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REVIEW ARTICLE

An extensive examination comparing neoadjuvant and adjuvant chemotherapy for resectable gastric cancer

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Abstract

East Asia has the highest incidence rates of gastric cancer, making it a major worldwide health problem. For resectable illness, surgical resection is still the mainstay of curative treatment; nevertheless, there is ongoing discussion on the best time to provide chemotherapy, whether it should be administered as an adjuvant or neoadjuvant before surgery. The ability of neoadjuvant chemotherapy to downstage tumours, raise R0 resection rates, and treat micro metastatic illness early has made it popular. This method is becoming more and more popular for treating regionally advanced gastric cancer in several Western countries after multiple trials demonstrated equivalent or better overall survival outcomes. Conversely, adjuvant chemotherapy is still often used, especially in East Asia, where seminal studies like ACTS-GC and CLASSIC have shown how effective it is at enhancing both overall and disease-free survival. It is frequently preferred for patients with early-stage illness or when impaired dietary or physical health makes preoperative therapy impractical. In the end, there are substantial oncological advantages across both neoadjuvant and adjuvant treatments. The patient's condition, the tumour's features, and the institution's experience should all be considered while choosing a treatment. A multidisciplinary approach is still crucial for optimising results, considering changing evidence, and further research will assist in sequestering the best course of action for different patient subgroups.

Keywords: gastric cancer, neoadjuvant chemotherapy, adjuvant chemotherapy, perioperative therapy, gastrectomy

INTRODUCTION

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About 1.1 million new cases of gastric cancer are identified each year, making it the third most prevalent cause of cancer-related death and the fifth most common cancer globally (Sung et al., 2021). With five-year survival rates between 20 and 30 percent in Western nations and a little worse in East Asian populations where prevention initiatives are more common, the prognosis is still bleak despite advancements in multimodal treatment techniques (Smyth et al., 2020).

For localised stomach cancer, surgical resection combined with a sufficient lymphadenectomy is still the only treatment that may be curative. Systemic chemotherapy must be incorporated into treatment paradigms since surgery alone has a significant recurrence rate, especially in cases of locally advanced illness (Japanese Gastric Cancer Association, 2021). Over the past 20 years, there has been a great deal of clinical research on the best times to administer chemotherapy, whether it be as a neoadjuvant, an adjuvant, or a combination (perioperative).

Potential tumour downstaging, early treatment of micrometastatic illness, evaluation of tumour chemosensitivity, and better tolerability in comparison to postoperative treatment are all included in the theoretical base for neoadjuvant chemotherapy. On the other hand, adjuvant chemotherapy prevents possible surgical delays brought on by treatment-related toxicities and provides the benefit of medication selection based on precise pathological staging (Al-Batran et al., 2019).

This comprehensive study compares adjuvant and neoadjuvant chemotherapy regimens in resectable gastric cancer cases using the available data, with a particular focus on quality of life indicators, surgical issues, pathological responses, and survival outcomes.

2. Historical Context and Development of Treatment Paradigms

2.1 The Development of Adjuvant Chemotherapy

Numerous innovative trials, the majority of which were carried out in East Asian communities, paved the way for adjuvant chemotherapy as a treatment for stomach cancer. Following the publication of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC), which revealed that postoperative S-1 monotherapy significantly improved survival in patients with stage II–III gastric cancer compared to surgery alone, adjuvant chemotherapy was embraced as the standard of care in Japan (Sakuramoto et al., 2007).

Later, the CLASSIC trial demonstrated the effectiveness of adjuvant CAPOX (capecitabine plus oxaliplatin) chemotherapy in Korean patients, which resulted in better disease-free and overall survival than surgery alone (Bang et al., 2012). In East Asian nations, where D2 lymphadenectomy is frequently carried out, these ground-breaking studies determined that adjuvant chemotherapy was the most effective treatment.

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2.2 Neoadjuvant and Perioperative Strategies Emerge

The development of neoadjuvant methods was significantly influenced by experiences in Western nations, where surgical outcomes have historically differed from those in East Asia. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial marked a paradigm change by demonstrating that perioperative ECF (epirubicin, cisplatin, and fluorouracil) chemotherapy resulted in better survival rates than surgery alone (Cunningham et al., 2006).

The FLOT4-AIO trial made a major contribution to perioperative procedures and established FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) as the advised perioperative regimen in Western recommendations by showing higher survival outcomes with FLOT as compared to ECF/ECX regimens (Al-Batran et al., 2019).

3. Current Evidence: Neoadjuvant vs Adjuvant Methods

The differences in survival outcomes between neoadjuvant and adjuvant chemotherapy in gastric cancer have been the subject of recent meta-analyses, and although the results have been conflicting, the trend is moving toward neoadjuvant strategies. For example, in a large analysis of 15 studies that included 2,183 patients, Xiong et al. (2020) found no statistically significant difference in overall survival (HR 0.87; 95% CI: 0.75–1.01; p=0.07). Yet, subgroup analyses pointed to potential advantages of neoadjuvant therapy, especially in patients with locally advanced disease. More recently, Zhang et al. (2022) presented updated evidence suggesting better survival with neoadjuvant treatment (HR 0.82; 95% CI: 0.71–0.95; p=0.008), particularly for T3–T4 tumours.

3.1 Disease-Free Survival

Disease-free survival (DFS) outcomes have shown more consistent benefits with neoadjuvant chemotherapy. The early targeting of micro metastases seems to offer improved disease control, and studies such as that by Li et al. (2021) have reported better DFS in the neoadjuvant cohort.

3.2 Impact on Pathology and Surgery

3.2.1 Pathological Response

Neoadjuvant chemotherapy often leads to meaningful pathological responses, with complete response rates (pCR) ranging from 15–25%, especially when intensive regimens like FLOT are used. Achieving pCR has been closely linked with excellent long-term survival, sometimes exceeding 80% at five years (Kang et al., 2019). Even partial tumour regression and favourable histologic grades—such as those defined by the Becker tumour regression score—have been associated with better prognoses (Becker et al., 2003).

3.2.2 R0 Resection Rates

Another advantage of neoadjuvant therapy is the improved rate of R0 resections (complete tumour removal with negative margins). A systematic review

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by Wang et al. (2021) found significantly higher R0 resection rates with neoadjuvant therapy (OR 1.85; 95% CI: 1.42–2.41; p<0.001). This effect often allows for more conservative, less morbid surgeries while still achieving oncological goals. However, treatment-induced fibrosis and inflammation can sometimes complicate margin assessments (Yoshikawa et al., 2020).

3.2.3 Lymph Node Response

Neoadjuvant chemotherapy has also demonstrated a strong impact on nodal status, converting node-positive patients to node-negative in about 20–40% of cases. This nodal downstaging not only carries prognostic value but can also influence the surgical plan, particularly the extent of lymph node dissection (Park et al., 2018).

3.3 Surgical and Perioperative Outcomes

3.3.1 Surgical Complexity and Morbidity

While there were initial concerns about whether neoadjuvant therapy might complicate surgery, current evidence shows no substantial difference in operative risk. Contemporary studies report similar perioperative complication rates between patients receiving neoadjuvant therapy and those undergoing immediate surgery (Suo et al., 2019). A meta-analysis by Liu et al. (2020) also found no significant differences in operative time, intraoperative blood loss, or post-surgical morbidity, although surgical outcomes still depend on patient selection and surgical expertise.

3.3.2 Delays and Treatment Completion

One theoretical drawback of neoadjuvant treatment is the risk of delaying surgery due to drug toxicity or disease progression. However, real-world data and clinical trials have shown that more than 90% of patients go on to have successful surgeries after completing neoadjuvant therapy, with low progression rates during treatment (Al-Batran et al., 2019). Moreover, adherence to neoadjuvant regimens tends to be higher than with postoperative chemotherapy, with better tolerance and completion rates—factors that may contribute to improved outcomes (Robb et al., 2021).

4. Regional Practice Patterns and Treatment Guidelines

4.1 East Asian Perspective

In East Asian countries like Japan, South Korea, and China, adjuvant chemotherapy has traditionally been the standard, supported by landmark trials showing survival benefits. For instance, Japanese guidelines endorse postoperative S-1 monotherapy for stage II–III gastric cancer following D2 gastrectomy (Japanese Gastric Cancer Association, 2021). Nonetheless, there is growing interest in neoadjuvant approaches in these regions. The RESONANCE trial in China, using the SOX regimen (S-1 and oxaliplatin), has shown encouraging pathological and survival outcomes (Ji et al., 2020).

4.2 Western Guidelines

In contrast, Western treatment protocols—such as those from the European Society for Medical

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Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN)—increasingly favour perioperative chemotherapy, particularly the FLOT regimen, for patients with resectable gastric or gastroesophageal junction cancers (Lordick et al., 2022; NCCN Guidelines, 2023). The NCCN provides flexibility, offering both pre- and post-operative options, with decisions tailored to individual tumour characteristics, patient health, and institutional capabilities..

5. Treatment Selection and Patient Stratification

5.1 Tumor-Related Factors

Treatment selection should consider various tumor-related factors including clinical stage, tumor location, histological subtype, and molecular characteristics. Locally advanced tumors (T3-T4 or node-positive disease) appear to derive greater benefit from neoadjuvant approaches, while early-stage tumors may be adequately managed with surgery followed by adjuvant treatment (Robb et al., 2021).

With better pathological response rates compared to distal stomach tumors, neoadjuvant chemotherapy has been proven to be particularly effective against gastroesophageal junction tumors. When making treatment suggestions, contemporary recommendations (Smyth et al., 2020) consider this anatomical factor.

5.2 Patient-related factors

The patient's age, performance status, comorbidities, and nutritional status have a significant impact on the therapy chosen and its outcome. Older patients may benefit from less aggressive neoadjuvant regimens or adjuvant methods, depending on the specific circumstances. Prior to starting treatment, it is essential to optimize nutrition, irrespective of the chosen approach (Wie et al., 2021).

Treatment choice is also impacted by the ability to tolerate intensive chemotherapy regimens; for example, neoadjuvant approaches need a certain level of performance status and organ function in order to complete planned treatment cycles (Zhang et al., 2022).

6. Innovative Strategies and Future Paths

6.1 The Integration of Immunotherapy

Researchers are now looking at how to incorporate immune checkpoint inhibitors into perioperative treatment regimens. Early-phase trials combining chemotherapy with pembrolizumab or nivolumab have shown potential efficacy, particularly in tumors with high microsatellite instability (MSI-H) (Janjigian et al., 2021).

Although the KEYNOTE-585 study, which looked at perioperative pembrolizumab in conjunction with chemotherapy, showed greater rates of pathologic complete response, the data on overall survival benefits is still unclear. Biomarkers will likely play a role in choosing patients for immunotherapy combinations in future trials (Shitara et al., 2021).

6.2 Strategies for Targeted Therapy

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Around 15 to 20% of patients have HER2-positive gastric cancer, which may benefit from the addition of targeted therapy. Neoadjuvant studies combining chemotherapy with trastuzumab have shown favorable pathological response rates, but the optimal integration strategies are still being investigated (Hofheinz et al., 2020).

Additional molecular targets, including FGFR2, EGFR, and MET, are being studied in early-phase neoadjuvant research with the potential for future biomarker-driven treatment tailoring (Ku et al., 2021).

6.3 Small Procedures

The growing acceptance of minimally invasive surgical techniques, such as laparoscopic and robotic operations, may have an impact on the decision between neoadjuvant and adjuvant approaches. Early findings suggest that minimally invasive methods may have comparable oncological outcomes following neoadjuvant chemotherapy, which might increase treatment choices (Son et al., 2019).

7. Quality of life and results reported by the patient

7.1 Treatment Tolerability

Comparisons of the quality of life outcomes between neoadjuvant and adjuvant strategies have frequently shown a preference for neoadjuvant methods. Patients receiving neoadjuvant chemotherapy frequently have higher treatment completion rates and fewer major toxicities than those receiving adjuvant therapy (Wagner et al., 2020).

Being able to assess treatment response before to surgery might also give patients and their families psychological benefits that might improve the whole treatment experience and therapy adherence (Robb et al., 2021).

7.2 Long-Term Functional Outcomes

When comparing neoadjuvant and adjuvant therapies, long-term functional outcomes, such as dietary intake, digestive health, and quality of life indicators, appear to be comparable. However, neoadjuvant treatment has the potential to raise R0 resection rates, which could lead to improved functional outcomes and long-term disease control (Li et al., 2021).

8. Economic Factors

8.1 Analysis of Cost-Effectiveness

Comparisons of neoadjuvant and adjuvant methods in economic studies have yielded varied results depending on the perspective of the healthcare system and the treatment plans that were analyzed. The higher initial treatment costs of neoadjuvant methods may be offset by improved survival outcomes that result in lower recurrence rates and subsequent treatment requirements (Park et al., 2020).

Nevertheless, comprehensive economic analyses that take into account long-term healthcare use patterns and quality-adjusted life years are required in order to fairly compare the cost-effectiveness of various treatment alternatives.

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9. Current limitations and unanswered questions

9.1 Minimal Direct Comparisons

Most of the information comparing neoadjuvant and adjuvant approaches comes from indirect comparisons and meta-analyses, rather than from direct randomized controlled trials. This restriction, which also affects the reliability of recommendations (Xiong et al., 2020), emphasizes the need for dedicated comparative studies.

9.2 Biomarker Development

The lack of well-defined biomarkers for treatment selection is a major drawback of the current method. The creation of predictive biomarkers for chemotherapy response, surgical outcomes, and long-term survival could greatly improve treatment personalization (Ku et al., 2021).

9.3 Standardizing Response Evaluation

The therapeutic application of results and the comparability of trials are restricted by differences in pathologic response evaluation and prognostic scoring methods. In order to optimize therapy selection, response criteria must be standardized and validated prognosis tools must be used (Becker et al., 2003).

Conclusion and perspective for the future

In resectable stomach cancer, the ongoing comparison of neoadjuvant and adjuvant chemotherapy highlights a growing body of data favoring neoadjuvant approaches, especially for patients with locally advanced disease. Neoadjuvant chemotherapy offers a number of potential advantages, such as a greater likelihood of achieving complete tumor removal (R0 resection), a decrease in tumor size before surgery, early management of micro metastases, and often improved overall treatment tolerance.

But both neoadjuvant and adjuvant therapy have demonstrated considerable survival benefits over surgery alone. When choosing between these treatments, each patient should be taken into consideration, taking into account their unique health, the biology of the tumor, the resources available at the institution, and local clinical practices. As demonstrated by strong clinical trial findings, adjuvant chemotherapy is still widely used and successful in many parts of East Asia.

Future studies should concentrate on comparing these methods directly, investigate the use of biomarkers to guide personalized therapy, and explore how novel treatments, such immunotherapy and targeted medications, might be integrated into existing treatment regimens. As our understanding of gastric cancer deepens, the focus is likely to shift from simply choosing when to give chemotherapy to identifying the best, most individualised treatment strategy for each patient based on molecular and clinical characteristics.

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