MODERN PRINCIPLES OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED GASTRIC CANCER

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Abstract. *Gastric cancer remains one of the most lethal malignancies worldwide, particularly in cases diagnosed at a locally advanced stage. Despite advances in surgical techniques, the prognosis for such patients remains poor when surgery is used alone. Over the last two decades, neoadjuvant chemotherapy has emerged as a standard component of multimodal treatment, designed to downstage the tumor, improve R0 resection rates, and enhance overall survival.*

Modern clinical trials have validated the use of perioperative chemotherapy regimens, such as FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) and ECF (epirubicin, cisplatin, and fluorouracil), as effective strategies for managing locally advanced gastric cancer. These regimens not only facilitate curative resection but also target micrometastatic disease at an early stage. Moreover, the addition of targeted and immunotherapy agents based on molecular profiling—such as HER2 inhibitors and PD-1 blockade—has revolutionized the concept of individualized therapy.

This article discusses the evolution and current principles of neoadjuvant chemotherapy for gastric cancer, focusing on regimen selection, timing, and the role of precision medicine. The review also highlights the importance of multidisciplinary coordination among oncologists, surgeons, and radiologists to optimize patient outcomes and minimize treatment-related toxicity.

Keywords. *Neoadjuvant chemotherapy; gastric cancer; locally advanced tumor; FLOT regimen; ECF regimen; perioperative therapy; targeted therapy; immunotherapy; HER2; PD-1 blockade; precision oncology; tumor downstaging; R0 resection; multidisciplinary management.*

Introduction

Gastric cancer continues to be one of the leading causes of cancer-related mortality worldwide, particularly in East Asia, Eastern Europe, and parts of Central Asia. The majority of patients are diagnosed at an advanced or locally invasive stage, where curative resection alone is often insufficient to achieve long-term survival. Historically, the treatment of gastric cancer relied primarily on surgery; however, high recurrence rates and poor outcomes after surgery alone have prompted the evolution of a multimodal treatment strategy that integrates systemic therapy before and after surgical intervention.

The introduction of neoadjuvant chemotherapy (NACT) marked a paradigm shift in the management of locally advanced gastric cancer. Administering chemotherapy before surgery aims to reduce tumor size (downstaging), eliminate micrometastatic disease, and improve the likelihood of achieving an R0 resection — the complete removal of all tumor tissue with negative margins. In addition, early systemic therapy may help identify chemosensitive tumors and prevent postoperative relapse.

Several large-scale clinical trials, such as the MAGIC, FLOT4-AIO, and RESOLVE studies, have confirmed the clinical benefit of perioperative and neoadjuvant chemotherapy in gastric cancer. These studies demonstrated that preoperative chemotherapy significantly increases overall survival compared to surgery alone. Among these, the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel) has become the preferred standard due to its superior efficacy and tolerability compared to the older ECF regimen (epirubicin, cisplatin, and fluorouracil).

In recent years, the integration of molecular and genetic profiling has further advanced the personalization of gastric cancer treatment. The identification of biomarkers such as HER2 amplification, microsatellite instability (MSI), and PD-L1 expression has enabled the addition of targeted and immunotherapeutic agents to traditional chemotherapy, enhancing response rates and minimizing toxicity.

This article aims to review the current principles of neoadjuvant chemotherapy for locally advanced gastric cancer, summarize key evidence from landmark clinical trials, and explore future perspectives on the incorporation of precision medicine into preoperative treatment strategies. Understanding these modern

approaches is essential for optimizing therapeutic outcomes and improving the quality of life for patients with gastric cancer.

Main Body

1. The Rationale and Objectives of Neoadjuvant Chemotherapy

The fundamental goal of neoadjuvant chemotherapy (NACT) in gastric cancer is to improve the efficacy of surgical treatment through tumor downstaging, eradication of micrometastatic disease, and enhancement of the likelihood of achieving an R0 resection. Preoperative systemic therapy provides early control of microscopic metastases, increases the probability of curative resection, and allows for an in vivo assessment of tumor chemosensitivity.

In locally advanced stages (T3–T4 and/or N+), the tumor often invades adjacent structures or lymph nodes, making complete resection challenging. Neoadjuvant chemotherapy can shrink these tumors, enabling surgeons to perform less extensive, organ-preserving operations. Furthermore, it reduces postoperative relapse and distant metastasis rates, which are common causes of mortality in gastric cancer patients.

2. Evolution of Chemotherapy Regimens

The concept of perioperative and neoadjuvant chemotherapy gained global acceptance after several pivotal trials demonstrated survival benefits.

- **The MAGIC Trial (2006)** compared perioperative chemotherapy using the **ECF regimen (epirubicin, cisplatin, fluorouracil)** versus surgery alone and showed significant improvement in both progression-free and overall survival.
- **The FLOT4-AIO Trial (2019)** established the **FLOT regimen (fluorouracil, leucovorin, oxaliplatin, docetaxel)** as the current gold standard, offering superior median survival and higher pathological response rates than ECF.
- **The RESOLVE Trial (2021)** further confirmed the benefits of perioperative chemotherapy in Asian populations, emphasizing the role of regional differences in treatment optimization.

Compared to ECF, the FLOT regimen provides better tumor control and lower toxicity, making it the preferred choice for most patients with resectable locally advanced gastric cancer. However, patient tolerance and nutritional status must be considered, as aggressive regimens can cause hematologic and gastrointestinal side effects.

3. The Role of Multimodal Treatment

Effective management of locally advanced gastric cancer relies on a **multidisciplinary approach**, integrating chemotherapy, surgery, and, in some cases, radiotherapy.

Preoperative chemotherapy enhances surgical outcomes, while postoperative adjuvant therapy helps eliminate residual microscopic disease. The timing and coordination between oncologists, surgeons, and radiologists are crucial to maximize therapeutic benefits.

Emerging studies suggest that adding **radiotherapy** to chemotherapy in selected cases may further improve local control, although its use remains controversial outside of specific tumor locations or in cases of incomplete resection margins.

4. Advances in Targeted Therapy and Immunotherapy

Recent molecular discoveries have expanded the possibilities for personalized treatment in gastric cancer.

- **HER2-positive tumors** benefit from the addition of **trastuzumab**, a monoclonal antibody targeting the HER2 receptor, when combined with chemotherapy in the neoadjuvant setting.
- **PD-1 inhibitors (nivolumab, pembrolizumab)** have shown remarkable activity in **MSI-high** and **PD-L1–expressing** tumors, offering a new dimension to preoperative therapy.
- Trials are currently exploring **VEGF inhibitors (bevacizumab, ramucirumab)** and **Claudin18.2-targeted antibodies (zolbetuximab)** as potential neoadjuvant agents.

The integration of these targeted and immune-based therapies enhances the response rate and may help achieve complete or near-complete pathological responses in selected patient populations.

5. Surgical Implications and Pathological Response

Neoadjuvant chemotherapy improves the chances of performing curative resection while preserving healthy tissues. Tumor shrinkage enables more precise dissection and reduces the likelihood of positive margins.

Pathological response — the degree of tumor regression after chemotherapy — is an important prognostic factor. A complete pathological response (pCR) is

associated with a significantly lower risk of recurrence and improved overall survival. The evaluation of tumor regression grade (TRG) has become a standard method for assessing response quality.

Timing of surgery after neoadjuvant therapy typically ranges from **4 to 6 weeks** post-treatment, allowing for patient recovery while maintaining therapeutic efficacy. However, surgical outcomes depend heavily on preoperative nutritional support, as malnutrition is common among gastric cancer patients.

6. Current Challenges and Future Directions

Despite substantial progress, several challenges remain in optimizing neoadjuvant chemotherapy. Determining the **optimal duration and regimen**, managing **chemotherapy-induced toxicity**, and identifying **biomarkers of response** are key research priorities.

In the near future, **precision oncology** is expected to guide neoadjuvant treatment selection, incorporating genomic profiling, circulating tumor DNA (ctDNA) monitoring, and advanced imaging techniques. Artificial intelligence and predictive modeling may further help clinicians identify patients who would benefit most from specific preoperative strategies.

Ongoing trials are also investigating the combination of **immunotherapy with FLOT**, aiming to enhance tumor regression rates and achieve long-term disease control. The future of gastric cancer treatment lies in the integration of cytotoxic, molecular, and immune-based therapies into a unified, personalized treatment paradigm.

Discussion

The implementation of neoadjuvant chemotherapy (NACT) in locally advanced gastric cancer has revolutionized the treatment paradigm, transforming the disease from a primarily surgical challenge into a multidisciplinary therapeutic target. Numerous clinical studies have demonstrated that preoperative chemotherapy significantly improves survival outcomes, increases R0 resection rates, and provides a chance for long-term disease control. However, the success of this strategy depends on precise patient selection, optimal regimen choice, and careful perioperative management.

One of the most discussed aspects is the **comparison between perioperative and purely neoadjuvant strategies**. Western trials such as **MAGIC** and **FLOT4-**

AIO advocate perioperative treatment as the standard of care, while Eastern approaches often prioritize postoperative adjuvant chemotherapy following D2 lymphadenectomy. The difference is largely due to variations in surgical techniques, genetic background, and healthcare systems. These regional distinctions highlight the importance of **individualized treatment planning** rather than a one-size-fits-all approach.

Another key topic concerns the **assessment of tumor response**. Radiologic imaging, while helpful, often underestimates the actual pathological regression. Therefore, histopathological evaluation using **Tumor Regression Grade (TRG)** remains the gold standard for evaluating treatment efficacy. Studies have shown that patients who achieve a major or complete pathological response exhibit significantly better long-term outcomes, emphasizing the prognostic value of preoperative therapy.

Moreover, **chemotherapy resistance** continues to pose a major obstacle. Tumor heterogeneity and molecular alterations, such as **TP53 mutations**, **HER2 amplification**, or **EMT (epithelial–mesenchymal transition)**, can limit drug efficacy. Emerging biomarkers and molecular profiling technologies now allow clinicians to identify patients who are likely to benefit from specific regimens or targeted agents. Integration of **next-generation sequencing (NGS)** and **liquid biopsy** techniques may soon enable real-time monitoring of treatment response and early detection of resistance mechanisms.

In addition, the **toxicity profile** of neoadjuvant regimens must not be underestimated. Although modern combinations like FLOT provide superior survival benefits, they are associated with higher rates of neutropenia, neuropathy, and gastrointestinal complications. Hence, comprehensive supportive care, including nutritional optimization and prophylactic medication, is essential to maintain dose intensity and prevent treatment discontinuation.

Recent developments in **immunotherapy and targeted therapy** have opened new frontiers. For example, combining **PD-1 inhibitors** with standard chemotherapy regimens has yielded encouraging results in patients with **MSI-high** or **PD-L1–positive** tumors. Similarly, the addition of **trastuzumab** for HER2-positive gastric cancers has shown promising pathological responses in preoperative settings. Such advancements are gradually shifting the focus from

conventional cytotoxic regimens toward **precision-based and biomarker-driven therapies**.

Finally, future research should aim to define **optimal treatment algorithms** based on molecular subtypes, develop **predictive response models**, and establish **integrated multidisciplinary protocols** that combine chemotherapy, surgery, immunotherapy, and targeted drugs in a seamless clinical workflow. Collaboration between oncologists, surgeons, radiologists, and molecular biologists will be vital for translating scientific progress into tangible clinical benefits.

In conclusion, the modern principles of neoadjuvant chemotherapy in locally advanced gastric cancer rest upon a personalized, evidence-based, and multidisciplinary framework. As treatment strategies evolve, the combination of molecular diagnostics, innovative therapeutics, and patient-centered care promises to improve not only survival rates but also quality of life for patients facing this complex malignancy.

Conclusion

Neoadjuvant chemotherapy has become an integral component of the treatment strategy for locally advanced gastric cancer, representing one of the most significant advances in modern oncologic care. By enabling tumor downstaging, increasing the probability of R0 resection, and reducing recurrence risk, it has substantially improved both survival outcomes and the quality of surgical intervention.

The current evidence, supported by landmark studies such as **MAGIC**, **FLOT4-AIO**, and **RESOLVE**, demonstrates that perioperative and preoperative chemotherapy are superior to surgery alone. Among available regimens, **FLOT** is now considered the standard of care, offering improved overall and disease-free survival compared to older ECF-based therapies. However, treatment success depends on multidisciplinary coordination, adequate patient selection, and careful perioperative management.

The integration of **molecular-targeted therapies** and **immunotherapy** into the neoadjuvant setting is reshaping the therapeutic landscape. HER2-directed agents, PD-1 inhibitors, and novel biomarkers such as MSI and Claudin18.2 are paving the way toward personalized medicine. As research progresses, identifying

molecular predictors of treatment response will be essential for optimizing therapy and minimizing unnecessary toxicity.

Future perspectives in gastric cancer management are centered on **precision oncology**, where molecular profiling, artificial intelligence–based prediction models, and liquid biopsy technologies will guide individualized treatment plans. Continuous clinical trials, collaboration across disciplines, and adherence to evidence-based guidelines will remain vital in refining these strategies.

In conclusion, modern principles of neoadjuvant chemotherapy in locally advanced gastric cancer emphasize a **personalized, multidisciplinary, and biologically informed approach** that aligns therapeutic innovation with patient-centered care. This comprehensive model promises to enhance survival rates, reduce relapse risk, and improve the overall prognosis of gastric cancer patients worldwide.

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