EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 9.2 www.in-academy.uz/index.php/ejmns

BIOLOGY-DRIVEN MANAGEMENT OF LOCALLY ADVANCED STAGE III GASTRIC CANCER: A SITUATIONAL ANALYSIS AND PRACTICAL TREATMENT ALGORITHM

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https://doi.org/10.5281/zenodo.20678301

ARTICLE INFO

Received: 02nd June 2026
Accepted: 04th June 2026
Online: 05th June 2026

KEYWORDS

Gastric cancer; locally advanced gastric cancer; stage III; FLOT; XELOX; laparoscopic gastrectomy; neoadjuvant chemotherapy; MSI-H; HER2; CLDN18.2; precision oncology.

ABSTRACT

Gastric cancer remains one of the most clinically important malignancies worldwide, particularly in countries where population-based endoscopic screening is not routinely implemented and a considerable proportion of patients present with locally advanced disease. Stage III gastric cancer is traditionally regarded as a surgical disease requiring radical gastrectomy and D2 lymphadenectomy. However, modern evidence clearly demonstrates that surgery alone is insufficient for many patients, and multimodal treatment has become the cornerstone of curative-intent management.

Perioperative chemotherapy with FLOT has improved survival outcomes in resectable gastric and gastroesophageal junction adenocarcinoma and is widely considered a preferred standard for clinically fit patients. Nevertheless, the response to the same chemotherapy regimen varies substantially. Some tumors demonstrate major pathological regression, whereas others show minimal or no response. This heterogeneity cannot be explained by anatomical stage alone. Histological phenotype, tumor differentiation, Lauren classification, microsatellite instability, HER2 status, PD-L1 expression, CLDN18.2 expression, tumor microenvironment and patient-related factors may all influence treatment response and prognosis.

The aim of this article is to provide a situational analysis of current evidence in the management of locally advanced stage III gastric cancer and to propose a practical biology-driven algorithm for clinical decision-making. The central concept is that stage III gastric cancer should no longer be treated as a uniform clinical entity. Instead, treatment should be individualized according to tumor biology, patient fitness, technical resectability and availability of modern diagnostic resources. Such an approach is particularly relevant for oncology systems undergoing active modernization, where rational prioritization of molecular diagnostics, multidisciplinary decision-making and minimally invasive surgery may improve both short-term and long-term outcomes.

Introduction

Gastric cancer remains a major global oncological problem. Despite improvements in diagnostics, surgery, systemic therapy and perioperative care, outcomes for patients with locally advanced disease remain unsatisfactory. In many healthcare systems, stage III gastric cancer represents a frequent clinical scenario because early detection programs are either absent or insufficiently developed. As a result, surgeons and medical oncologists often face patients with tumors that are technically resectable but biologically aggressive.

Historically, radical surgery was considered the main curative treatment for gastric cancer. The quality of surgery, including the achievement of R0 resection and adequate D2 lymphadenectomy, remains critically important. However, stage III disease is not purely local. It is associated with a high probability of occult systemic spread, lymphatic dissemination and peritoneal recurrence. This explains why surgery alone is often unable to provide optimal long-term disease control.

The modern treatment paradigm has shifted toward multimodality therapy. Perioperative chemotherapy, adjuvant chemotherapy, chemoradiotherapy in selected settings, minimally invasive surgery and molecularly guided systemic treatment are now important components of the therapeutic landscape. However, a major unresolved question remains: why does the same treatment work very well in some patients and fail completely in others?

This question is especially relevant in the era of FLOT-based perioperative therapy. FLOT improved survival compared with older chemotherapy regimens, but it did not eliminate primary resistance. A significant proportion of patients do not achieve major pathological response, and some patients cannot complete the full perioperative program due to toxicity, postoperative complications or disease progression. Therefore, the challenge is not only to select the strongest chemotherapy regimen but to select the right strategy for the right patient.

The aim of this article is to analyze the current evidence and propose a practical biology-driven approach to stage III gastric cancer. The article focuses on several clinically important questions: when FLOT is appropriate, when XELOX/CAPOX may be more reasonable, whether tumor differentiation and diffuse phenotype matter, how molecular markers can guide treatment, and whether immediate surgery or non-surgical strategies may be considered in selected subgroups.

Materials and Methods

This article was designed as a narrative review and situational analysis. Current evidence was summarized from major randomized clinical trials, international guidelines and contemporary studies addressing perioperative chemotherapy, adjuvant therapy, laparoscopic surgery, molecular classification and immunotherapy in gastric and gastroesophageal junction cancer.

The analysis focused on the following domains:

1. The role of perioperative chemotherapy in resectable locally advanced gastric cancer.

2. The clinical meaning of histological subtype and tumor differentiation.
3. The practical choice between FLOT and doublet regimens such as XELOX/CAPOX.
4. The role of molecular biomarkers, including MSI/MMR, HER2, PD-L1 and CLDN18.2.
5. The place of minimally invasive surgery in stage III gastric cancer.
6. The development of a practical treatment algorithm for multidisciplinary use.

The proposed algorithm is not intended to replace national or international guidelines. It is designed as a practical framework for clinical discussion, particularly in oncology systems where the integration of molecular diagnostics and multimodality treatment is still developing.

Results and Discussion

1. Stage III gastric cancer is not a single disease

The first important concept is that stage III gastric cancer is anatomically defined but biologically heterogeneous. Two patients may have the same TNM stage but completely different tumor behavior. One patient may have an intestinal-type, microsatellite-stable, chemotherapy-sensitive tumor. Another may have a diffuse or signet-ring phenotype with infiltrative growth, poor differentiation and high risk of peritoneal recurrence.

These two patients should not necessarily receive the same strategy. Anatomical staging remains essential, but it is no longer sufficient. Modern treatment decisions should combine TNM stage with tumor biology, patient fitness and expected response to systemic therapy.

Lauren classification remains clinically useful. Intestinal-type gastric cancer is generally more associated with gland-forming morphology and may demonstrate better responsiveness to chemotherapy. Diffuse-type tumors, especially those with signet-ring cell features, are often associated with infiltrative growth, peritoneal spread and lower response rates to cytotoxic chemotherapy. Poor differentiation also tends to correlate with more aggressive tumor behavior.

Therefore, a modern report for stage III gastric cancer should not only state “adenocarcinoma of the stomach”. It should include histological subtype, grade, Lauren phenotype if possible, lymphovascular invasion when available and molecular markers that can influence systemic treatment.

2. FLOT: standard of care, but not a universal solution

The FLOT regimen became a major standard in the perioperative treatment of resectable gastric and gastroesophageal junction adenocarcinoma. In the FLOT4-AIO trial, perioperative FLOT improved median overall survival compared with ECF/ECX. This established docetaxel-containing triplet chemotherapy as a preferred option for fit patients with resectable locally advanced disease.

However, the clinical interpretation of FLOT should be balanced. FLOT is a strong regimen, but it is not a universal answer for all patients. The benefit observed in clinical trials reflects a selected population with adequate performance status and organ function. In real-world practice, many patients are older, nutritionally compromised or have

comorbidities that limit tolerance to intensive therapy.

Moreover, not every tumor is equally sensitive to FLOT. Some patients achieve significant tumor regression and become excellent surgical candidates. Others show little response, and the preoperative treatment may delay potentially curative surgery. This is particularly important in diffuse, poorly differentiated and signet-ring phenotypes, where the expected benefit from cytotoxic therapy may be lower.

Therefore, the correct question is not "Should all patients receive FLOT?" but rather "Which patient is most likely to benefit from FLOT, and which patient requires another strategy?"

In practical terms, FLOT is most appropriate for patients with:

- ECOG performance status 0–1;
- adequate renal, hepatic and bone marrow function;
- acceptable nutritional status;
- resectable locally advanced disease;
- no severe neuropathy or major contraindication to taxanes/oxaliplatin;
- tumor biology that does not strongly suggest primary chemoresistance.

3. When XELOX/CAPOX may be a better practical decision

XELOX/CAPOX should not be presented as superior to FLOT for all patients. However, it may be a more realistic and safer option for selected patients. In clinical oncology, the most effective regimen is not always the most intensive regimen; it is the regimen that the patient can actually complete without unacceptable toxicity.

Doublet therapy with capecitabine and oxaliplatin has strong evidence in the adjuvant setting after D2 gastrectomy. For patients who are frail, elderly, nutritionally depleted or have borderline performance status, XELOX/CAPOX may offer a more feasible balance between efficacy and tolerability.

This is particularly important in healthcare systems where supportive care resources, nutritional support, toxicity monitoring and access to granulocyte-colony stimulating factors may vary. In such settings, overuse of intensive triplet therapy can lead to complications, treatment interruption and delayed surgery.

Therefore, XELOX/CAPOX may be considered in:

- elderly or frail patients;
- ECOG 2 patients;
- patients with reduced tolerance to triplet chemotherapy;
- patients with high risk of FLOT-related toxicity;
- patients in whom the primary goal is to complete multimodality treatment safely.

The key principle is individualization. De-escalation should not be viewed as undertreatment when it allows the patient to complete the intended treatment pathway.

4. Oxaliplatin or cisplatin: why oxaliplatin is preferred in most modern strategies

Platinum remains an essential component of systemic therapy in gastric cancer. Historically, cisplatin was widely used. However, oxaliplatin has become more common in modern perioperative and adjuvant regimens due to its more convenient administration and more favorable toxicity profile.

Cisplatin is associated with nephrotoxicity, ototoxicity, nausea,

vomiting and the need for intensive hydration. These factors may be problematic in patients with borderline renal function, older age or poor general condition. Oxaliplatin is associated mainly with neuropathy and myelosuppression, but it is generally easier to integrate into outpatient treatment protocols.

For most patients with stage III gastric cancer, oxaliplatin-based regimens such as FLOT or XELOX/CAPOX provide a practical advantage. Cisplatin may still have a role in selected settings, but it is no longer the default platinum backbone for many perioperative strategies.

5. Molecular stratification: from optional testing to clinical necessity

Modern management of gastric cancer increasingly depends on molecular testing. In metastatic disease, biomarkers already guide treatment selection. In resectable stage III disease, their role is still evolving, but they are becoming increasingly important.

At minimum, the following markers should be considered:

1. MSI/MMR status.
2. HER2 status.
3. PD-L1 combined positive score.
4. CLDN18.2 expression where available.
5. EBV status in selected academic settings.

MSI-H/dMMR tumors are particularly important. They often demonstrate an immunogenic phenotype and may respond strongly to immune checkpoint inhibitors. At the same time, the benefit of conventional chemotherapy in this subgroup may be limited. This does not mean that surgery should be routinely omitted in stage III gastric cancer, but it does mean that MSI-H/dMMR patients require separate multidisciplinary discussion.

HER2 is a well-established target in advanced gastric cancer. Its perioperative role is still under investigation, but HER2 testing remains important because recurrence or progression may require HER2-directed therapy.

PD-L1 is not a perfect biomarker, but higher expression is generally associated with greater probability of benefit from checkpoint inhibitors in advanced disease. Its role in perioperative treatment is expanding.

CLDN18.2 is one of the most important emerging targets. Zolbetuximab has shown benefit in CLDN18.2-positive, HER2-negative advanced gastric and gastroesophageal junction adenocarcinoma. However, these results should not be directly transferred to resectable stage III disease without caution. At present, CLDN18.2 is best viewed as a marker of future therapeutic relevance in the perioperative setting.

6. Immunotherapy in resectable disease: promising but not yet universal

Immune checkpoint inhibitors have changed the treatment of advanced gastric and gastroesophageal cancers. More recently, their role in resectable disease has become one of the most active areas of clinical research.

The most biologically convincing subgroup is MSI-H/dMMR gastric cancer. In this group, neoadjuvant immunotherapy can produce deep responses, including major pathological response and pathological complete response in selected studies. However,

non-operative management remains investigational and should not be applied routinely outside clinical trials or highly specialized multidisciplinary protocols.

For unselected stage III gastric cancer, perioperative immunotherapy is still being defined. Some recent trials suggest that combining checkpoint inhibitors with FLOT may improve outcomes in resectable gastric and gastroesophageal junction cancer. However, not every patient will benefit equally, and biomarkers remain crucial for rational implementation.

Thus, the role of immunotherapy in stage III gastric cancer should be described carefully:

- It is highly relevant in MSI-H/dMMR tumors.
- It is promising in combination with perioperative chemotherapy.
- It is not yet a universal replacement for surgery or chemotherapy.
- Its use should be guided by biomarkers, evidence and availability.

7. Surgery: still central, but no longer isolated

Surgery remains the cornerstone of curative treatment for resectable stage III gastric cancer. The goal is R0 resection with adequate lymphadenectomy, preferably D2 in experienced centers. However, surgery should not be isolated from systemic strategy.

The timing of surgery depends on tumor biology, symptoms, resectability and response to systemic treatment. For most fit patients, perioperative therapy followed by surgery is appropriate. For patients with bleeding, obstruction, perforation risk or inability to tolerate neoadjuvant therapy, upfront surgery may be necessary.

For diffuse or signet-ring tumors, the decision is more complex. Some clinicians argue that poor response to chemotherapy supports earlier surgery. Others emphasize the high risk of systemic and peritoneal recurrence and the need for systemic treatment. In such cases, diagnostic laparoscopy, peritoneal cytology and multidisciplinary review are especially important.

The most dangerous approach is automatic decision-making. Neither “FLOT for everyone” nor “surgery first for everyone” is acceptable. Surgery should be integrated into a personalized plan.

8. Role of laparoscopic surgery in locally advanced gastric cancer

Minimally invasive surgery has become increasingly important in gastric cancer. For early gastric cancer, laparoscopic surgery is widely accepted in experienced centers. For locally advanced disease, adoption has been more cautious because of concerns about D2 lymphadenectomy, oncological radicality and long-term outcomes.

However, modern randomized trials from East Asia have shown that laparoscopic distal gastrectomy can provide non-inferior survival outcomes compared with open surgery in selected patients with locally advanced gastric cancer, while reducing some postoperative or late complications. These findings support the use of minimally invasive surgery when performed by trained surgeons in high-volume settings.

In stage III gastric cancer, the potential advantages of laparoscopy are particularly relevant:

- reduced blood loss;

- less postoperative pain;
- faster mobilization;
- shorter hospital stay;
- earlier functional recovery;
- potentially earlier start of adjuvant therapy.

The key condition is quality control. Laparoscopic surgery should not compromise R0 resection, lymph node yield or oncological principles. It should be implemented through structured training, case selection and audit of outcomes.

Proposed Biology-Driven Treatment Algorithm

Step 1. Baseline staging and clinical assessment

All patients with suspected stage III gastric cancer should undergo:

- upper gastrointestinal endoscopy with multiple biopsies;
- contrast-enhanced CT of the chest, abdomen and pelvis;
- assessment of ECOG performance status;
- nutritional assessment;
- laboratory evaluation;
- diagnostic laparoscopy in patients with high risk of peritoneal dissemination;
- multidisciplinary tumor board review.

Step 2. Pathological and molecular assessment

The pathology report should include:

- histological subtype;
- tumor grade;
- Lauren classification if possible;
- MSI/MMR status;
- HER2 status;
- PD-L1 CPS;
- CLDN18.2 expression if available.

Step 3. Treatment selection

Group 1: Fit patient, MSS, intestinal phenotype, resectable disease

Preferred strategy: perioperative FLOT followed by radical surgery and postoperative therapy if feasible.

Group 2: Frail patient or borderline performance status

Preferred strategy: XELOX/CAPOX or individualized de-escalation. The goal is safe completion of multimodality treatment.

Group 3: MSI-H/dMMR tumor

Preferred strategy: multidisciplinary discussion. Immunotherapy or clinical trial should be considered where available. Surgery remains standard but may be individualized depending on response and evidence.

Group 4: Diffuse/signet-ring phenotype

Preferred strategy: careful staging, diagnostic laparoscopy, peritoneal cytology if available, and individualized decision between perioperative therapy and earlier surgery. Standard FLOT should not be automatic.

Group 5: HER2-positive tumor

Preferred strategy: standard curative-intent treatment with documentation of HER2 status. HER2-directed therapy is established in advanced disease; perioperative use should follow evidence, access and guideline recommendations.

Group 6: CLDN18.2-positive, HER2-negative tumor

Preferred strategy: standard curative-intent treatment in resectable disease. CLDN18.2 should be documented because of its therapeutic relevance in advanced disease and potential future perioperative application.

Step 4. Response assessment and surgery

After neoadjuvant therapy, reassessment should include imaging, clinical evaluation and MDT discussion. Surgery should be performed if R0 resection is feasible and the patient remains fit for operation.

Step 5. Postoperative strategy

Postoperative treatment should depend on:

- pathological stage;
- regression grade;
- R0/R1 status;
- lymph node involvement;
- complications;
- recovery speed;
- molecular markers;
- ability to tolerate systemic therapy.

Practical Implications for Oncology Systems

A biology-driven strategy requires more than individual clinical knowledge. It requires system-level organization. The following priorities are particularly important:

1. Standardized endoscopic biopsy protocols.
2. Reliable pathology reporting.
3. Access to basic immunohistochemistry.
4. Routine MSI/MMR and HER2 testing.
5. Gradual implementation of PD-L1 and CLDN18.2 testing.
6. Mandatory multidisciplinary tumor boards.
7. Training in D2 lymphadenectomy and minimally invasive gastrectomy.
8. Monitoring of R0 rate, lymph node yield, complications, recurrence and survival.
9. Development of national gastric cancer registries.
10. Integration of systemic therapy and surgery into a single treatment pathway.

For countries with developing oncology infrastructure, the first step is not necessarily universal access to all expensive molecular tests. The first step is standardization of the minimum diagnostic and treatment pathway. MSI/MMR and HER2 testing should be prioritized because they can directly influence treatment planning and future therapy. PD-L1 and CLDN18.2 can be added progressively as access improves.

Conclusion

Locally advanced stage III gastric cancer should no longer be treated as a uniform disease. The same TNM stage can include tumors with very different biological behavior, chemotherapy sensitivity and risk of recurrence. FLOT remains an important standard for clinically fit patients, but it should not be used automatically in every case. XELOX/CAPOX remains a valuable option for patients who cannot tolerate intensive triplet therapy. MSI-H/dMMR, HER2, PD-L1 and CLDN18.2 are becoming increasingly important for treatment planning.

Surgery remains central to curative treatment, but it must be integrated into a broader multimodal and biology-driven strategy. Minimally invasive surgery may improve recovery in selected patients when oncological principles are preserved. The future of stage III gastric cancer treatment lies in the transition from a stage-based model to a biology-based model.

The most important practical message is simple: we should not treat only the stage; we should treat the tumor biology of a particular patient.

Conflicts of Interest

The author declares no conflicts of interest.

Funding

No external funding was received for the preparation of this article.

Ethical Statement

This article is a narrative review and situational analysis. It does not include individual patient data; therefore, ethical approval was not required. If institutional clinical data are added in a future version, approval from the local ethics committee will be required.

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