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Surgical Perspective on Neoadjuvant Therapy in Resectable Gastric Cancer

Rezektabl Mide Kanserinde Neoadjuvan Tedaviye Cerrahi Bakış Açısı

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Abstract

Objective: Perioperative chemotherapy is recommended in Western guidelines for resectable stage ≥T2 gastric cancer. However, its feasibility in real-world settings, particularly when upfront surgery is a viable option, remains uncertain.

Methods: A single-center, retrospective observational study was conducted that included 22 patients diagnosed with clinically resectable, non-obstructive, non-bleeding, locally advanced gastric cancer (T3-T4 and/or cN+). Resectability and clinical staging were assessed using computed tomography (CT), positron emission tomography-CT and endoscopic ultrasonography. Patients were categorized based on treatment completion and postoperative outcomes. Demographic and clinical variables were analyzed using descriptive statistical methods.

Results: Of the 22 patients, 5 (22.7%) were unable to complete neoadjuvant chemotherapy (NAC) due to tumor-related bleeding (n=4) or disease progression (n=1). Seventeen patients (77.3%) completed NAC and underwent surgery; among them, 4 (23.5%) experienced major postoperative complications, including anastomotic leak (n=1), duodenal stump leak (n=2), and pancreatic fistula (n=1). Overall, 7 patients (31.8%) developed serious complications, and 2 patients (9.1%) died of complete anastomotic dehiscence.

Conclusion: A significant proportion of patients did not complete NAC because of gastric cancer-related complications, which necessitated early surgery under suboptimal conditions. These patients experienced high rates of postoperative morbidity and mortality. Based on these findings and in accordance with East Asian Guidelines, our institution now favors upfront surgery followed by adjuvant chemotherapy for comparable cases. Future randomized trials should incorporate real-world experience to better inform patient selection and treatment planning.

Keywords: Gastric, cancer, resectability, perioperative, neoadjuvant, complications

Öz

Amaç: Rezektabl evre ≥T2 mide kanserinde perioperatif kemoterapi, Batı kılavuzlarında önerilmektedir. Ancak, özellikle doğrudan cerrahinin uygulanabilir bir seçenek olduğu durumlarda, gerçek yaşam koşullarındaki uygulanabilirliği belirsizliğini korumaktadır.

Yöntem: Klinik olarak rezektabl, obstrüksiyon ve aktif kanaması olmayan, lokal ileri mide kanseri (T3-T4 ve/veya cN+) tanısı konmuş 22 hastayı içeren tek merkezli, retrospektif gözlemsel bir çalışma gerçekleştirildi. Rezektabilite ve klinik evreleme; bilgisayarlı tomografi, pozitron emisyon tomografisi ve endoskopik ultrasonografi kullanılarak değerlendirildi. Hastalar, tedavi tamamlama durumu ve postoperatif sonuçlarına göre kategorize edildi. Demografik ve klinik değişkenler tanımlayıcı istatistiksel yöntemlerle analiz edildi.

Bulgular: Yirmi iki hastanın 5'i (%22,7), tümörle ilişkili kanama (n=4) veya hastalık progresyonu (n=1) nedeniyle neoadjuvan kemoterapiyi (NAK) tamamlayamadı. On yedi hasta (%77,3) NAK'ı tamamladı ve cerrahi uygulandı; bu hastaların 4'ünde (%23,5) anastomoz kaçağı (n=1), duodenum güdük

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Öz

kaçağı (n=2) ve pankreas fistülü (n=1) gibi majör postoperatif komplikasyonlar gelişti. Genel olarak, 7 hastada (%31,8) ciddi komplikasyon gelişti ve 2 hasta (%9,1) tam anastomoz ayrışması nedeniyle hayatını kaybetti.

Sonuç: NAK'ı, mide kanserine bağlı komplikasyonlar nedeniyle tamamlayamayan önemli sayıda hasta, suboptimal koşullarda erken cerrahiye ihtiyaç duydu. Bu hastalarda postoperatif morbidite ve mortalite oranları yüksekti. Bu bulgular doğrultusunda ve Doğu Asya kılavuzlarıyla uyumlu olarak, kurumumuz benzer olgularda upfront cerrahi sonrası adjuvan kemoterapiyi tercih etmektedir. Gelecekteki randomize çalışmalar, hasta seçimi ve tedavi planlamasında gerçek yaşam deneyimlerini de dikkate almalıdır.

Anahtar Kelimeler: Mide, kanser, rezektabilite, perioperatif, neoadjuvan, komplikasyonlar

Introduction

Surgical approaches to gastric cancer have evolved in parallel with advancements in operative techniques and systemic treatment strategies. The concept of perioperative chemotherapy gained prominence in Europe through the MAGIC and FNCLCC/FFCD trials. The subsequent adoption of the 5-fluorouracil, leucovorin, oxaliplatin, docetaxel regimen improved treatment tolerability and completion rates, enabling more patients to proceed with adjuvant chemotherapy[1].

The MAGIC, ACCORD07, and CRITICS trials were among the first to demonstrate survival benefits of perioperative or neoadjuvant chemotherapy (NAC), particularly in non-East Asian populations. More recent trials, such as PRODIGY and ARTIST 2, further reinforced this benefit by showing significant tumor downstaging and improvements in disease-free survival[2-5]. According to current international guidelines, the indication for neoadjuvant or perioperative chemotherapy in gastric cancer varies by tumor stage and nodal status. The National Comprehensive Cancer Network (NCCN) 2024 and the European Society for Medical Oncology 2022 Guidelines recommend perioperative chemotherapy for patients with clinical stage T2 or higher or those with node-positive (cN+) disease. Although interest in neoadjuvant strategies continues to grow, their applicability across all patient groups remains uncertain. Tumor progression during treatment can preclude surgery, and the specific contribution of surgery-particularly its quality and timing-has yet to be clearly defined[6,7].

In East Asia, different strategies are employed to manage resectable T3-T4 and/or cN+ gastric cancer. The 2023 Chinese Society of Clinical Oncology (CSCO) Guidelines upgraded NAC to a grade I recommendation for clinical stage III (cT3-T4 Nany) gastric cancerbased on increasing evidence supporting improved R0 resection rates and survival outcomes[8]. In contrast, the 2024 Korean Gastric Cancer Association Guideline continues to prioritize upfront D2 surgery for resectable T3-T4 and/or cN+ disease and reserves NAC or perioperative therapy for high-risk or borderline patients[9]. The 2021 Japanese Gastric Cancer Treatment Guidelines similarly limit NAC to more advanced cases, such as cT4b tumors or bulky nodal disease. With the exception of the recent CSCO update, most Asian guidelines continue to favor initiating treatment with upfront surgery[10].

This variation underscores the importance of precise staging and individualized treatment planning, tailored to both tumor burden and regional practice standards. In this study, we evaluated the clinical course and outcomes of patients with resectable gastric cancer who were scheduled for neoadjuvant therapy at our institution, focusing specifically on patients who failed to complete treatment; the necessity and timing of surgery among such patients; and the postoperative outcomes of patients who completed NAC. Based on these findings, we seek to highlight the ongoing relevance of upfront surgery as a viable approach in appropriately selected patients.

Materials and Methods

Study Design and Patient Selection

This retrospective observational study was conducted at Aydın Adnan Menderes University Hospital and included patients diagnosed with resectable gastric adenocarcinoma between January 2022 and March 2024. A total of 38 patients were referred to the medical oncology department for NAC. Of these, 16 did not return to our institution to initiate treatment. Of these, 10 patients were later admitted to our center for adjuvant therapy, while 6 were lost to follow-up. Therefore, the final analysis included 22 patients who received NAC and underwent surgery at our institution.

All patients were clinically staged as T3-T4 and/or cN+, with no evidence of gastric outlet obstruction or active gastrointestinal bleeding. Resectability was assessed using contrast-enhanced thoracoabdominal computed

tomography (CT), positron emission tomography-CT (PET-CT), and endoscopic ultrasonography (EUS), in accordance with the NCCN 2024 Guidelines. All treatment decisions were made in multidisciplinary tumor board meetings.

Data Collection and Variables

Demographic and clinical data were retrieved from patient charts and the institutional electronic medical record system. Variables included age, sex, tumor location, clinical stage, NAC regimen, and completion status, surgical approach, postoperative complications, and treatment-related mortality. Surgical outcomes, including anastomotic leakage, duodenal stump leakage, and in-hospital death, were also recorded.

Patient Grouping

Based on clinical course, patients were divided into the following three groups:

1. Patients who failed to complete NAC due to bleeding or progression and underwent early surgery.

2. Patients who completed NAC, underwent surgery after 4-6 weeks, and experienced major postoperative complications.

3. Patients who completed NAC underwent surgery after 4-6 weeks and had an uneventful postoperative course.

Among the five patients who did not complete NAC, four required surgery due to gastrointestinal bleeding. All underwent two sessions of endoscopic hemostasis, which included argon plasma coagulation, cauterization, and epinephrine injection. Surgical intervention was performed when bleeding could not be controlled.

Inclusion and Exclusion Criteria

Patients aged 18 years or older with histologically confirmed gastric adenocarcinoma were eligible for inclusion. All patients had clinically staged T3 or T4 tumors and/or cN+ status, as determined by thoracoabdominal contrast-enhanced CT, PET-CT, or EUS. Only patients who were deemed resectable with curative intent according to the NCCN 2024 guidelines and who did not have gastric outlet obstruction or active upper gastrointestinal bleeding at the time of diagnosis were included. Furthermore, all patients were required to be referred for NAC and to subsequently undergo surgery at our institution.

Patients were excluded if they had distant metastases, synchronous malignancies, or had received definitive chemoradiotherapy without surgical intent. Those who underwent upfront surgery without neoadjuvant treatment or who had surgery performed at an external institution were also excluded. Incomplete or missing medical records required for analysis constituted an additional exclusion criterion.

Statistical Analysis

Descriptive statistical methods were used to summarize the data. Continuous variables were presented as mean ± standard deviation, and categorical variables as counts and percentages. Clinical outcomes and complication rates were compared across the three patient groups. Statistical analyses were performed using SPSS version 29 (IBM Corp., Armonk, NY, USA).

Ethics Statement

This study was approved by the Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (approval no: 04, date: 27.06.2025). Written informed consent was obtained from all participants prior to data collection. All procedures were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki.

Results

A total of 22 patients with clinically resectable, non-obstructive, non-bleeding, locally advanced gastric cancer (T3-T4 and/or cN+) were included in the final analysis. The mean age was 61.4±9.2 years; 68.2% (n=15) were male. At diagnosis, 54.5% (n=12) of patients had T3 tumors, 45.5% (n=10) had T4 tumors, and 81.8% (n=18) were clinically cN+.

Five patients (22.7%) were unable to complete NAC: four because of tumor bleeding and one because of disease progression leading to peritoneal carcinomatosis. Among these, two patients developed complete anastomotic dehiscence and died in the postoperative period. One patient developed a duodenal stump leak that resolved with conservative management, and another recovered uneventfully after emergency surgery. This subgroup had a postoperative morbidity rate of 60% and a mortality rate of 40%.

Seventeen patients (77.3%) completed neoadjuvant therapy and underwent surgery within 4-6 weeks. Of these, four (23.5%) developed postoperative complications: one patient had an anastomotic leak, two patients developed duodenal

stump leaks, and one patient who underwent distal pancreatectomy developed a pancreatic fistula confined to a large pseudocyst in the pancreatic bed. Duodenal stump leaks were resolved conservatively. The patient with the anastomotic leak was successfully treated with endoscopic stenting. The remaining 13 patients (76.5%) had uneventful postoperative recoveries.

Overall, major postoperative complications occurred in seven patients (31.8%) across all subgroups, and mortality occurred in two of 22 patients (9.1%). However, in patients who could not complete neoadjuvant therapy, morbidity and mortality rates were 75% and 50%, respectively (Table 1).

Discussion

While NAC is endorsed by Western guidelines and appears to yield better survival outcomes in selected patient groups, our study sought to emphasize two critical issues often overlooked: postoperative morbidity in patients who complete NAC, and increased morbidity and mortality in patients who fail to complete it.

In our series, 4 of 17 patients (23.5%) who completed NAC and underwent surgery after 4-6 weeks experienced major postoperative complications, including anastomotic leak, duodenal stump leak, and pancreatic fistula. This rate is comparable to the complication rates reported in OGSG1205 (26.3%)[11] and Wang et al.[12] (20.6%). Furthermore, this complication rate contrasts with findings from a recent study by Aydoğan et al.[13] conducted at our institution, which reported no worse survival outcomes for patients undergoing upfront surgery than for those receiving NAC. These observations suggest that completing NAC does not eliminate postoperative morbidity and that complication risk remains substantial.

Among the 5 patients who could not complete NAC due to bleeding or disease progression, 3 experienced major complications, and 2 died from anastomotic dehiscence. This corresponds to a morbidity rate of 60% and a mortality rate of 40; these rates are markedly higher than those in the group that completed NAC[14,15]. These findings underline the severe risks encountered during surgery among patients who are unable to complete chemotherapy. Dağıstanlı[16] reported postoperative morbidity and mortality rates of 21.7% and 4.5%, respectively, in patients with locally advanced gastric cancer who did not receive neoadjuvant therapy; additional organ resection was required in more than half of cases because of invasion of adjacent organs. Based on these findings, the authors suggested that the absence of neoadjuvant therapy might contribute to increased surgical complexity and morbidity. In contrast, our results indicate that high morbidity and mortality occurred particularly among patients who could not complete neoadjuvant therapy and required urgent surgery for tumor-related complications, whereas upfront surgery in selected patients without obstruction or active bleeding was not associated with worse outcomes.

In all such cases, chemotherapy discontinuation was due to tumor-related complications rather than systemic toxicity. Bleeding and progression disrupted the treatment plan and necessitated emergency (unplanned) surgery under suboptimal conditions. This highlights the tumor's clinical course and biological behavior as critical barriers to completion of NAC[17].

Table 1. Demographic and clinical characteristics according to neoadjuvant therapy completion and surgical outcomes

Variable	All patients (n=22)	Unable to complete NAC (n=5)	Completed NAC (n=17)
Age (mean ± SD)	61.4±9.2	62.6±8.4	60.0±9.3
Sex (male)	15 (68.2%)	3 (60.0%)	12 (70.6%)
T stage (T3)	12 (54.5%)	2 (40.0%)	10 (58.8%)
T stage (T4)	10 (45.5%)	3 (60.0%)	7 (41.2%)
Node-positive	18 (81.8%)	4 (80.0%)	14 (82.4%)
Anastomotic leak	3 (13.6%)	2 (40%)	1 (5.9%)
Duodenal stump leak	3 (13.6%)	1 (20%)	2 (11.8%)
Pancreatic leak	1 (4.5%)	0 (0%)	1 (5.9%)
Morbidity	9 (40.9%)	3 (60.0%)	4 (23.5%)
Mortality	2 (9.1%)	2 (40.0%)	0 (0%)

SD: Standard deviation, NAC: Neoadjuvant chemotherapy

One patient developed peritoneal carcinomatosis during NAC and became inoperable. This case exemplifies the risk of disease progression during chemotherapy, which can entirely eliminate the window for curative surgery, and is especially concerning for patients with a high tumor burden.

Unplanned surgeries in patients who failed to complete NAC led to poor outcomes, including mortality and serious morbidity. These results are likely attributable to the urgent timing of surgery and the compromised condition of the patient[18].

In patients with resectable T3-T4 gastric cancer, the possibility that early surgery will be required because of tumor-related complications undermines the rationale for offering NAC to patients with earlier-stage disease (e.g., borderline T2 or low-burden N+). Such an approach would conflict with the principles of oncologic safety[19].

Of the 38 patients initially planned for NAC in our center, 16 sought treatment elsewhere. Ten of these were confirmed to have undergone surgery at other institutions and later returned for adjuvant therapy, while no data could be obtained for the remaining six. These patterns suggest that NAC adoption may still be limited among surgeons in our region, potentially due to similar challenges encountered in clinical practice[20,21].

Although studies comparing NAC+surgery+adjuvant therapy to surgery+adjuvant therapy have demonstrated survival benefits, they often exclude patients who fail to complete NAC. This exclusion may lead to an overestimation of the real-world efficacy of neoadjuvant treatment. Accordingly, our institutional strategy aligns more closely with East Asian guidelines that recommend upfront surgery followed by adjuvant therapy in resectable, non-obstructive, non-bleeding gastric cancer cases[22].

Taken together, our findings indicate that, although NAC is supported by international guidelines, its applicability in real-world practice remains limited, particularly for specific patient subsets. Patients who fail to complete NAC face substantial risks of complications and mortality, and even among those who complete treatment, significant morbidity persists. These real-world challenges, such as low treatment completion rates and high rates of postoperative complications, should be carefully considered when assessing the feasibility of neoadjuvant strategies in the management of gastric cancer.

Study Limitations

This study has several limitations inherent to its retrospective and single-center design. The relatively small sample size limits the generalizability of the findings, and potential selection bias may have influenced outcomes, particularly since only patients who received both neoadjuvant therapy and surgery at our institution were included. Furthermore, excluding patients who received part of their treatment at external institutions may have introduced selection bias, as their outcomes could have differed from those treated entirely at our center. Because this was not a randomized controlled trial, causal relationships between completion of neoadjuvant therapy and surgical outcomes cannot be definitively established. Despite these limitations, the study provides valuable real-world insights into the feasibility and postoperative outcomes of neoadjuvant treatment in resectable gastric cancer.

Conclusion

This study demonstrates that a considerable proportion of patients with clinically resectable, non-obstructive, non-bleeding, locally advanced gastric cancer were unable to complete neoadjuvant therapy and subsequently experienced high postoperative morbidity and mortality. Based on these findings and aligned with East Asian treatment guidelines, our institutional approach has shifted to prioritize upfront surgery followed by adjuvant chemotherapy in patients with similar clinical profiles. Further randomized controlled trials incorporating real-world data and focusing specifically on this patient subgroup are warranted.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (approval no: 04, date: 27.06.2025).

Informed Consent: Written informed consent was obtained from all participants prior to data collection.

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Footnotes

Authorship Contributions

Concept: A.E., E.B.C., Design: A.E., E.B.C., Data Collection or Processing: O.A., A.E.S., Analysis or Interpretation: A.E., O.A., Literature Search: O.A., A.E.S., Writing: A.E., E.B.C.

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