Multimodality Treatment for Locally Advanced Gastric Adenocarcinoma

Thejal Srikumar, MD, MPH[a], Raghav Sundar, MBBS, PhD[b,c,*]

KEYWORDS

• Gastric cancer • Multimodality • Perioperative • Chemotherapy • Chemoradiation

KEY POINTS

- Locally advanced gastric adenocarcinoma has poor survival with surgery alone.
- Additional systemic therapy in the peri-operative and adjuvant setting improves survival.
- Choice of multimodal approach requires clinical context, discussion at a multidisciplinary tumor board, and consideration of other factors.
- Studies are underway to evaluate the use of novel therapies, including immunotherapy and targeted therapy.

INTRODUCTION

Gastric cancer (GC) poses a significant health care burden worldwide, ranking fifth in prevalence and cancer-related mortality worldwide.[1] Geographically, Asia experiences a higher incidence, leading to robust national screening programs in countries like Japan and South Korea, facilitating early tumor detection. Conversely, GC commonly manifests at advanced stages in the United States (US) and Europe, driving diverse treatment strategies globally. The diffuse subtype, more prevalent in Asia, presents challenges due to its aggressive nature, often resulting in linitis plastica—a condition characterized by stomach wall thickening akin to a leather bottle.[2] Surgeons encounter difficulties in achieving clear resection margins due to the infiltrative nature of these tumors. Concurrently, there is a rising incidence of gastroesophageal junction (GEJ) cancers in the West, linked to obesity-related Barrett's esophagus, predominantly affecting younger individuals.[3] Surgical approaches for GEJ tumors vary significantly

[a] Yale University School of Medicine, 333 Cedar Street, New Haven, CT, USA; [b] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, Singapore 119228, Singapore; [c] Department of Haematology-Oncology, National University Cancer Institute, Singapore
* Corresponding author. Yong Loo Lin School of Medicine, National University of Singapore, Singapore.
E-mail address: mdcragh@nus.edu.sg

Surg Clin N Am 105 (2025) 75–94
https://doi.org/10.1016/j.suc.2024.06.007 **surgical.theclinics.com**

from distal gastric tumors, requiring careful consideration of location and extent of invasion for optimal resection margins.

Various trials have explored integrating systemic and radiation therapies into pre- and post-operative care to improve surgical outcomes and reduce distant metastases in gastric or GEJ cancers. These approaches have enhanced surgical outcomes and yielded clinically meaningful gains in event-free survival (EFS) and overall survival (OS). This chapter focuses on multimodal treatment strategies for locally advanced gastric adenocarcinoma (LAGC), with an emphasis on GC management. While GEJ tumors were included in some perioperative systemic therapy trials for GC and esophageal trials, they will only be briefly discussed here. Upper and mid-thoracic esophageal tumors, including squamous cell cancers, are beyond this article's scope and have been extensively covered elsewhere.[4] We delve into systemic therapy's role in various settings, such as peri-operative and adjuvant, and its integration with radiation therapy. Special treatment considerations based on cancer molecular classification are also explored, alongside current and future directions in the field, concluding with post-treatment surveillance.

ROLE OF SYSTEMIC THERAPY IN LOCALLY ADVANCED GASTRIC CANCER

In the early 2000s, 3 distinct approaches emerged for managing LAGC. In the US, the standard-of-care became upfront resection of the primary gastric tumor followed by adjuvant chemoradiation, following the INT-0116 study.[5] Meanwhile, Japan and Korea's national screening programs facilitated early tumor detection, leading to trials exploring adjuvant chemotherapy post-surgery. In Europe, where patients often present with advanced disease, peri-operative chemotherapy followed by surgery was investigated to downsize tumors and study biology. Presently, surgery followed by adjuvant chemotherapy or peri-operative chemotherapy and surgery are widely adopted globally, with declining roles for radiation therapy. The choice between these approaches is often determined by geography, but factors like fitness for surgery, co-morbidities, tumor characteristics, and surgical feasibility are discussed in multi-disciplinary tumor boards to tailor treatment for individual patients (**Table 1**).[6–10]

PERI-OPERATIVE THERAPY

The landmark trial that established the role of peri-operative chemotherapy in the management of LAGC was the MAGIC trial (**Table 2**). This trial compared peri-operative epirubicin, cisplatin, and 5-fluorouracil (FU; ECF) and surgery to surgery alone in patients with resectable LAGC, and found that the peri-operative group had had significantly less advanced tumors at time of surgery, higher percentage of curative surgery, higher overall survival (OS) and progression-free survival (PFS), with similar post-operative complications and mortality.[11] Of all patients randomized to the peri-operative arm, only 42% completed all 6 cycles of chemotherapy, and 55% received any post-operative treatment. The peri-operative treatment approach allows suitable patients to receive chemotherapy before surgery, while delaying it until after surgery could mean some patients missing out on chemotherapy entirely.

Similarly, the ACCORD-07/FFCD 9703 trial randomized patients with resectable LAGC to peri-operative chemotherapy (with cisplatin and FU; CF) or surgery alone (see **Table 2**).[12] The peri-operative chemotherapy group had better 5-year OS and 5-year disease-free survival (DFS) with similar postoperative morbidity. Although a higher dose of cisplatin was utilized in this trial, considering the comparable survival outcomes to MAGIC, questions arose regarding the additional efficacy of epirubicin.

Table 1
Geographic differences in combined modality treatment approach for gastric cancer

	National Comprehensive Cancer Network (USA)[6]	European Society for Medical Oncology[7,8]	Japanese Gastric Cancer Association[9]	Korean Gastric Cancer Association[10]
Minimum Stage for Multimodality Therapy Consideration	cT2	Stage IB (>T1 or ≥N0M0)	Pathologic stage II (excluding pT1)	Pathologic stage II
Extent of Nodal Dissection	• D1 • Modified D2 (≥16 lymph nodes examined)	D2 standard	D2 standard	D2 standard
Preferred Therapeutic Approach	Peri-operative chemotherapy	Peri-operative chemotherapy	Adjuvant chemotherapy	Adjuvant chemotherapy
Alternative Treatment Strategies	• Pre-operative chemoradiation considered in GEJ • Post-operative chemoradiation and chemotherapy if <D2 dissection or R1 resection	• Pre-operative chemoradiation considered in GEJ • Post-operative chemotherapy if ≥stage IB and no pre-operative chemotherapy • Post-operative chemoradiation if no pre-operative chemotherapy and <D2 dissection or R1	• Pre-operative chemotherapy in bulky lymphadenopathy	• Consider pre-operative treatment in cT4Nx or cT2-3N+ • Consider post-operative chemotherapy in <D2 or R1

Abbreviation: GEJ, gastroesophageal junction.

Table 2
Major peri-operative therapy trials

Trial	Study Location	N	Stage	Cancer Site	Experimental Arm	Control Arm	Surgical Resection	Post-Operative Chemotherapy Started	PFS/DFS	5-y OS
MAGIC[11]	United Kingdom	503	≥Stage II (M0)	• Gastric 74% • Lower Esophagus 15% • GEJ 12%	• Peri-operative ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, fluorouracil 200 mg/m^2) + surgery	Surgery	Curative 69% vs 66%	55%	5-y PFS HR 0.66	36% vs 23%
ACCORD-07/FFCD[12]	France	224	Resectable and non-metastatic	• Gastric 25% • Lower esophagus 11% • GEJ 64%	• Peri-operative CF (cisplatin 100 mg/m^2, fluorouracil 800 mg/m^2) + surgery	Surgery	R0 87% vs 74%	50%	5-y DFS 34% vs 19%	38% vs 24%
FLOT4[13]	Germany	716	≥cT2 and/or cN+	• Gastric 44% • GEJ Siewert 1 23% • GEJ Siewert 2/3 33%	• Peri-operative FLOT (docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, 5-fluorouracil 2600 mg/m^2)	Peri-operative ECF/ECX (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, fluorouracil 200 mg/m^2 or capecitabine 1250 mg/m^2)	R0 85% vs 78%	60% vs 52%	Median DFS 30 mo vs 18 mo (HR 0.75)	45% vs 36%

Abbreviations: CF, cisplatin, fluorouracil; CI, confidence interval; ECF, epirubicin, cisplatin, fluorouracil; ECX, epirubicin, cisplatin, xeloda (capecitabine); GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; UICC, International Union Against Cancer; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; DFS, disease-free survival.

The FLOT4 study compared 2 different peri-operative chemotherapy regimens, ECF/ECX and FU plus leucovorin, oxaliplatin, and docetaxel (FLOT) in resectable, non-metastatic gastric or GEJ cancer[13] (see **Table 2**). Pathologic stage of tumor at time of surgery was lower in the FLOT group than in ECF/ECX, with a higher rate of margin-free (R0). OS was higher in the FLOT group, though survival benefit was not seen in the diffuse histologic subtype. Serious adverse events were similar in both groups, with the FLOT group having more Grade 3/4 diarrhea, vomiting, neutropenia, infections, and peripheral neuropathy. Given these results, peri-operative FLOT has become a standard-of-care treatment option in LAGC.

ADJUVANT THERAPY

Several studies have now shown the benefit of adjuvant chemotherapy in LAGC. The ACTS-GC study evaluated the benefit of adjuvant chemotherapy (either S-1 or observation) in patients with LAGC who underwent gastrectomy with lymphadenectomy[14] (**Table 3**). (S-1 is an oral formulation that consists of a 5-FU pro-drug combined with biochemical modulators; this drug is not available in the US). At 5 years, OS and relapse-free survival (RFS) were higher in the adjuvant therapy group, and benefit was most seen in stage II disease.[15] Due to this trial, adjuvant S-1 remains a standard-of-care after LAGC surgery in Japan.

The CLASSIC trial evaluated patients who underwent surgery for LAGC and randomized to adjuvant chemotherapy with oral capecitabine plus intravenous oxaliplatin (XELOX) versus observation after surgery only[16] (see **Table 3**). 3-year DFS was significantly higher in the XELOX group. The patients who received chemotherapy had higher rates of Grade 3 or 4 adverse events, namely nausea, neutropenia, and decreased appetite. While cross-trial comparisons are discouraged, the advantages observed in stage III patients with node-positive disease using the CLASSIC regimen must be considered. We suggest that adjuvant XELOX is preferred for stage III disease in patients with good performance status. However, due to its lower toxicity, where available, S-1 is considered a reasonable alternative for stage II and more frail patients. The limited benefit of adjuvant S-1 in Stage III patients led to the JACCRO-G07 trial comparing surgery followed by adjuvant S-1 with docetaxel against S-1 alone[17] (see **Table 3**). There was higher RFS and OS in the adjuvant S-1+docetaxel group, though more Grade 3 or 4 adverse events were observed.[18]

The results of CLASSIC and JACCRO-G07 showed broadly similar 5-year RFS and OS, and while these regimens have not been compared head-to-head in a standalone trial, both XELOX and S-1+docetaxel are considered acceptable standard-of-care adjuvant regimens in Asia after upfront surgery for stage III and node-positive disease.

COMPARISON OF PERI-OPERATIVE AND ADJUVANT THERAPY

Deciding between peri-operative and adjuvant chemotherapy strategies for LAGC is complex due to their comparable survival advantages. Cross-trial comparisons are challenging due to variations in disease characteristics and treatment responses globally. Intervention arms in Western studies demonstrate inferior survival compared to surgery-alone arms in Asian studies. A few randomized phase III trials are investigating this issue.

The RESOLVE trial randomized high-risk T4 LAGC patients undergoing surgery into 3 arms: adjuvant XELOX, adjuvant S-1 and Oxaliplatin (SOX), or peri-operative SOX (**Table 4**).[19] In the adjuvant arms, greater than 20% of patients did not receive post-operative chemotherapy. DFS and R0 resection were superior in the peri-operative

Table 3
Major adjuvant therapy trials

Trial	Study Location	N	Stage and Surgery Type	Surgery Type	Cancer Site	Experimental Arm	Control Arm	3-y RFS/ DFS	3-y OS
ACTS-GC[14]	Japan	1059	Stage II (excluding T1), IIIA, or IIIB	≥D2 & R0 resection	• Gastric 100%	Surgery + adjuvant S-1 (40 mg/m^2)	Surgery	RFS 72% vs 60%	80% vs 70%
CLASSIC[16]	South Korea	1035	Stage II, IIIA, or IIIB	D2 & R0 resection	• Gastric 98% • GEJ 2%	Surgery + adjuvant XELOX (capecitabine 1000 mg/m^2 twice daily, oxaliplatin 130 mg/m^2)	Surgery	DFS 74% vs 59%	83% vs 78%
JACCRO-G07[17,18]	Japan	915	Stage III	≥D2 & R0 resection	• Gastric 100%	Surgery + adjuvant S-1 (80 mg for BSA<1.25 m^2, 100 mg for ≥1.25 and <1.5 m^2, 120 mg for ≥1.5 m^2) + Docetaxel (40 mg/m^2)	Surgery + Adjuvant S-1(80 mg for BSA<1.25 m^2, 100 mg for ≥1.25 and <1.5 m^2, 120 mg for ≥1.5 m^2)	RFS 66% vs 50%	78% vs 71%

Abbreviations: BSA, body surface area; DFS, disease-free survival; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival; XELOX, xeloda (capecitabine) + oxaliplatin.

Table 4
Trials comparing peri-operative and adjuvant therapy

Trial	Study Location	N	Stage	Cancer Site	Experimental Arm	Control Arm	R0 Surgical Resection	Post-Operative Chemotherapy Started	DFS/PFS	OS
RESOLVE[19,20]	China	1022	cT4aN + M0 or cT4bNanyM0	• Gastric 64% • GEJ 36%	• Peri-operative SOX (S-1 40–60 mg twice daily, oxaliplatin 130 mg/m^2) • Adjuvant SOX (S-1 40–60 mg twice daily, oxaliplatin 130 mg/m^2)	• Adjuvant XELOX (capecitabine 1000 mg/m^2 twice daily, oxaliplatin 130 mg/m^2)	93% vs 88% vs 87%	66% vs 72% vs 73%	3-y DFS 59% vs 57% vs 51%	5-y OS 60% vs 61% vs 52%
PRODIGY[21]	South Korea	530	cT2-3N + or T4Nany	• Gastric 94% • GEJ 6%	• Neoadjuvant DOS (docetaxel 50 mg/m^2, oxaliplatin 100 mg/m^2, S-1 40 mg/m^2 twice daily) + surgery + adjuvant S-1 (40–60 mg twice daily)	• Surgery + adjuvant S-1 (40–60 mg twice daily)	95% vs 84%	96% vs 91% (who had R0)	3-y PFS 66% vs 60%	3-y OS 74% vs 73%

Abbreviations: DFS, disease-free survival; DOS, docetaxel + oxaliplatin + S-1; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SOX, S-1+oxaliplatin; XELOX, xeloda (capecitabine) + oxaliplatin.

SOX group compared to adjuvant XELOX. Although not statistically compared, survival was similar in the perioperative and adjuvant SOX groups. Post-hoc analysis revealed fewer completed peri-operative chemotherapy compared to adjuvant XELOX or SOX.

The PRODIGY trial randomized LAGC patients planned for surgery to peri-operative treatment (pre-operative Docetaxel, Oxaliplatin, and S-1 [DOS] plus adjuvant S-1) or adjuvant S-1 alone (see **Table 4**).[21,20] Most patients had T4 and node-positive disease. The peri-operative group showed higher PFS, especially in advanced cases (T4 and node-positive). Three-year OS did not significantly differ, though the study was not powered for this comparison. Completion rates for post-operative treatment were similar in both groups.

Choosing between peri-operative and adjuvant treatments is challenging with the PRODIGY and RESOLVE trials offering some insights but lacking conclusive evidence. Starting with peri-operative chemotherapy may downstage tumors and enhances R0 resection, but risks include tumor progression and delay of surgery due to chemotherapy complications. Adjuvant therapy may be preferred for patients with symptomatic primary tumors needing immediate surgical intervention for bleeding or obstruction. Overall, there is a global trend toward the peri-operative approach for more advanced disease (T4 or N2).

CHEMORADIATION

In LAGC, the addition of radiation therapy to chemotherapy has shown limited benefit. The INT-0116 study compared adjuvant chemoradiation (with FU and leucovorin) post-surgery versus surgery alone[5] (**Table 5**). Adjuvant chemoradiation led to higher OS and RFS, but patients with diffuse histology did not significantly benefit from treatment.[22] While chemoradiotherapy decreased local relapse from 29% to 19%, it is possible that the survival improvement compensated for surgical undertreatment. Only 10% of patients had D2 gastrectomy and 54% received less than a D1 resection, indicating undertreatment from a surgical standpoint. For example, in the Dutch D1D2 trial, D2 surgery decreased local relapse in comparison to D1 surgery from 22% to 12%.[23]

The ARTIST trial evaluated adjuvant chemotherapy alone (capecitabine and cisplatin, XP) versus adjuvant chemoradiation (with XP)[24] (see **Table 5**). DFS and OS were similar between both arms of treatment. Subgroup analysis revealed that the chemoradiation arm had improved DFS in patients with nodal disease, leading to the ARTIST2 trial,[25] which compared 3 adjuvant regimens: S-1, SOX, and SOX plus radiation (SOXRT)[26] (see **Table 5**). DFS was longer in the SOX and SOXRT arms compared to S-1 only, establishing SOX as a possible standard-of-care for adjuvant treatment. While neither powered for, nor planned for formal statistical comparison, DFS was similar between adjuvant SOX and SOXRT. In the CRITICS trial, peri-operative chemotherapy was compared to pre-operative chemotherapy followed by post-operative chemoradiation[27] (see **Table 5**). In the intention-to-treat analysis, median OS was not significantly different between treatment arms. However, in per-protocol analysis, post-operative chemotherapy had better OS than post-operative chemoradiation. Therefore, the addition of radiation to peri-operative chemotherapy did not improve survival.

Considering these findings, the decision to administer adjuvant chemoradiotherapy hinges on several factors, such as high risk of local relapse, a less extensive resection (D0 or D1), insufficient lymph nodes sampled (<15), or positive margins. While adjuvant radiation's role is more restricted, neoadjuvant chemoradiotherapy remains standard practice in various scenarios, as detailed in the subsequent GEJ section.

Table 5
Chemoradiation trials

Trial	Study Location	N	Stage	Surgical Resection	Cancer Site	Experimental Arm	Control Arm	RFS/DFS/EFS	OS
INT-0116[5]	United States	556	Stage IB through IVM0	Complete Resection (10% D2, 36% D1, 54% D0)	• Gastric 80% • GEJ 20%	• Surgery + adjuvant chemoradiotherapy (with FU 425 mg/m^2 + leucovorin 20 mg/m^2)	• Surgery	3-y RFS 48% vs 31%	3-y OS 50% vs 41%
ARTIST[24,25]	South Korea	458	All but Stage IA, IB, M1	D2 & R0 resection	• Gastric 100%	• Surgery + adjuvant chemoradiotherapy (with XP, Capecitabine 1000 mg/m^2 twice daily, cisplatin 60 mg/m^2)	• Surgery + adjuvant XP (Capecitabine 1000 mg/m^2 twice daily, cisplatin 60 mg/m^2)	3-y DFS 78% vs 74%	5 y OS 75% vs 73%
ARTIST2[26]	South Korea	546	Stage II or III	D2 & R0 resection	• Gastric 100%	• Surgery + adjuvant chemoradiotherapy (with SOX, S-1 40–60 mg twice daily, oxaliplatin 130 mg/m^2) • Surgery + adjuvant SOX (S-1 40–60 mg twice daily, oxaliplatin 130 mg/m^2)	• Surgery + adjuvant S-1 (40–60 mg twice daily)	3-y DFS 73% vs 74% vs 65%	Not reported

(*continued on next page*)

Table 5
(*continued*)

Trial	Study Location	N	Stage	Surgical Resection	Cancer Site	Experimental Arm	Control Arm	RFS/DFS/EFS	OS
CRITICS[27]	Netherlands	788	Stage IB-IVA	Not specified	• Gastric 83% • GEJ 17%	• Neoadjuvant epirubicin (50 mg/m^2), cisplatin (60 mg/m^2) or oxaliplatin (130 mg/m^2), and capecitabine (1000 mg/m^2 twice daily) + surgery + adjuvant chemoradiotherapy (with cisplatin 20 mg/m^2 + xeloda 575 mg/m^2)	• Neoadjuvant epirubicin (50 mg/m^2), cisplatin (60 mg/m^2) or oxaliplatin (130 mg/m^2), and capecitabine (1000 mg/m^2) + surgery + adjuvant chemotherapy (epirubicin, cisplatin or oxaliplatin, and capecitabine at same doses)	5-y EFS 38% vs 39%	5 y OS 40% vs 42%

Abbreviations: DFS, disease-free survival; EFS, event-free survival; FU, fluorouracil; GEJ, gastroesophageal junction; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival; SOX, S-1 + oxaliplatin; XP, xeloda (capecitabine) plus cisplatin.

DEFINITIVE CHEMORADIATION

For patients ineligible for surgery due to performance status or disease extent, definitive chemoradiation is explored, although primarily in esophageal cancer. The RTOG 85-01 trial showed improved 5-year OS with chemotherapy (CF) added to radiation in thoracic esophageal cancer.[28] The PRODIGE5/ACCORD17 trial compared FOLFOX to CF in esophageal cancer, finding no significant difference in median PFS.[29] The ongoing SANO trial assesses active surveillance versus surgery after neoadjuvant chemoradiotherapy in esophageal cancer; preliminary findings suggest non-inferior OS.[30] Further research is needed to assess this approach in gastric and GEJ cancer patients.

GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

Besides studies primarily focusing on GC, GEJ adenocarcinoma has been explored independently and within esophageal cancer research. The POET study, comparing preoperative chemotherapy (CF) to chemoradiotherapy (CF followed by cisplatin + etoposide + radiation) before surgery in GEJ adenocarcinoma patients, radiation improved pathologic complete response (PCR) rates at resection.[31] Long-term follow-up indicated improved local PFS with chemoradiotherapy, while OS and in-hospital mortality showed no significant differences.[32]

The CROSS study evaluated the benefit of neoadjuvant chemoradiotherapy in patients with cancers of the esophagus or GEJ.[33] Patients were randomized either to surgery alone or weekly carboplatin and paclitaxel with concurrent radiotherapy followed by surgery. R0 resection was higher in the neoadjuvant chemoradiotherapy group and PCR was 29%, with similar postoperative complications. Long-term follow-up showed improvement in OS in the neoadjuvant chemoradiotherapy group.[34]

The Neo-AEGIS study compared CROSS chemoradiotherapy to perioperative chemotherapy (modified MAGIC or FLOT regimen) in esophageal or GEJ adenocarcinoma patients.[35] Despite closing prematurely and being underpowered, no significant difference was found in median OS and PFS. However, the chemoradiotherapy group showed higher PCR and R0 resection rates. Post-operative mortality was similar between groups. The results of the randomized phase III ESOPEC trial demonstrated the superiority of FLOT to CROSS and is now changing the standard of care in this space (data released after this manuscript was written).

IMMUNOTHERAPY

Ongoing trials are assessing various anti-PD-1/PD-L1 immune checkpoint inhibitor efficacies in LAGC. The CheckMate 577 study explored adjuvant nivolumab versus placebo in neoadjuvant chemoradiotherapy-treated esophageal or GEJ cancer patients after R0 resection that had not achieved PCR.[36] Nivolumab showed higher median DFS, especially in the esophageal subtype and higher nodal stages. The interim analysis of the Keynote 585 reported the addition of pembrolizumab to chemotherapy (CF or FLOT), revealing improved PCR rates, but did not meet statistical significance for EFS improvement. Median OS (data not mature) did not significantly differ between the arms.[37] The ongoing MATTERHORN study, evaluating durvalumab in addition to peri-operative FLOT, reported significant improvement in PCR rates in interim analysis.[38] The ATTRACTION-5 study assessing nivolumab in combination with post-operative adjuvant chemotherapy did not meet the RFS endpoint.[39] NEOSUMMIT-01 is evaluating perioperative toripalimab and chemotherapy, with higher tumor

regression and pCR in the chemoimmunotherapy group; surgical outcomes were comparable.[40] The PANDA trial added neoadjuvant atezolizumab to docetaxel, oxaliplatin, and capecitabine followed by surgery, showing a major pathologic response in 70% and 45% PCR; 13 patients remained disease-free at median 47-month follow-up.[41] Besides chemoimmunotherapy, the ongoing DRAGON-IV study is investigating peri-operative chemoimmunotherapy (peri-operative SOX + camrelizumab) plus VEGF inhibitor (rivoceranib, SOXRC) versus chemotherapy (SOX) alone, showing higher pCR in the SOXRC group; survival analysis is ongoing.[42]

SUBTYPE CONSIDERATIONS

HER2 Positive Gastric Cancer

HER2-targeted drugs are beneficial in metastatic GC. The PETRARCA trial compared peri-operative FLOT to FLOT or Trastuzumab or Pertuzumab in HER2-positive resectable GEJ or GC.[43] Trastuzumab or pertuzumab showed significantly higher PCR and improved nodal negativity. Median DFS and OS were not reached in the trastuzumab or pertuzumab group. The PETRARCA trial closed prematurely due to JACOB trial results (which showed that adding pertuzumab to trastuzumab and chemotherapy in first-line HER2 positive metastatic gastric of GEJ cancer patients did not improve survival).[44] The ongoing INNOVATION trial assesses pertuzumab in addition to chemotherapy and trastuzumab in HER2-positive gastric or GEJ cancer peri-operative treatment.[45]

Mismatch Repair Protein Deficient Gastric Cancer

Mismatch repair proteins (MMR) play a crucial role in DNA replication error correction. Deficiency in MMR can lead to microsatellite instability (MSI-H) and replication error accumulation. Historically, MSI-H patients have poor responses to chemotherapy, but emerging evidence suggests a major benefit from immunotherapy.[46] A meta-analysis of MSI-H GC patients from various trials showed longer DFS and OS compared to MSI-stable patients and inferior results when treated with chemotherapy compared to surgery alone.[47] Data are emerging regarding the role of immunotherapy in dMMR/MSI-H LAGC from trials such as DANTE (peri-operative atezolizumab + FLOT), INFINITY (neoadjuvant tremelimumab and durvalumab) and NEONIPIGA (neoadjuvant ipilimumab and nivolumab with adjuvant nivolumab) reporting very high PCR rates for patients with dMMR/MSI-H LAGC (**Table 6**).[48–51]

Aggressive Histology

Special consideration has been given to the treatment of patients with more aggressive histology in GC. The PRODIGE19 study evaluated adjuvant versus peri-operative ECF in patients with signet ring cell gastric carcinomas (which are thought to be more chemotherapy-resistant).[52] The results of this Phase II trial showed higher R0 resection in the peri-operative chemotherapy group (88% vs 78%), but no significant difference in median OS. The JCOG0501 study evaluated peri-operative S-1+cisplatin versus adjuvant S-1 in patients with Borrmann type 4 (including linitis plastica and scirrhous type) and large type 3 (ulcero-invasive) GC, and found no significant difference in 3-year OS.[53]

SURVEILLANCE

Post-treatment surveillance for LAGC varies based on stage and treatment. Generally, guidelines recommend periodic clinician visits with history and physical examinations. Some suggest periodic computed tomography scans of the chest, abdomen, and

Table 6
Trials with immunotherapy for microsatellite high gastric cancer

Trial	Study Location	N	Stage	Cancer Site	dMMR/ MSI-H	Experimental Arm	Control Arm	R0 Surgical Resection	pCR in dMMR/MSI-H	pCR in all Patients
DANTE[48]	Germany	295	≥cT2 and/or cN+ with no M1	• Gastric 39% • GEJ 61%	8%	• FLOT (docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 2600 mg/m^2) + atezolizumab (840 mg in combination followed by 1200 mg monotherapy)	• FLOT (docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 2600 mg/m^2)	93% vs 91%	63% vs 27%	24% vs 15%
INFINITY[49]	Italy	18	cT2-T4, Nany	Gastric and GEJ, % not reported	100%	• Neoadjuvant Tremilimumab 300 mg + durvalumab 1500 mg + surgery	None	Not reported	60%	60%
NEONIPIGA[50]	France	32	cT2-T4, Nx, M0	• Gastric 50% • GEJ 50%	100%	• Neoadjuvant nivolumab 240 mg and ipilimumab 1 mg/kg + surgery + adjuvant nivolumab 480 mg	None	100%	59%	59%

Abbreviations: dMMR, deficient MMR; FLOT, docetaxel + oxaliplatin + leucovorin + fluorouracil; GEJ, gastroesophageal junction; MSI-H, microsatellite instability high; PCR, pathologic complete response.

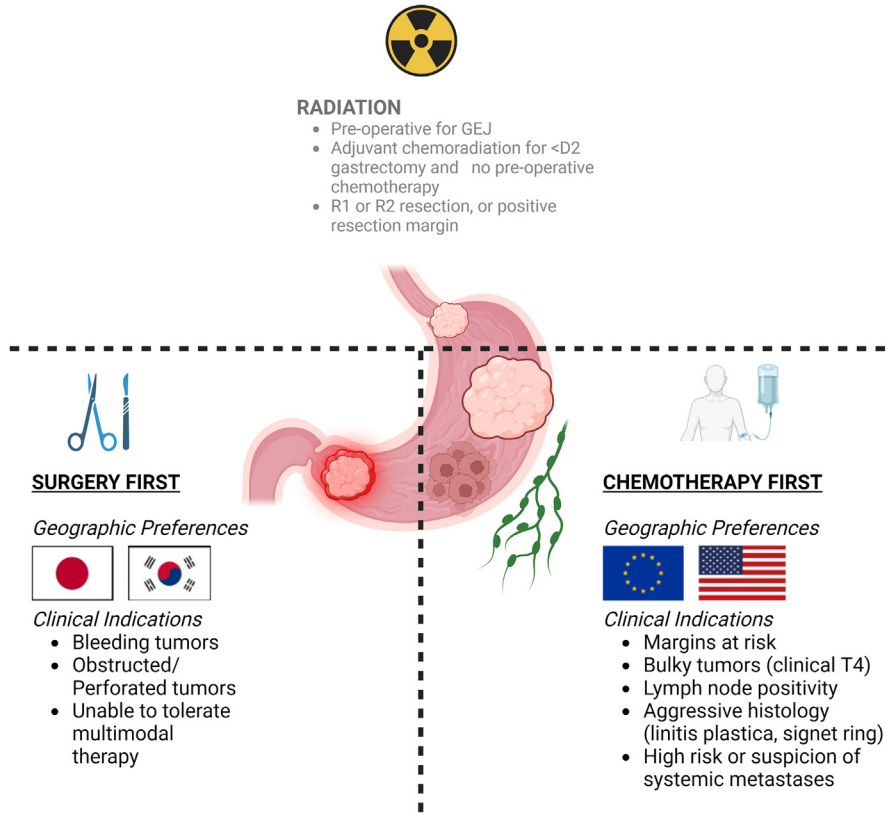

Fig. 1. Treatment considerations. The multi-modality treatment strategy of locally advanced gastric cancer varies globally. Asian countries like Japan and South Korea have traditionally preferred a surgery-first approach. However, based on the emerging data and trials for peri-operative chemotherapy approaches, there has been a shift toward peri-operative chemotherapy (or "hemotherapy first" in Asia, especially in clinical indications such as bulky T4 tumors. Europe and North America have traditionally leaned towards a perioperative chemotherapy approach, although in specific clinical conditions such as tumor perforation, upfront surgery could be considered. Radiation therapy was typically restricted to GEJ tumors, and used in a pre-operative fashion with concurrent chemotherapy, although less favored recently based on the ESOPEC trial. Rarely, in patients that have undergone less than D2 lymph node dissection, or surgical resection with positive margins, adjuvant chemoradiation may be considered. This figure aims to highlight general principles and is not meant to be used as strict definition. Each individual case should undergo a multi-disciplinary discussion to determine the best treatment approach. (Created with BioRender.com.)

pelvis with contrast for up to 5 years. Nutritional support and monitoring for deficiencies are advised, with upper endoscopy as needed after partial or subtotal gastrectomy[7,54] However, these guidelines were formulated in an era when metastases meant palliative intent treatment for Stage IV GC. With the evolving data on managing oligometastatic disease in GC more aggressively, akin to colorectal cancer, incorporating locoregional therapies, and surveillance guidelines may need to become more intensive to detect early or oligometastatic relapse.

An emerging tool in surveillance of GC is the role of circulating tumor DNA (ctDNA). Research has demonstrated that serial plasma monitoring of ctDNA can predict short RFS and relapse in curative-stage patients, along with indicating poor OS in those with

metastatic disease. Moreover, in GEJ cancer patients, the detection of ctDNA at any post-surgery time point has been linked to poorer RFS.[55,56]

There is emerging recognition of oligometastatic GC as potentially curable with multimodality therapy, akin to LAGC. The FLOT-3 trial examined patients with LAGC and limited metastases, assessing induction chemotherapy followed by surgical resection. Notably, patients with limited metastatic disease who underwent neoadjuvant chemotherapy followed by surgery showed improved survival compared to chemotherapy alone.[57] Additionally, the ongoing RENAISSANCE trial is investigating the benefit of chemotherapy alone versus chemotherapy followed by surgical resection in limited-metastatic gastric and GEJ adenocarcinoma patients.[58]

SUMMARY

Treating LAGC poses ongoing challenges, but treatment options have expanded beyond surgery alone. Both peri-operative and adjuvant treatments have shown survival benefits, but the choice varies globally and should be personalized (Fig. 1). Peri-operative chemotherapy is often considered if margins are at risk, tumors are bulky, or aggressive biology such as diffuse histology or signet ring cells is present. Pre-operative chemotherapy aids in tumor downstaging, R0 resection, and survival. Upfront surgery may be prioritized for refractory tumor bleeding or obstruction. Post-operative chemotherapy, after D2 gastrectomy, typically involves doublet chemotherapy for Stage III or N+ disease. The role of integrating immunotherapy into the treatment paradigm, particularly in dMMR/MSI-H is rapidly emerging, as are targeted treatments for subsets like HER2+. Yet, OS rates remain relatively low, emphasizing the need for continued development of treatments and strategies to enhance outcomes in LAGC.

CLINICS CARE POINTS

- Multi-modality treatment including chemotherapy and surgery forms the cornerstone of the management of locally advanced gastric cancer.
- The choice of peri-operative chemotherapy versus surgery followed by adjuvant chemotherapy is heavily influenced by institution and geographic specific preferences, but clinical factors such as bleeding, obstruction, lymphadenopathy, histology, bulkiness of tumor, concern regarding margins, or metastases also play an important role.
- Several studies are ongoing in evaluating immunotherapy in the treatment of locally advanced gastric cancer and data for the role of utilizing these agents in exquisitely sensitive subtypes such as mismatch repair deficient disease are rapidly emerging.

DISCLOSURES

Dr T. Srikumar does not have any disclosures. R. Sundar: reports attending advisory board meetings for Bristol Myers Squibb, Merck, Eisai, Bayer, Taiho, Novartis, MSD, GSK, DKSH, Astellas, Pierre-Fabre, Tavotek, Astra Zeneca, Sanofi, Daichii Sankyo, Beigene; receiving honoraria for talks from MSD, Eli Lilly, BMS, Roche, Taiho, Astra Zeneca, DKSH, Ipsen, Daiichi Sankyo, Beigene, Astellas; receiving travel support from Roche, Astra Zeneca, Taiho, Eisai, DKSH, Ipsen, Cytomed, Paxman Coolers; receiving research funding from Paxman Coolers, MSD, United States, Natera, United States, CytoMed Therapeutics and has patents pending with licensing to Paxman and Auristone.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209–49.
2. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut 2020;69(9):1564–71.
3. Shah SC, McKinley M, Gupta S, et al. Population-based analysis of differences in gastric cancer incidence among races and ethnicities in individuals age 50 years and older. Gastroenterology 2020;159(5):1705–14.e2.
4. Egyud MR, Tseng JF, Suzuki K. Multidisciplinary therapy of esophageal cancer. Surg Clin North Am 2019;99(3):419–37.
5. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345(10):725–30.
6. National Comprehensive Cancer Network. Gastric Cancer (Version 3.2023). Available at: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. [Accessed 4 March 2024].
7. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(10):1005–20.
8. Obermannová R, Alsina M, Cervantes A, et al. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(10):992–1004.
9. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). Gastric Cancer. 2023;26(1):1-25.
10. Kim TH, Kim IH, Kang SJ, et al. Korean Practice Guidelines for Gastric Cancer 2022: An Evidence-based, Multidisciplinary Approach. J Gastric Cancer 2023;23(1):3–106.
11. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11–20.
12. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29(13):1715–21.
13. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393(10184):1948–57.
14. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357(18):1810–20.
15. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III Gastric Cancer. J Clin Oncol 2011;29(33):4387–93.
16. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379(9813):315–21.

17. Yoshida K, Kodera Y, Kochi M, et al. Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage iii gastric cancer: interim analysis of JACCRO GC-07, a Randomized Controlled Trial. J Clin Oncol 2019;37(15):1296–304.
18. Kakeji Y, Yoshida K, Kodera Y, et al. Three-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 plus docetaxel versus S-1 alone in stage III gastric cancer: JACCRO GC-07. Gastric Cancer 2022;25(1):188–96.
19. Zhang X, Liang H, Li Z, et al. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. Lancet Oncol 2021;22(8):1081–92.
20. Zhang X, Li Z, Liang H, et al. LBA78 Overall survival of perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy: An updated analysis of RESOLVE trial. Ann Oncol 2023;34:S1318–9.
21. Kang YK, Yook JH, Park YK, et al. PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer. J Clin Oncol 2021;39(26):2903–13.
22. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30(19):2327–33.
23. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11(5):439–49.
24. Lee J, Lim DH, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30(3):268–73.
25. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol 2015;33(28):3130–6.
26. Park SH, Lim DH, Sohn TS, et al. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial(☆). Ann Oncol 2021;32(3):368–74.
27. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018;19(5):616–28.
28. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281(17):1623–7.
29. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15(3):305–14.

30. van der Wilk BJ, Eyck BM, Wijnhoven BPL, et al. LBA75 Neoadjuvant chemoradiotherapy followed by surgery versus active surveillance for oesophageal cancer (SANO-trial): A phase-III stepped-wedge cluster randomised trial. Ann Oncol 2023;34:S1317.
31. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009; 27(6):851–6.
32. Stahl M, Walz MK, Riera-Knorrenschild J, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. Eur J Cancer 2017;81:183–90.
33. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366(22):2074–84.
34. Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16(9):1090–8.
35. Reynolds JV, Preston SR, O'Neill B, et al. Trimodality therapy versus perioperative chemotherapy in the management of locally advanced adenocarcinoma of the oesophagus and oesophagogastric junction (Neo-AEGIS): an open-label, randomised, phase 3 trial. Lancet Gastroenterol Hepatol 2023;8(11):1015–27.
36. Kelly RJ, Ajani JA, Kuzdzal J, et al. adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021;384(13):1191–203.
37. Shitara K, Rha SY, Wyrwicz LS, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. Lancet Oncol 2023. https://doi.org/10.1016/s1470-2045(23)00541-7.
38. Janjigian Y, Al-Batran S, Wainberg Z, et al. LBA73 Pathological complete response (pCR) to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): Interim results of the global, phase III MATTERHORN study. Ann Oncol 2023;34:S1315–6.
39. Terashima M, Kang Y-K, Kim Y-W, et al. ATTRACTION-5: A phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III (pStage III) gastric or gastroesophageal junction (G/GEJ) cancer. J Clin Oncol 2023;41(16_suppl):4000.
40. Yuan SQ, Nie RC, Jin Y, et al. Perioperative toripalimab and chemotherapy in locally advanced gastric or gastro-esophageal junction cancer: a randomized phase 2 trial. Nat Med 2024. https://doi.org/10.1038/s41591-023-02721-w.
41. Verschoor YL, van de Haar J, van den Berg JG, et al. Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial. Nat Med 2024. https://doi.org/10.1038/s41591-023-02758-x.
42. Li C, Zheng Y, Shi Z, et al. 1512MO Perioperative camrelizumab (C) combined with rivoceranib (R) and chemotherapy (chemo) versus chemo for locally advanced resectable gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The first interim analysis of a randomized, phase III trial (DRAGON IV). Ann Oncol 2023;34:S852.

43. Hofheinz RD, Merx K, Haag GM, et al. FLOT Versus FLOT/Trastuzumab/Pertuzumab Perioperative Therapy of Human Epidermal Growth Factor Receptor 2-Positive Resectable Esophagogastric Adenocarcinoma: A Randomized Phase II Trial of the AIO EGA Study Group. J Clin Oncol 2022;40(32):3750–61.
44. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol 2018;19(10):1372–84.
45. Wagner AD, Grabsch HI, Mauer M, et al. EORTC-1203-GITCG - the "INNOVATION"-trial: Effect of chemotherapy alone versus chemotherapy plus trastuzumab, versus chemotherapy plus trastuzumab plus pertuzumab, in the perioperative treatment of HER2 positive, gastric and gastroesophageal junction adenocarcinoma on pathologic response rate: a randomized phase II-intergroup trial of the EORTC-Gastrointestinal Tract Cancer Group, Korean Cancer Study Group and Dutch Upper GI-Cancer group. BMC Cancer 2019;19(1):494.
46. Lorenzon L, Biondi A, Santoro G, et al. Microsatellite instability in gastric cancer: An institutional case series analysis in patients treated with neoadjuvant therapy. Clinical Surgical Oncology 2024;3(1):100031.
47. Pietrantonio F, Miceli R, Raimondi A, et al. Individual patient data meta-analysis of the value of microsatellite instability as a biomarker in gastric cancer. J Clin Oncol 2019;37(35):3392–400.
48. Lorenzen S, Götze TO, Thuss-Patience P, et al. Perioperative atezolizumab plus fluorouracil, leucovorin, oxaliplatin, and docetaxel for resectable esophagogastric cancer: interim results from the randomized, multicenter, phase II/III DANTE/IKF-s633 Trial. J Clin Oncol 2024;42(4):410–20.
49. Pietrantonio F, Raimondi A, Lonardi S, et al. INFINITY: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). J Clin Oncol 2023;41(4_suppl):358.
50. André T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability–high gastric or esophagogastric junction adenocarcinoma: The GERCOR NEONIPIGA phase II study. J Clin Oncol 2023;41(2):255.
51. Al-Batran S-E, Lorenzen S, Thuss-Patience PC, et al. Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. J Clin Oncol 2022;40(16_suppl):4003.
52. Eveno C, Adenis A, Bouche O, et al. Adjuvant chemotherapy versus perioperative chemotherapy (CTx) for resectable gastric signet ring cell (SRC) gastric cancer: A multicenter, randomized phase II study (PRODIGE 19). J Clin Oncol 2019;37(15_suppl):4019.
53. Iwasaki Y, Terashima M, Mizusawa J, et al. Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial. Gastric Cancer 2021;24(2):492–502.
54. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw 2022;20(2):167–92.

55. Openshaw MR, Suwaidan AA, Ottolini B, et al. Longitudinal monitoring of circulating tumour DNA improves prognostication and relapse detection in gastroesophageal adenocarcinoma. Br J Cancer 2020;123(8):1271–9.
56. Huffman BM, Aushev VN, Budde GL, et al. Analysis of Circulating Tumor DNA to Predict Risk of Recurrence in Patients With Esophageal and Gastric Cancers. JCO Precis Oncol 2022;6:e2200420.
57. Al-Batran SE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 Trial. JAMA Oncol 2017;3(9):1237–44.
58. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. BMC Cancer 2017;17(1):893.