4.7)</td>
</tr>
<tr>
<td>cT stage</td>
<td>T3</td>
<td>3(8.8)</td>
<td>4(9.3)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>30(88.2)</td>
<td>37(86.2)</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>1(2.9)</td>
<td>2(4.7)</td>
</tr>
<tr>
<td>cN stage</td>
<td>N1</td>
<td>2(5.9)</td>
<td>1(2.3)</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>22(64.7)</td>
<td>27(62.8)</td>
</tr>
<tr>
<td></td>
<td>N3</td>
<td>10(29.4)</td>
<td>15(34.9)</td>
</tr>
<tr>
<td>Type of Gastrectomy</td>
<td>Distal</td>
<td>17(50.0)</td>
<td>23(53.5)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>17(50.0)</td>
<td>20(46.5)</td>
</tr>
<tr>
<td>Postop Chemo</td>
<td>Yes</td>
<td>26(76.5)</td>
<td>31(72.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5(14.7)</td>
<td>11(25.6)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3(8.8)</td>
<td>1(2.3)</td>
</tr>
</tbody>
</table>

*Fisher's Exact Test
Table 2
Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>NAC plus Surgery</th>
<th>Direct Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0- I</td>
<td>27(79.4)</td>
<td>21(72.4)</td>
</tr>
<tr>
<td>Grade II</td>
<td>6(17.6)</td>
<td>7(24.1)</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>1(2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>0</td>
<td>1(3.4)</td>
</tr>
<tr>
<td>Grade V</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3
Postoperative Pathology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stage</th>
<th>NAC plus Surgery</th>
<th>Direct Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ypTNM</td>
<td>pCR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>1(2.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>11(32.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>19(55.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pTNM</td>
<td>I</td>
<td>9(20.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>5(11.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>29(67.4)</td>
</tr>
</tbody>
</table>

Discussion

For the last three decades, it has been reported that more than 2300 articles have been published regarding neoadjuvant chemotherapy for gastric cancer (10); however, very few of them are widely accepted, and if there is only one article that should be remembered as a pioneering concept for neoadjuvant chemotherapy, it is the MAGIC trial (1), despite not being the first one to report. Despite exponential growth in terms of publications on neoadjuvant chemotherapy, most of these studies have been conducted in a few countries. China, the USA, and Japan scored as among the top three countries in these studies (10). There is still no joint agreement or strict guidelines to recommend that neoadjuvant chemotherapy be mandatory for gastric cancer. This may be due to conflicting results from different centers (6, 7, 11–13) or perhaps somewhat deficient study designs in the past, and none of them answered the fundamental question of whether perioperative or neoadjuvant chemotherapy plus surgery is superior to surgery plus adjuvant chemotherapy (1, 2, 3). Most research on neoadjuvant chemotherapy has focused on comparing the efficacy between different types of chemotherapy regimens, mainly focusing on radiological or pathological responses to therapy (15, 16). Al-Batran SE. published the initial results of the FLOT 4 trial and demonstrated that the FLOT regimen was better than ECF or ECX in terms...
of pathological regression and tolerance (15). Sah BK published initial reports of comparative results of pathological efficacy between triplet chemotherapy FLOT and doublet chemotherapy SOX. There was no significant difference between neoadjuvant FLOT and SOX in terms of tumor regression grading; however, the five-year overall survival rate has not yet been published (16). In addition, we did not find any studies that claimed the superiority of NAC over AC in terms of overall survival. Even in the final results of the FLOT 4 trial in 2019, the five-year overall survival rate was much lower than that reported in the CLASSIC trial (2, 17). The main concern regarding neoadjuvant chemotherapy in Japan is the accuracy of clinical TNM staging (8), and it should be noted that 20.9% of patients in the surgery-first group were pTNM stage I in this study. Because this would have affected the comparison of OS, we further compared the OS between the two groups excluding pathological stages I and II, although this was not required because a similar probability of misdiagnosis was also anticipated in the NAC group. Nonetheless, there was no difference in the OS between the two groups, even after excluding early stage tumors (Fig. 2).

There are several shortcomings in this study, mainly due to the retrospective nature of the analysis; the number of patients included in this study was too small to achieve any convincing conclusion. Hundreds of patients were excluded for valid reasons (Supplementary Table 1) to eliminate the disparity between the two groups. There were no data on the adverse effects of chemotherapy; therefore, we did not analyze it because the focus of this study was to compare the overall survival rate, and many adverse effects were not recorded in standard forms. In addition, there are several types of chemotherapy regimens; although the types of chemotherapy might have somehow influenced the result, previous studies have shown that the CAPOX and SOX regimens were similarly effective for gastric cancer (3). Even SOX was as effective as the FLOT regimen in terms of pathological regression (16). Nevertheless, despite being a small-scale retrospective study, the results of this study are quite interesting, and it raises the fundamental question of whether neoadjuvant chemotherapy is beneficial because the CLASSIC trial has shown that the 5-year overall survival rate is 78% for patients who underwent surgery first and then received postoperative or adjuvant chemotherapy (AC). Therefore, any rationale for alteration to this treatment should only be considered for two basic reasons: either to increase the overall survival rate or to decrease the toxic side effects of chemotherapy. By analyzing these data, we neither denied the use of neoadjuvant chemotherapy nor questioned its efficacy in terms of overall survival. However, at the very least, this study concludes that chemotherapy either perioperatively or postoperatively is similarly effective. Whether the addition of preoperative chemotherapy is beneficial in terms of OS remains unclear. There is still a need for a better-designed study. Perhaps future studies should focus on the non-inferiority test and not on the superiority test between the two modes. If NAC is similarly effective to AC, it would be better to conduct a large-scale study that compares total preoperative chemotherapy plus surgery (no postoperative chemotherapy) with surgery first plus postoperative chemotherapy.

Despite the lack of concrete data to support this, we can easily assume that preoperative chemotherapy is better in terms of completion of required cycles than postoperative chemotherapy after major surgery. Owing to postoperative complications, a certain number of patients cannot start adjuvant chemotherapy on time or are simply unable to receive chemotherapy.
The results of this study do not negate the need for further studies on neoadjuvant chemotherapy. However, it is necessary to design future studies to better understand the limitations of conventional chemotherapy. Whether the addition of immunotherapy or targeted therapy is beneficial for long-term survival remains unknown.

**Conclusion**

There was no significant difference in the five-year overall survival rate between patients who underwent perioperative chemotherapy plus surgery and those who underwent surgery plus postoperative chemotherapy. A well-controlled prospective study is necessary to confirm whether perioperative chemotherapy is superior to postoperative chemotherapy in patients with GC.

**Declarations**

**Ethics approval and consent to participate**

The Ethics Committee of Ruijin Hospital approved this study and waived the need for informed consent due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki (revised in 2013).

**Consent for publication**

This manuscript does not contain any individual data that identifies the patients included in this study.

**Patients and the public**

Patients and the general public were not involved in the design of this study because of the retrospective nature of this study.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

The overall cost of this research will be funded by grants from the National Natural Science Foundation of China No. 81871904 (ZG Zhu) and No. 82103396 (ZJ Yu).

**Author contributions**
BKS designed the study, collected patient data, drafted the manuscript, ZJY followed up with patients for overall survival, and revised the manuscript. SL assisted in data collection from the central database of the unit. YNZ and ZLZ revised the drafts of the manuscript. CL and ZGZ participated in the design of the study and critically revised the drafts of the manuscript. All authors meet the criteria for publication; all authors have read and approved the final manuscript.

Acknowledgments

The authors thank all the clinicians in the gastrointestinal department for their support in conducting this study. We would also like to thank Mrs. Qin Yu for recording data in the central database.

References


dates

Figures
Figure 1

Kaplan-Meier (K-M) Plot for OS
Figure 2

Kaplan-Meier (K-M) Plot for OS (only pTNM III in Direct Surgery group)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx