

Predicting Response to Perioperative Chemotherapy in Resectable Gastric Cancer: Integrating Clinical, Pathological, Molecular, and Host-Related Biomarkers

Rasha Haggag, Ola M. Elfaragy, Ahmad Barakat Waley, Manar Saad Mohamed Ramadan, Lamiaa M. Kamel

1 Medical Oncology Department - Faculty of Medicine, Zagazig University,

2 Clinical Pathology Department - Faculty of Medicine, Zagazig University,

Corresponding author: Manar Saad Mohamed Ramadan

ABSTRACT

Perioperative chemotherapy has transformed the management of locally advanced resectable gastric and gastroesophageal junction adenocarcinoma, with fluorouracil, leucovorin, oxaliplatin, and docetaxel representing a central contemporary regimen. However, therapeutic benefit is heterogeneous. Some patients achieve profound pathological regression and durable survival, whereas others experience minimal tumor response, early metastatic progression, treatment toxicity, or postoperative recurrence. Accurate prediction of treatment response before and during perioperative therapy could therefore reduce ineffective treatment and support individualized multimodality strategies. Traditional clinical variables—including TNM stage, tumor location, performance status, Lauren phenotype, and signet-ring/diffuse histology—provide important but incomplete prognostic information. Pathological tumor regression after neoadjuvant therapy is strongly associated with outcome but is available only after treatment and surgery. Molecular classification has introduced additional biomarkers, particularly microsatellite instability/mismatch-repair deficiency, HER2 amplification, Epstein-Barr virus status, and immune-related characteristics. MSI-high tumors represent a biologically important subgroup with favorable prognosis and uncertain benefit from conventional cytotoxic perioperative chemotherapy, while demonstrating remarkable sensitivity to checkpoint blockade in early studies. Circulating tumor DNA, metabolic imaging, radiomics, inflammatory biomarkers, nutritional status, and indices such as HALP provide complementary approaches for evaluating tumor burden and host biology. Recent perioperative immunotherapy trials further demonstrate that response prediction is becoming increasingly relevant as therapeutic options expand. This review evaluates established and emerging determinants of response to perioperative treatment and proposes an integrated framework combining tumor pathology, molecular biology, host immune-nutritional status, imaging, and molecular residual disease to advance precision perioperative oncology in gastric cancer.

Keywords: gastric cancer, perioperative chemotherapy, FLOT, treatment response

INTRODUCTION

Curative treatment of locally advanced gastric cancer requires successful coordination of systemic therapy, radical surgery, lymphadenectomy, pathological assessment, postoperative recovery, and appropriate surveillance. Surgery alone is insufficient for many patients with cT2 or node-positive disease because clinically occult micrometastatic disease may already exist at presentation. Perioperative chemotherapy was therefore developed to treat systemic disease early, reduce tumor burden, improve R0 resection rates, and select patients whose rapidly progressive biology may make major surgery futile. [1]

The MAGIC trial established proof of principle for perioperative chemotherapy by demonstrating improved progression-free and overall survival with perioperative epirubicin, cisplatin, and fluorouracil compared with surgery

alone. The French FNCLCC/FFCD trial independently supported the perioperative strategy using fluorouracil and cisplatin. These studies established multimodality treatment as an oncological standard in Western practice. [1, 2]

The therapeutic landscape changed substantially with FLOT4. Compared with epirubicin-based therapy, perioperative FLOT improved median overall survival and produced better pathological outcomes, leading to its adoption as the reference regimen for fit patients with resectable, locally advanced gastric or gastroesophageal junction adenocarcinoma. However, even with FLOT, a clinically important proportion of patients fail to achieve meaningful regression or ultimately relapse. [3]

The central research gap is therefore no longer whether perioperative therapy is beneficial at the population level, but **which patient is most likely to benefit from which perioperative strategy**. Current treatment selection remains driven largely by anatomical stage and fitness, while reliable pretreatment predictors of chemotherapy sensitivity remain limited. This review examines clinical, pathological, molecular, imaging, circulating, and host-related biomarkers that could refine prediction of response and recurrence.

Methods

This narrative review evaluates established and emerging determinants of response to perioperative treatment in resectable gastric and gastroesophageal junction adenocarcinoma. The evidence considered was restricted to publications available through December 2024. Sources were identified through targeted online searches of PubMed-indexed literature and journal websites, together with examination of references cited in relevant trials and reviews. Search concepts combined gastric or gastroesophageal junction cancer with perioperative or neoadjuvant chemotherapy, FLOT, pathological response, MSI/MMR, HER2, checkpoint inhibition, FDG-PET, radiomics, circulating tumor DNA, and immune-nutritional biomarkers. Randomized therapeutic trials, prospective biomarker investigations, and systematic reviews were prioritized; retrospective cohorts were included where prospective data were limited. The synthesis considered the chemotherapy backbone, disease site, histological and molecular characteristics, response definition, follow-up, and whether a finding represented prognosis, treatment response, or a demonstrated treatment-by-biomarker interaction. Citation details were checked against publication records, and trial descriptions were aligned with reports within the specified literature period. Findings were integrated descriptively rather than pooled quantitatively. This review did not use a registered systematic-review protocol or formal risk-of-bias scoring framework.

Evolution of Perioperative Chemotherapy

Perioperative therapy offers several theoretical advantages over postoperative treatment alone. Preoperative chemotherapy is delivered when patients generally have better physiological reserve, before postoperative nutritional deterioration and surgical morbidity. It provides an opportunity for tumor downstaging, facilitates assessment of treatment sensitivity, and may eradicate micrometastatic disease at an earlier point in the disease course. The major limitation is exposure to ineffective therapy in nonresponders, with possible disease progression before potentially curative surgery. [3]

The MAGIC regimen represented a major advance, but subsequent experience highlighted limitations associated with epirubicin-containing therapy. FLOT was developed to exploit the activity of docetaxel, oxaliplatin, and fluoropyrimidines while maintaining a feasible perioperative schedule. In FLOT4, 716 patients with resectable cT2 or node-positive gastric/GEJ adenocarcinoma were randomized, and FLOT extended median survival compared with ECF/ECX. [3]

Although FLOT4 established the benefit of FLOT, its outcomes may not be reproduced uniformly in routine practice, where patient selection, physiological reserve, and treatment delivery can differ from those in the trial. Older age, frailty, nutritional compromise, postoperative complications, and treatment-related toxicity influence the proportion of patients completing all planned perioperative cycles. Prediction of response must therefore encompass not only intrinsic chemosensitivity but also the probability that the host can successfully complete a multimodality treatment pathway. [3]

Pathological Response: The Most Direct Measure of Chemosensitivity

Histopathological tumor regression is a direct measure of the biological effect of preoperative therapy. Several regression systems exist, including the Becker classification and Mandard-type scoring. The Becker system evaluates the percentage of residual viable tumor relative to the previous tumor bed and was specifically developed in gastric carcinoma after neoadjuvant chemotherapy. [4]

In a larger series of 480 gastric adenocarcinomas treated with preoperative chemotherapy, Becker and colleagues confirmed the prognostic importance of histopathological regression. Patients achieving major regression had more favorable outcomes than nonresponders, although post-treatment pathological stage remained highly influential. Consequently, regression grading provides information beyond a simple binary assessment of resection status. [5]

Pathological complete response is particularly attractive as an endpoint in clinical trials because it is measurable earlier than overall survival. However, pCR is relatively uncommon with chemotherapy alone, and it is not a perfect surrogate for long-term outcome. Nodal sterilization, ypT stage, margin status, lymphovascular invasion, and the pattern of residual disease may all modify recurrence risk. Response assessment should therefore integrate regression grade with the complete post-treatment pathological stage. [5]

An additional limitation is that pathological response is available only after neoadjuvant treatment and resection. It can identify prognosis and guide postoperative risk discussions but cannot rescue a patient from receiving an ineffective preoperative regimen. The clinically more valuable challenge is predicting regression *before* or very early during therapy. [5]

Clinical Stage and Disease Burden

Clinical T and N stage remain fundamental variables. Greater primary-tumor depth and bulky nodal involvement generally reflect higher tumor burden and greater recurrence risk. However, preoperative staging has imperfect accuracy, particularly for nodal disease and small-volume peritoneal dissemination. Diagnostic laparoscopy therefore remains important in patients at substantial risk for occult peritoneal disease. [6]

Even after accurate staging, TNM provides limited information regarding chemotherapy sensitivity. Two patients with cT3N1 disease can display markedly different pathological responses to identical FLOT treatment. Anatomical stage should consequently be viewed as the foundation of risk assessment rather than a complete predictive biomarker. [6]

Histological Phenotype and Signet-Ring Cell Biology

Lauren diffuse-type and signet-ring cell-rich gastric carcinomas represent a biologically important subgroup. These tumors are characterized by discohesive growth, frequent peritoneal dissemination, distinct molecular alterations, and—in several retrospective datasets—lower response to conventional preoperative chemotherapy. Historical multicenter evidence suggested limited benefit from perioperative chemotherapy in signet-ring cell adenocarcinoma. [7]

However, these data must be interpreted cautiously because many studies predated FLOT and were retrospective. More recent analyses have continued to associate signet-ring histology with poorer outcomes during perioperative FLOT, but treatment selection bias and small sample size remain important. Signet-ring positivity should therefore be regarded as a high-risk biological feature rather than an established indication to omit perioperative therapy. [8]

The appropriate future approach is prospective stratification. Diffuse and signet-ring tumors should be specifically represented in clinical trials assessing chemotherapy, immunotherapy, intraperitoneal strategies, and molecularly targeted treatment, rather than extrapolating results from predominantly intestinal-type populations. [8]

Molecular Classification: From Prognosis Toward Treatment Selection

The TCGA molecular classification transformed understanding of gastric adenocarcinoma by identifying four major groups: Epstein-Barr virus-associated tumors, microsatellite unstable tumors, genomically stable tumors, and chromosomal-instability tumors. These groups differ in mutational burden, epigenetic characteristics, receptor-tyrosine-kinase alterations, immune biology, and histological associations. [9]

Molecular classification does not yet replace conventional perioperative decision-making, but it reveals why a single chemotherapy strategy is unlikely to be equally effective across all gastric cancers. Genomically stable tumors are enriched for diffuse histology, while chromosomal-instability tumors frequently contain potentially targetable receptor alterations. MSI and EBV-associated tumors display particularly distinct immune characteristics. [9]

MSI-H/dMMR: The Most Clinically Relevant Predictive Subgroup

Microsatellite instability-high/mismatch-repair-deficient gastric cancer is among the strongest established molecular prognostic subgroups in resectable disease. An individual-patient-data meta-analysis combining major randomized adjuvant and perioperative studies demonstrated favorable prognosis for MSI-high tumors and raised concern that the incremental benefit from conventional cytotoxic chemotherapy may be substantially smaller than in microsatellite-stable disease. [10]

This observation has major therapeutic implications. The favorable prognosis of MSI-high tumors and their uncertain incremental benefit from cytotoxic chemotherapy raise the possibility that some patients may require a different perioperative strategy. However, retrospective subgroup findings do not justify automatic omission of chemotherapy in every MSI-high patient; clinical stage, resectability, comorbidity, and multidisciplinary assessment remain essential. At the same time, MSI-high tumors are highly immunogenic and sensitive to checkpoint blockade, creating an opportunity for biomarker-selected perioperative or neoadjuvant immunotherapy and prospective evaluation of treatment de-escalation. [10, 11]

The GERCOR NEONIPIGA phase II study evaluated neoadjuvant nivolumab plus ipilimumab followed by surgery and adjuvant nivolumab in localized MSI-high/dMMR gastric and GEJ adenocarcinoma. A pathological complete response occurred in approximately 59% of operated patients, an exceptionally high rate compared with historical chemotherapy experience. These data support MSI/MMR testing at diagnosis in locally advanced resectable disease and provide proof of principle for molecularly selected neoadjuvant immunotherapy. [11]

HER2 and Targeted Perioperative Therapy

HER2 amplification has a validated therapeutic role in advanced gastric cancer, but its role in resectable disease remains under investigation. The PETRARCA randomized phase II study evaluated trastuzumab and pertuzumab added to FLOT in HER2-positive resectable esophagogastric adenocarcinoma. Addition of dual HER2 blockade increased pathological complete response from approximately 12% to 35% and increased pathological nodal negativity, although toxicity—particularly diarrhea—was higher and the trial did not proceed to definitive phase III validation. [12]

These results illustrate both the promise and difficulty of molecularly targeted perioperative therapy. A biomarker may identify a biologically rational target, but improved pathological response does not automatically establish an overall-survival standard. HER2-directed treatment in resectable disease therefore remains an area for biomarker-driven trials rather than universal routine substitution for validated perioperative regimens. [12]

PD-L1, Immune Biology, and Perioperative Checkpoint Inhibition

Checkpoint inhibition has established a major role in metastatic gastric cancer and has consequently moved into curative-intent trials. The key question is whether immunotherapy should be applied broadly alongside chemotherapy or selectively according to biomarkers such as MSI, PD-L1 expression, EBV status, tumor mutational burden, or composite immune signatures. [13]

The DANTE study evaluated atezolizumab with perioperative FLOT. Interim phase II analysis demonstrated that adding atezolizumab was feasible and increased pathological regression, with signals of greater benefit in biomarker-enriched populations. However, pathological response is not equivalent to definitive survival benefit, and longer follow-up is essential. [13]

KEYNOTE-585 evaluated perioperative pembrolizumab or placebo combined with chemotherapy, followed by pembrolizumab or placebo monotherapy, in a randomized, double-blind phase III study. The main cohort comprised 804 patients treated with cisplatin plus a fluoropyrimidine, while a separate cohort included 203 patients receiving FLOT. In the main cohort, pembrolizumab increased pathological complete response from 2.0% to 12.9%. Median event-free survival was numerically longer, at 44.4 versus 25.3 months (HR 0.81, 95% CI 0.67–0.99; $P = 0.0198$), but the result did not meet the prespecified significance threshold of $P = 0.0178$. Overall survival was not significantly improved in the reported interim analysis (HR 0.90, 95% CI 0.73–1.12). Thus, improved pathological regression did not establish a significant event-free or overall-survival benefit in that report. The chemotherapy backbone and smaller FLOT cohort should also be considered when interpreting these findings. [14]

MATTERHORN was designed as a global, randomized, double-blind, placebo-controlled phase III study of durvalumab with perioperative FLOT, followed by durvalumab monotherapy, in resectable gastric and gastroesophageal junction adenocarcinoma. Its primary endpoint was event-free survival, with pathological response and overall survival forming additional efficacy assessments. Early pathological results reported a complete response in 19.2% of patients receiving durvalumab plus FLOT compared with 7.2% receiving placebo plus FLOT. This improvement provided a rationale for further evaluation of perioperative chemoimmunotherapy, but pathological response alone was insufficient to establish a survival advantage. The trial therefore illustrates why response-based findings and long-term clinical benefit should be evaluated separately. [15, 16]

The early findings of these perioperative immunotherapy studies argue against treating immunotherapy sensitivity as a single, uniform property. MSI status, PD-L1 expression, chemotherapy backbone, duration of adjuvant immunotherapy, disease site, and pathological response may all influence observed treatment effects. Differences in trial populations, cohort sizes, endpoints, and statistical designs also prevent direct conclusions about the relative efficacy of individual checkpoint inhibitors. Future studies should prioritize prespecified treatment-by-biomarker interactions rather than relying only on subgroup response rates or comparisons between separate trials. [14, 16]

FDG-PET as an Early Response Biomarker

Functional imaging offers the opportunity to assess treatment effect before morphological shrinkage becomes evident. A prospective study of locally advanced esophagogastric junction adenocarcinoma demonstrated that early reduction in FDG uptake after initiation of chemotherapy predicted subsequent histopathological response and survival among tumors sufficiently FDG-avid for quantitative assessment. [17]

The limitations are important. Diffuse and mucinous gastric tumors may have low baseline FDG avidity, limiting evaluability. PET methodology, timing, metabolic thresholds, and chemotherapy regimens also vary. Therefore, FDG-PET is best considered a potentially useful response-adaptive tool in selected metabolically active tumors rather than a universal gastric cancer biomarker. [17]

CT Radiomics and Artificial Intelligence

Radiomics attempts to extract quantitative features from conventional imaging that reflect tumor heterogeneity, texture, morphology, and surrounding tissue characteristics. Multiple retrospective studies have developed CT-based models for predicting neoadjuvant chemotherapy response in gastric cancer. A 2024 systematic review and meta-analysis showed promising discrimination, with improved performance when radiomic data were integrated with clinical variables. [18]

However, radiomics currently faces major obstacles to clinical implementation. Many models are single-center and retrospectively developed, scanner protocols differ, segmentation is labor intensive, and external validation is

limited. The risk of overfitting is substantial. Prospective multicenter standardization is necessary before AI-generated response probabilities should influence omission, escalation, or alteration of curative treatment. [18]

Circulating Tumor DNA and Molecular Residual Disease

Circulating tumor DNA may provide one of the most powerful future methods for dynamic response assessment. Unlike conventional serum tumor markers, ctDNA can directly reflect tumor-derived genomic or epigenomic material. Changes during preoperative treatment may indicate molecular response, while postoperative detection can reveal residual disease before radiological recurrence. [19]

A prospective gastric cancer cohort using deep sequencing demonstrated that postoperative ctDNA positivity strongly predicted recurrence, with molecular detection preceding radiographic relapse in many patients. These data suggest that ctDNA may ultimately identify a subgroup with exceptionally high residual risk despite apparently curative surgery. [19]

Evidence from a multicenter real-world analysis of esophageal, gastroesophageal junction, and gastric cancers also associated postoperative ctDNA detection with increased recurrence risk. Detection during the molecular residual disease window and subsequent surveillance provided information beyond conventional clinicopathological assessment, supporting the potential value of serial sampling. However, this was a retrospective study of heterogeneous esophagogastric populations rather than a prospective, gastric-only perioperative cohort. Its findings should therefore be interpreted as prognostic evidence requiring further validation, and not as proof that ctDNA-directed changes in treatment improve survival. [20]

The most attractive future use is not simply prognosis but intervention. Postoperative ctDNA-positive patients could potentially receive intensified or biomarker-directed therapy, whereas persistently ctDNA-negative patients might eventually be candidates for treatment de-escalation. Such strategies require randomized trials demonstrating that ctDNA-guided management improves clinical outcomes. [20]

Host Immune-Nutritional Status as a Response Modifier

Tumor biology alone does not determine perioperative treatment success. Patients must tolerate several months of chemotherapy, undergo gastrectomy, recover nutritionally, and ideally complete postoperative therapy. Baseline anemia, hypoalbuminemia, lymphopenia, systemic inflammation, weight loss, sarcopenia, and poor performance status may reduce chemotherapy dose intensity and increase surgical risk. [21]

The HALP score integrates hemoglobin, albumin, lymphocytes, and platelets and was originally shown to have independent prognostic significance in a large gastric cancer gastrectomy cohort. Although most HALP data are prognostic rather than treatment-predictive, its biological components are directly relevant to perioperative fitness and tumor-associated inflammation. [21]

More contemporary studies have continued to identify HALP as a potentially useful risk marker in curatively treated gastric cancer. The key unanswered question is whether HALP predicts chemotherapy response independently of tumor stage, histology, MSI status, and treatment completion. Prospective perioperative cohorts are particularly important because chemotherapy itself substantially changes every component of the HALP score. [22]

NLR, PLR, CRP-based indices, and sarcopenia provide overlapping host information. Rather than searching for a single “best” inflammatory ratio, research should determine whether combinations of host biomarkers add clinically meaningful discrimination to tumor-based models. A biomarker that improves a statistical model but does not change treatment decisions has limited practical value. [23]

Treatment Completion as an Underappreciated Biomarker

A major feature of perioperative therapy is the asymmetry between preoperative and postoperative treatment delivery. Patients generally tolerate neoadjuvant therapy better than postoperative therapy, when weight loss,

surgical complications, fatigue, altered gastrointestinal anatomy, and reduced functional reserve may delay or prevent treatment completion. [3]

This observation suggests that “response prediction” should include prediction of treatment feasibility. A patient with biologically chemosensitive disease but profound sarcopenia and nutritional depletion may achieve less population-level benefit because therapy cannot be delivered as intended. Conversely, early supportive intervention might improve dose intensity and postoperative recovery without changing intrinsic tumor chemosensitivity. [3]

Future predictive models should therefore incorporate ECOG performance status, nutritional screening, weight trajectory, sarcopenia, inflammatory indices, organ function, treatment toxicity, and postoperative complications alongside molecular tumor markers. [3]

An Integrated Model for Precision Perioperative Oncology

No single biomarker currently provides sufficient accuracy to determine perioperative treatment independently. A more realistic research model should use sequential layers of information; the framework described here is a proposal requiring prospective validation. At diagnosis, clinical stage, laparoscopy where indicated, histology, MSI/MMR, HER2 where relevant to trial selection, performance status, body composition, and immune-nutritional markers could establish baseline risk. During neoadjuvant treatment, clinical response, CT or PET response where appropriate, changes in host biomarkers, and ctDNA kinetics could identify early resistance. [6, 24]

After surgery, pathological tumor regression, ypTNM stage, nodal status, margin status, lymphovascular invasion, and postoperative ctDNA could redefine recurrence risk. A validated postoperative treatment strategy could then be based not simply on the regimen chosen months earlier but on the total biological response observed throughout the perioperative journey. [5, 20]

Such a strategy could eventually produce four clinically meaningful groups: biologically favorable/chemotherapy-sensitive disease; favorable molecular subtypes requiring treatment de-escalation; high-risk but treatment-responsive disease requiring completion or escalation; and resistant disease requiring a change in therapeutic mechanism. This framework describes a possible transition from uniform perioperative chemotherapy to adaptive precision perioperative oncology, but treatment changes based on these proposed groups require evidence that they preserve or improve cure rates.

Prospective biomarker studies must be embedded within randomized therapeutic trials. Archival retrospective analyses can generate hypotheses but cannot reliably distinguish prognostic from predictive effects. Sampling schedules should be standardized at diagnosis, during neoadjuvant treatment, immediately before surgery, after surgery, and during surveillance.

MSI/MMR should be incorporated routinely in research algorithms because it currently provides the strongest biologically coherent example of a subgroup potentially requiring a different curative strategy. HER2, PD-L1, EBV, ctDNA, radiomic signatures, histological phenotype, and host immune-nutritional status should then be evaluated in complementary rather than competing models.

Future research should prioritize clinically interpretable endpoints. A model should demonstrate not only statistical discrimination but also calibration, external validity, decision-curve benefit, reproducibility, cost-effectiveness, and an ability to change management without compromising cure.

Limitations

The findings of this review should be interpreted within several methodological constraints. Its narrative design allows discussion of diverse response markers but does not eliminate selection or interpretation bias, and no exhaustive search or formal risk-of-bias assessment was performed. Much of the biomarker evidence comes from small retrospective cohorts with variable chemotherapy regimens, histological composition, sampling schedules, assay platforms, and response definitions. Apparent predictive performance may therefore reflect confounding, overfitting, or an underlying prognostic association rather than a reproducible treatment-specific effect. Differences

between gastric and gastroesophageal junction populations also limit unrestricted extrapolation. Pathological complete response is an informative endpoint but should not be treated as a universally validated substitute for long-term survival; improved regression alone cannot establish a new curative standard. Molecular, imaging, and circulating markers are additionally limited by intratumoral heterogeneity, assay sensitivity, and incomplete external validation. The proposed integrated framework consequently remains a research strategy rather than an established algorithm for treatment escalation or de-escalation. Prospective multicenter studies and randomized evaluations of biomarker-directed management are needed to determine whether these tools improve treatment delivery and oncological outcomes without compromising cure.

Conclusion

Prediction of response to perioperative therapy in resectable gastric cancer is evolving from conventional anatomical staging toward multidimensional biological assessment. FLOT remains a central systemic backbone, but marked heterogeneity in pathological response and recurrence demonstrates the limitations of a uniform strategy. MSI/MMR, histological phenotype, pathological regression, ctDNA, advanced imaging, and host immune-nutritional status provide complementary information, while modern immunotherapy trials are rapidly changing the perioperative landscape. The future of gastric cancer management is likely to depend on sequential, integrated risk assessment that combines tumor biology with dynamic treatment response and patient physiological reserve rather than relying on any single biomarker. Clinical adoption should therefore depend on prospective validation and demonstration of management benefit, while favorable pathological findings from perioperative immunotherapy studies should be interpreted alongside their survival endpoints. Host biomarkers and emerging technologies can refine assessment, but they should not independently determine the omission or substitution of established curative treatment.

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