Review Article on Current Management of Upper Gastrointestinal Malignancies

Current management of gastric adenocarcinoma: a narrative review

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Abstract: Gastric adenocarcinoma is a leading cause of cancer death worldwide. The management of this aggressive malignancy largely depends on tumor characteristics especially stage. Superficial early-stage gastric cancer can be safely managed by endoscopic resection, though clear negative deep and lateral margins must be obtained. Optimal surgical resection is an essential part of the treatment for locally advanced gastric adenocarcinoma, with perioperative and adjuvant therapies having significant impact on long-term outcomes. Chemoradiation is reserved for patients with suboptimal surgical resection. Recent therapeutic advances have prolonged survival in patients with metastatic gastric adenocarcinoma, include checkpoint inhibitors and biomarker-directed therapy. Targeted therapies in gastric adenocarcinoma include monoclonal antibodies directed against vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor-2 (VEGFR-2), and human epidermal growth factor receptor 2 (HER2). While anti-VEGF therapies were not found beneficial in the perioperative setting, the effectiveness of HER2 targeted agents in resectable HER2-positive gastric adenocarcinoma is being studied. Microsatellite instability (MSI) varies greatly in patients with gastric adenocarcinoma between 5–20% based on ethnic origin, tumour heterogeneity and staging. The role chemotherapy in the perioperative setting for patients with MSI-high tumors remains controversial while immunotherapy demonstrates promising results in preliminary studies. Immune checkpoint inhibitors in combination with chemotherapy has been shown to improve outcomes in patients with metastatic gastric adenocarcinoma who express programmed cell death 1 ligand 1 (PD-L1) and is now being investigated in the perioperative setting.

Keywords: Gastric adenocarcinoma; gastrectomy; perioperative therapy; systemic therapy

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Introduction

Stomach cancer was the fifth most common cancer worldwide in 2020 (excluding non-melanoma skin cancer) with 1.1 million new cases, and the fourth leading cause of cancer death with approximately 800,000 deaths (1,2). Incidence rates are highest in Eastern Asia and Eastern Europe, while rates in Northern America and Northern Europe are equivalent to those in Africa and are generally low (1,2). Incidence and mortality rates from non-cardia gastric cancer (GC) are declining in the last half a century while the relative increase seen in gastric cardia cancers appears to be stabilized, at least for the United States and

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Table 1 The search strategy summary

Items	Specification
Date of search	June 2022
Databases and other sources searched	PubMed, ClinicalTrials.gov
Search terms used	Gastric cancer, endoscopic resection, EMR, ESD, perioperative, neoadjuvant, adjuvant, metastatic, targeted therapy, immune checkpoint inhibitors
Timeframe	Up to June 2022
Inclusion and exclusion criteria	Excluded: non-English studies
Selection process	Y Nevo conducted the selection; L Ferri approved the selection of studies

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Netherlands (1-6). A new and contrasting observation, that warrants further validation, is an incidence increase in GC (both cardia and noncardia) in young adults aged 50 and below in both high and low-risk countries, and particularly in males (7,8).

Clinical staging dictates prognosis and treatment strategy. Using the National Cancer Database, the 5-year survival estimates in the 8th edition of the American Joint Committee on Cancer (AJCC) manual were IA: 81%; IB: 68.5%; IIA: 59.3%; IIB: 46.4%; IIIA: 30.5%; IIIB: 20.1%; IIIC: 8.3%; IV: 5.6% (9). According to the Surveillance, Epidemiology, and End Results Program (SEER), the stage distribution of cases in 2011–2019 was 29.4% for localized disease, 24.4% for regional disease, 33.6% for distant advanced disease and 12.6% unknown (10). The high incidence of GC in the eastern countries has led to the implementation of population-based screening programs. Those programs may result in a 'stage-shift' with earlier-stage detection where more curative intent treatments are available (11).

Rational and objective

From organ sparing endoscopic resection for early disease, through multimodality treatments with minimally invasive surgical approaches and novel targeted therapies for metastatic disease, the management of gastric adenocarcinoma has advanced considerably over the past few years. This review will discuss the current management gastric adenocarcinoma and recent therapeutic advances.

Gastroesophageal junction (GEJ) adenocarcinoma

For this review on gastric adenocarcinoma, we will apply only on Siewert type III GEJ (12).

Siewert type I tumors that arise from the distal esophagus and infiltrate the GEJ from above and tumors of the true GEJ (Siewert type II) will not be discussed in this review.

Methods

This review is based on literature search that was conducted in June 2022 through PubMed database and ClinicalTrials.gov registry. We included phase 2/3 studies as well as retrospective and observational analysis (*Table 1*).

Early gastric cancer (EGC), localized disease

EGC is defined as adenocarcinoma limited to the mucosa or submucosa (*Figure 1*), regardless of lymph node metastasis (11,13). The mainstay of treatment is resection, either endoscopic resection or surgery. Endoscopic resection, either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is widely adopted in the East and has shown successful results in the treatment of EGC (14-16). Endoscopic resection is advised for tumors that have a very low possibility of lymph node metastasis and are amendable for complete resection (17). A multicenter retrospective study from Korea reporting EMR long-term outcomes in EGC found no cancer-related death in more than 3 years of follow-up and only 6% local recurrence rate (18). EMR is a valid option in patients with EGC, but proper patient selection is important to achieve good clinical outcomes. Achieving complete resection by EMR is dependent upon several parameters including the gross endoscopic type, the tumor grade, and the depth of invasion (14). As stated by the European Society of Gastrointestinal Endoscopy, EMR is a valid option for lesions smaller than 10–15 mm with a very low probability of advanced histology (19). EMR has some limitations and often results in piecemeal

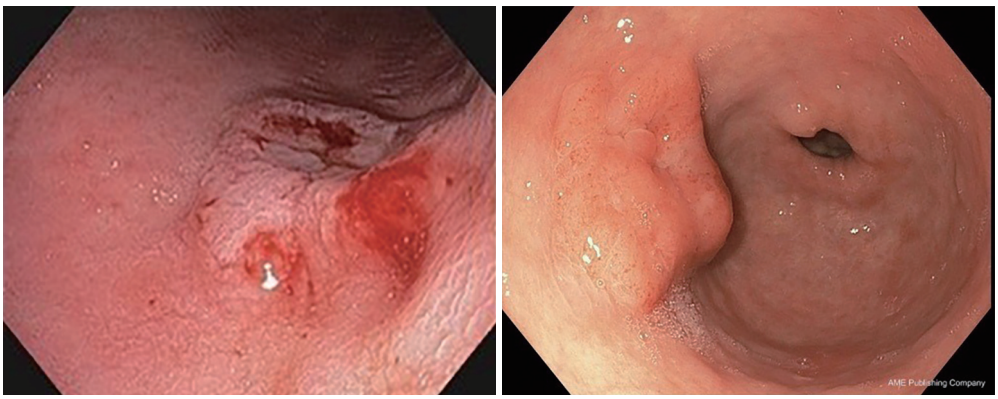

Figure 1 Early gastric cancer, cT1N0.

resection that may lead to high local recurrence rates (20). ESD allows for *en-bloc* resection (*Figure 2*) and precise histological assessment of EGC and has been shown to be more effective than EMR (20-23). For lesions greater than 5 mm the complete resection rate was significantly better for ESD than EMR, whereas for lesions less than 5 mm the rates were not different (20,23,24). ESD has also shown comparable outcomes to surgery for EGC in terms of overall and disease specific survival. it is usually associated with shorter hospital stay, lower cost, and better quality of life (25-27). ESD has become the treatment of choice for EGC in Asia (28,29) and is gaining acceptance in the West (30). According to National Comprehensive Cancer Network (NCCN) guideline (version 2.2022) EGC that is less than or equal to 2 cm in diameter, well to moderately differentiated, does not invade submucosa, does not exhibit lymph-vascular invasion (LVI) and has clear lateral and deep margins can be treated with EMR or ESD (12). The Japanese Gastric Cancer association (JGCA) guidelines (5^{th} edition) further include two more types of EGC as an indication for ESD: a differentiated-type adenocarcinoma without ulcerative findings, in which the depth of invasion is clinically diagnosed as T1a and the diameter is >2 cm. A differentiated-type adenocarcinoma with ulcerative findings, in which the depth of invasion is clinically diagnosed as T1a and the diameter is ≤3 cm (31). For EGC tumors that do not fulfil those indications surgical resection should be considered.

Locally advanced GC

The treatment strategy for locally advanced GC (*Figure 3*) has changed from surgery alone to a multimodality approach. However, surgery alone offers poor overall survival (OS) whereas the multimodality therapy has been shown to significantly increase OS in patients with locally advanced disease (32-35).

Surgical resection

The principle of surgery includes gastrectomy with clear margins and appropriate lymph node dissection. Currently, there is no consensus as for the adequate distance between the tumor and the resection margin to ensure complete tumor excision with negative margins (R0) and minimize the risk for local recurrence. While previously recommending resection margins >4 cm from the gross tumor, the recent (version 2.2022) NCCN guideline recommends adequate gastric resection to achieve negative microscopic margins (12). In the European Society of Medical Oncology (ESMO) recommends a 5-cm macroscopic proximal margin for intestinal type cancers and 8 cm in diffuse type cancers when performing a subtotal gastrectomy. If those margins cannot be secured, a total gastrectomy is advised (36). In the JGCA guidelines the growth pattern is considered. In an expensive growth pattern for a proximal margin of 3 cm is recommended whereas for an infiltrative growth pattern a 5-cm margin is advised. A frozen section is recommended when those margins cannot be secured (31,37). The safety and efficacy of the laparoscopic approach has been evaluated in several trials. The KLASS-02-RCT was a Korean trial which showed lower rate of complications in laparoscopic gastrectomy with D2 lymphadenectomy for locally advanced GC (16.6% *vs.* 24.1%, P=0.003), less post-

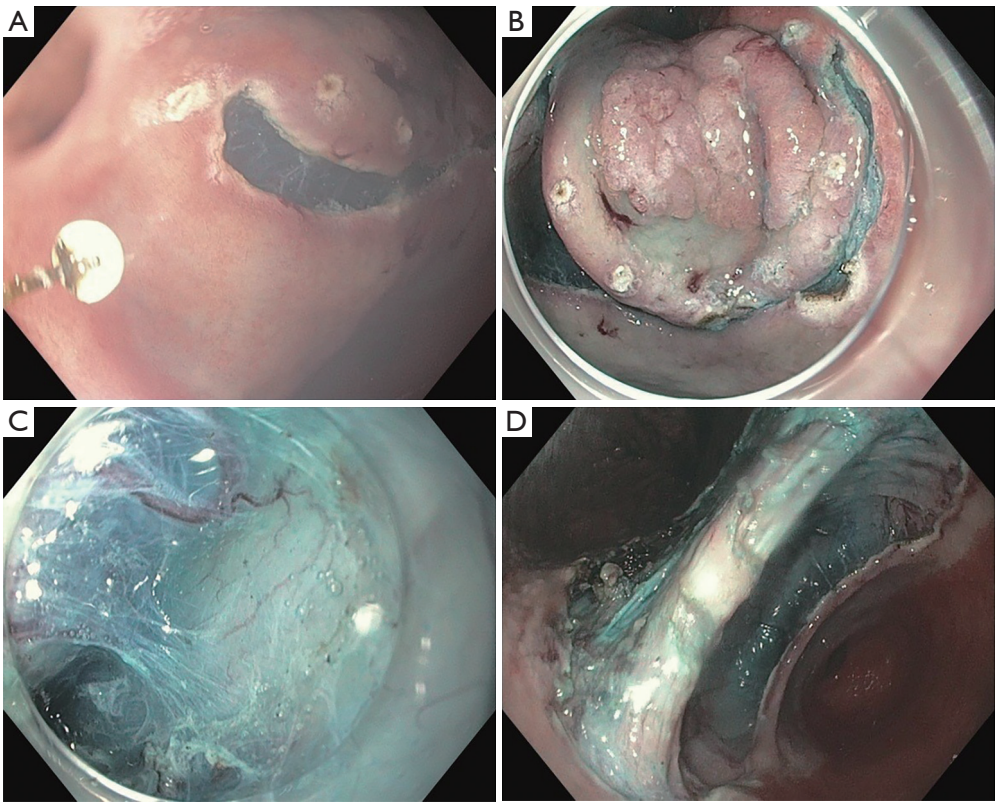

Figure 2 Endoscopic submucosal dissection of early gastric cancer. (A,B) Precutting the surrounding mucosa around the tumor; (C,D) dissecting the connective tissue of the submucosa beneath the tumor.

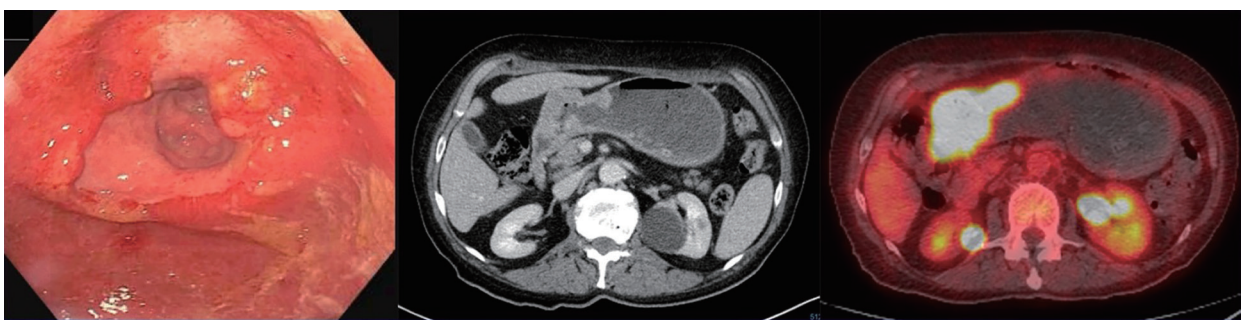

Figure 3 Locally advanced (cT3N1) moderately differentiated gastric adenocarcinoma.

operative pain, and shorter length of hospital stay (8.1 *vs.* 9.3 days, P=0.005) compared with open surgery (38). The long-term outcomes of the KLASS-02 trial demonstrated comparable disease-free survival (DFS) outcomes (39). The LOGICA trial was a multicenter Western RCT comparing laparoscopic to open gastrectomy that did not find a difference in complication rate (44% *vs.* 42%, P=0.91) or length of stay (7 days in both groups, P=0.34), though the cohort included also total gastrectomy. The oncological efficacy including R0 resection rate (95% *vs.* 95%, P=1.00), and median lymph node yield (29 *vs.* 29 nodes, P=0.49) was similar in both groups (40). Accordingly, we recommend performing gastrectomy in the approach, laparoscopic or open, for which local expertise exists as both approaches are acceptable and can achieve the stated goals of the operation, safe resection of the tumour in an ontologically appropriate

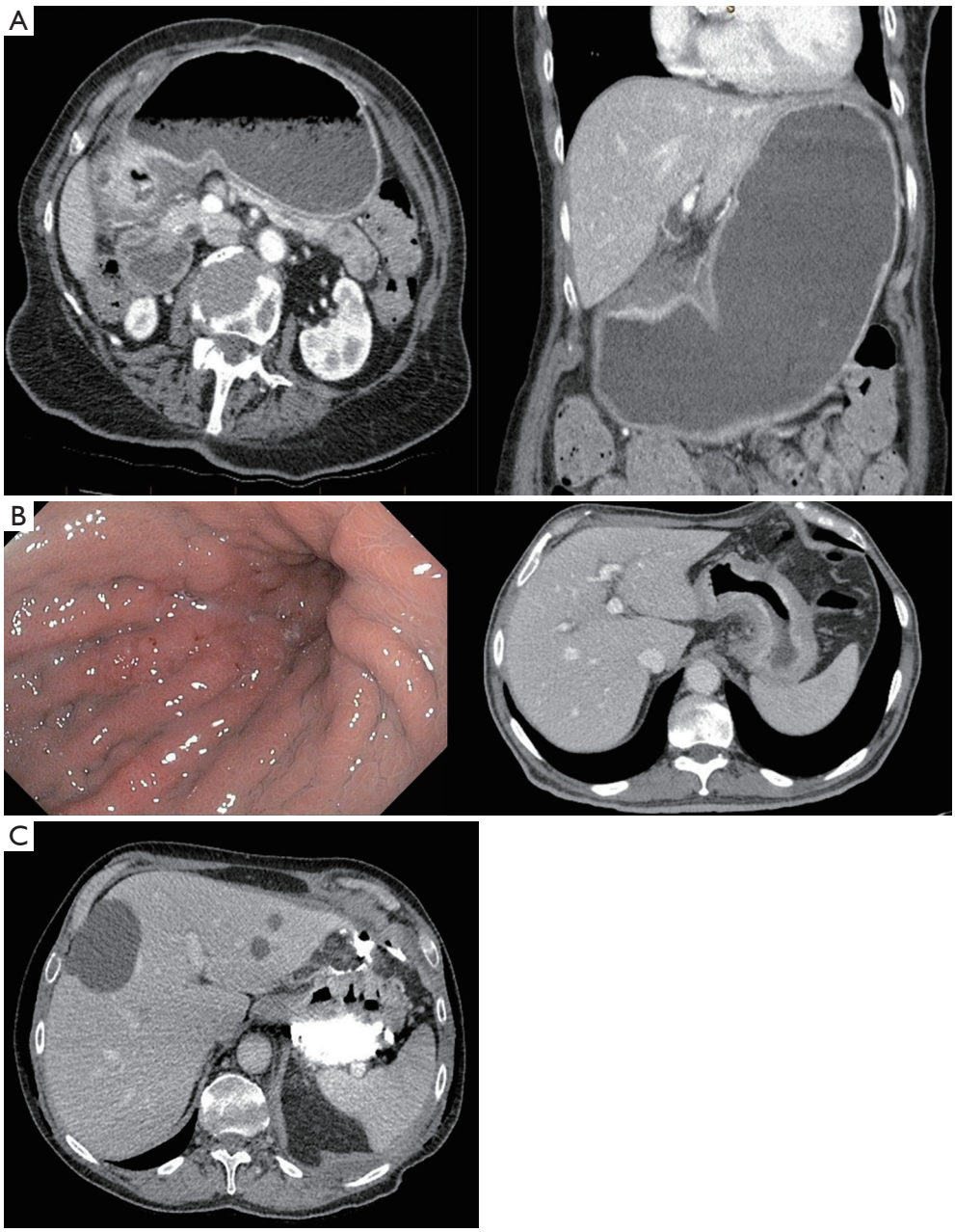

Figure 4 Clinical scenarios where an open surgical approach is preferred. (A) Gastric outlet obstruction due to gastric adenocarcinoma; (B) signet ring cell gastric adenocarcinoma; (C) perforated gastric adenocarcinoma.

manner (negative margins and extended lymphadenectomy). In addition, there are some conditions which may not lend themselves to a laparoscopic approach for which an open operation may be better suited including gastric outlet obstruction with a massively dilated stomach (*Figure 4A*), very bulky gastric tumours with linitis plastica (*Figure 4B*), and perforated tumours (*Figure 4C*).

Lymph node dissection

The extent of lymph nodes dissection is still a matter of ongoing debate. D1 lymphadenectomy includes removal of all the perigastric lymph nodes, whereas a D2 lymph nodes dissection involves the removal of nodes along the vessels including the left gastric, common hepatic, celiac, and splenic

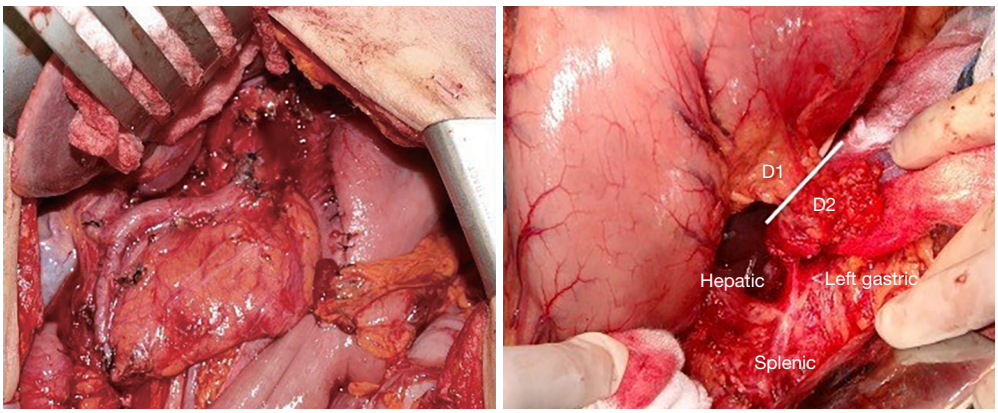

Figure 5 D2 lymph node dissection.

artery (*Figure 5*). In the JGCA guidelines, D2 dissection is indicated for potentially curable T2–T4 tumours, as well as for cT1N+ tumors (11,31). Six randomized controlled trials (RCTs) compared a more limited to extended lymphadenectomy in GC (41-47). Initial results from two large RCTs performed at Netherlands and UK didn't find a significant survival benefit of D2 *vs.* D1 lymph nodes dissection (43,44). In a 15-year median follow-up of the Dutch trial, it was shown that D2 lymphadenectomy significantly reduced recurrence and death rates (48). The Taiwanese RCT demonstrated a benefit of extended lymphadenectomy on 5-year OS and 5-year disease-specific survival (45) and in all other RCTs survival rates were similar between D1 and D2 lymphadenectomy. The Italian trial showed that D1 lymphadenectomy may be better patients older than 70 years old and in early GC (46). Both the Dutch the British and other trials showed increased morbidity and mortality after D2 dissection largely attributed to splenectomy and/or pancreatectomy, once a mandatory part of the D2 lymphadenectomy (43,44,49). After adjustment for splenectomy and/or pancreatectomy, the morbidity difference that was seen in the British trial became non-significant. In the Dutch trial splenectomy or pancreatico-splenectomy decreased mean OS after 15 years in both the D1 and D2 dissection group. A significant 15-year survival benefit was seen when D2 lymphadenectomy was done without splenectomy and/or pancreatectomy. Demonstrated also by the Taiwanese RCT with increased 5-year OS and DFS with spleen and/or pancreas preserving lymphadenectomy (43-45,47). A meta-analysis including the Dutch, the British and the Taiwanese RCTs concerning lymphadenectomy with or without pancreatico-splenectomy demonstrated a survival benefit for D2 compared to D1 (50). D2 lymphadenectomy improves survival as long as the morbidity is kept low, without splenectomy/pancreatectomy unless properly indicated.

Multimodality treatment

The multimodality approach has been proven to prolong survival in locally-advanced gastric adenocarcinoma (34,35). In Western countries, perioperative chemotherapy with a docetaxel-based triplet therapy {e.g., FLOT [5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel]} before and after surgery is the standard. In Asian countries, like Japan, Korea and China, adjuvant chemotherapy is preferred (11). Chemotherapy in the pre-operative setting is usually better tolerated than in the post-operative period, and may improve survival due to eradication of occult micrometastasis (51); however, both approaches are well established and accepted.

Perioperative chemotherapy

The perioperative approach was introduced by the MAGIC trial, in which 503 patients with stage II or greater adenocarcinoma of the stomach, GEJ and lower oesophagus were randomized to receive ECF (epirubicin, cisplatin, and 5-FU) before and after surgery or surgery alone (52). Perioperative ECF demonstrated a significant improvement in 5-year OS (36% *vs.* 23%, P=0.009) and progression-free survival (PFS) (35% *vs.* 25%, P<0.001). A subsequent study, the French ACCORD-07 trial (53) demonstrated similar results and survival benefit of perioperative chemotherapy

and surgery over surgery alone (5-year OS: 38% *vs.* 24%, P=0.02) though using doublet regimen of fluoropyrimidine/platinum instead of an anthracycline-based triplet regimen of the MAGIC trial. The FLOT4 study randomized patients to receive perioperative FLOT or ECF.

DFS and OS were significantly improved in patients who received FLOT (DFS: 30 *vs.* 18 months, P=0.0036; OS 50 *vs.* 35 months, P=0.012). Postoperative complications and mortality were similar in both groups (54). For medically fit patients, FLOT is now considered standard of care perioperative chemotherapy in gastric adenocarcinoma. However, not all eligible patients with locally-advanced GC are amenable to receive neoadjuvant therapy due to clinical scenarios precluding their ability to tolerate the treatment. These include the significant bleeding, gastric outlet obstruction, or perforation with active infection. In such cases it is recommended for the patient to undergo upfront resection, if feasible, followed by some forms of adjuvant therapies (chemotherapy or chemoradiation—see below).

Adjuvant chemotherapy

Surgical resection followed by adjuvant chemotherapy is the standard of care in Asia, and most of the data supporting this approach comes from Asian countries (55,56). The Japanese Adjuvant Chemotherapy Trial of S-1 for GC (ACTS-GC) trial examined the role of adjuvant S-1 (oral fluoropyrimidine) following surgery with D2 lymphadenectomy for stage II and III gastric adenocarcinoma (55). The adjuvant chemotherapy group of S-1 demonstrated superior 5-year OS outcomes compared with surgery alone [71.7% *vs.* 61.1%, 95% confidence interval (CI): 0.54–0.83] (57).

The CLASSIC study was a phase III RCT which randomized 1,035 patients with stage II–IIIB GC who underwent gastrectomy D2 lymph node dissection to receive adjuvant chemotherapy (capecitabine and oxaliplatin) or observation only. Five-year OS was significantly improved in the chemotherapy group (78% *vs.* 69%, P=0.0015) (56,58). Adding taxane in the adjuvant setting has shown improved outcomes in the Japanese Clinical Cancer Research Organization (JACCRO) GC-07 trial, in which 915 patients with lymph node-positive stage IIA–IVA GC were randomized following curative gastrectomy with D2 lymphadenectomy to postoperative S-1 plus docetaxel or S-1. The docetaxel group had improved 3-year relapse-free survival (RFS) (66% *vs.* 50%, P<0.001) (59).

Adjuvant chemoradiotherapy

Since the introduction of the landmark Intergroup 0116 trial (INT-0116) (32), more than 20 years ago, post-operative chemoradiotherapy is no longer the standard of care for resectable gastric adenocarcinoma, and is instead reserved for patients with residual disease following surgery or those who received less than D2 lymphadenectomy (12,51). In the INT-0116, 556 patients were randomized to receive postoperative chemotherapy and chemoradiation with 5-FU/leucovorin or surgery followed by observation alone, and both showed improved 3-year OS (50% *vs.* 41%, P=0.005) and 3-year RFS (48% *vs.* 31%, P<0.001) (32), with continued strong benefit from the tri-modality treatment at 10-year follow-up (60). A reduction in local and regional recurrence was primarily responsible for the survival benefit in the chemoradiotherapy group (19% *vs.* 29% and 65% *vs.* 72%, respectively). However, the study was criticized as only 10% of patients underwent formal D2 lymphadenectomy and 54% underwent D0 dissection. A subsequent phase III trial, the Korean ARTIST trial examined the effects of radiation following surgery with appropriate lymph node dissection, but showed no benefit in survival (61). Patients were randomized to receive adjuvant chemotherapy (capecitabine and cisplatin) alone or in combination with radiotherapy. Five-year OS (75% *vs.* 73%) and 3-year DFS (78% *vs.* 74%) were similar in the two groups (61,62). The adjuvant chemoradiotherapy treatment of patients with node-positive cancer demonstrated improved DFS, but a subsequent study (ARTIST-II) specifically designed to evaluate this subgroup of patients who had undergone D2 lymphadenectomy and were node-positive did not show any significant difference in DFS when combined with adjuvant chemoradiotherapy (63). The Dutch CRITICS trial also did not show any significant difference in the median OS of perioperative ECF or preoperative ECF followed by adjuvant chemoradiation (37 *vs.* 43 months, P=0.90) (64). Taken together these data suggest that radiation therapy may not provide benefit patients for whom adequate local control was achieved with surgery. However, in patients with pathologically proven locally advanced disease (pT3 and/or N1-3) who did not receive a formal D2 dissection or with positive margins, the addition of radiation to chemotherapy in the adjuvant setting is recommended despite the absence of solid phase 3 data (65). *Figure 6* illustrates our current approach to managing gastric adenocarcinoma.

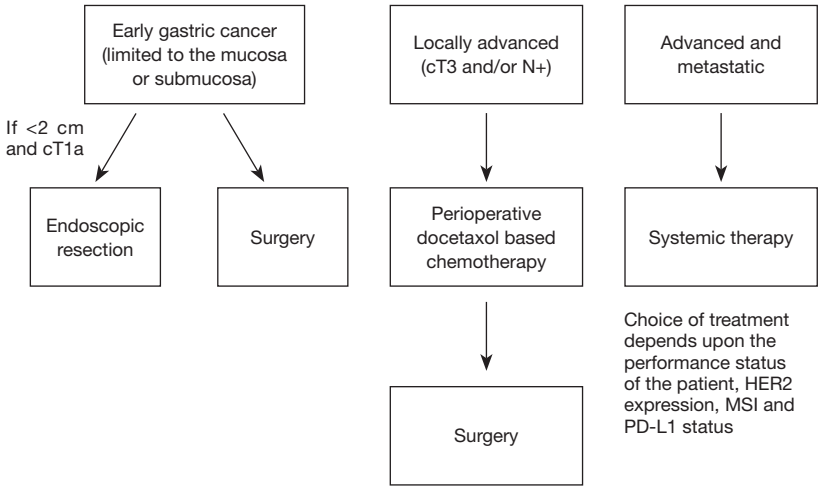

Figure 6 Therapy flowchart. HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; PD-L1, programmed cell death ligand 1.

Perioperative targeted therapies

Targeted therapies in GC include monoclonal antibodies directed against Vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor-2 (VEGFR-2), and human epidermal growth factor receptor 2 (HER2). In patients with advanced/metastatic GC, targeted therapies have become the standard of care in addition to chemotherapy (66-68), and was studies as a possible combination in the context of perioperative care. As a part of the UK ST03 study, bevacizumab an anti-VEGFR monoclonal antibody was added to preoperative ECX chemotherapy, but no survival benefits were observed. Additionally, bevacizumab was associated with increased wound healing complications (69). According to the phase II FLOT7-RAMSES trial reported in an abstract form, ramucirumab was added to perioperative FLOT to improve R0 resection rates (97% *vs.* 83%, P=0.0049), but not the pathological response (27% *vs.* 30%, P=0.7363). The Ramucirumab arm had increased mortality (5.9% *vs.* 2.5%), that occurred in patients with Siewert type I GEJ adenocarcinoma (70). Approximately 10-25% of GC's overexpress HER2. The PETRARCA phase II randomized trial reported as an abstract, showed that the addition of trastuzumab/pertuzumab (anti HER2 monoclonal antibodies) to perioperative FLOT significantly improves pathological complete response (pCR) rate (35% *vs.* 12%, P=0.02) on the other hand, the extent of diarrhea and leukopenia has increased (71). In the Dutch phase II HER-FLOT single-arm trial, trastuzumab was combined with FLOT in 56 patients with locally advanced resectable gastro-esophageal adenocarcinoma (72). The primary endpoint of pCR >20% was reached, with approximately 50% of patients achieving complete or near-complete remission and the 3-year OS rate was 82.1%. There were only mild adverse reactions. Further results are needed to demonstrate the effectiveness of HER2 targeted agents in the perioperative treatment of HER2-positive GC (73).

Biomarkers

Molecular markers and histopathologic tumor features are recently appearing as important factors in patients' outcomes (74-76). Cancer Genome Atlas (TCGA) and Asian Cancer Research Group (ACRG) have developed detailed genomic characterizations of GC (74,75). The TGCA identified four molecular subtypes of OG cancer—Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), genomic stable and chromosomal unstable tumour subtypes (74)—and the ACRG identified MSI, microsatellite stable/epithelial to mesenchymal transition (MSS/EMT), MSS/TP53+ and MSS/TP53− as subtypes with prognostic values (75).

MSI

In patients with GC, MSI varies greatly (74,77,78) based on the ethnic origin of the cohorts (Asian *vs.* Caucasian), tumor heterogeneity, and MSI assays used. There is a significant difference between MSI for node-negative disease, which is

up to 20%, and MSI for metastatic disease, which is only 5% (75,78). In addition to an older age (65 years) and female gender, MSI GCs are less likely to involve lymph nodes, and to invade serosal layers (78-80). There was a greater survival benefit in patients with MSI high compared to microsatellite stable (MSS) patients in a meta-analysis of the MAGIC, CLASSIC, ARTIST, and ITACA-S trials (77.5% *vs.* 59.3%). However, those with MSI-high who received chemotherapy and surgery had worse outcomes than patients who underwent surgery alone (5-year OS: 75% *vs.* 83%), suggesting no benefit from chemotherapy (81). In patients with MSI-high GC, the role of perioperative or adjuvant chemotherapy remains controversial. The high mutation rate in MSI-high tumors, amends them more sensitive to immunotherapy and is an area of ongoing investigation (74,82), with some very exciting data emerging suggesting excellent pathological response with combined programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4) blockade in the neoadjuvant setting (83). These promising response data await survival outcomes prior to be applied routinely in this disease.

Programmed cell death 1 ligand 1 (PD-L1)

More than 40% of human GC samples express PD-L1 (84). Accumulating evidence indicates that immune checkpoint inhibition (ICI) in combination with chemotherapy improve outcomes in patients with advanced or metastatic PD-L1 GC (85). A perioperative regimen of docetaxel-based chemotherapy in combination with PD-L1 blockade is investigated in two ongoing phase III trials. The MATTERHORN study examining neoadjuvant durvalumab (an anti-PD-L1 antibody) and FLOT chemotherapy followed by adjuvant durvalumab monotherapy in patients with resectable gastric/GEJ cancer (86). KEYNOTE-585 randomized patients with locally-advanced gastric or GEJ adenocarcinoma to perioperative chemotherapy with or without pembrolizumab (anti-PD-1) (87).

Epstein-Barr virus

EBV-positive GC accounts for 2–20% of total GC cases and is probably affected by environmental and geographical factors as it is slightly less prevalent in Asians than in Caucasians (88,89). EBV-positive GC occurs mostly in young males and localizes to the proximal stomach (88,89). EBV-positive tumours have a strong immunogenic pattern with PD-L1 expression, making them good candidate for PD-L1 blockade therapy (89,90). Several reports have demonstrated an intense response of EBV-positive GC to ICI (91); however, prospective data is still lacking. The ongoing French IMHOTEP phase II trial (NCT04795661) is assessing the role of pembrolizumab in the neoadjuvant setting for EBV-positive or MSI high GC (92). *Table 2* summarizes selected targeted therapies and biomarker-directed trials.

Metastatic GC

The treatment of advanced/metastatic GC is composed of several cytotoxic agents and targeted therapies, whereas surgery is usually reserved for palliation of tumor-related symptoms such as bleeding and obstruction (93). The goals of treatment in the metastatic setting are palliative in intent and focused on improving the quality of life and prolongation of life. Treatment decisions are made based on the patient's performance status, co-morbidities, and the regimen's toxicity profile. In addition to improving symptoms and disease burden, systemic chemotherapy increases OS to an average of 12 months compared with 4 months with supportive care alone (94,95). When compared to single-agent chemotherapy, combination chemotherapy usually results in better response rates and longer survival times (94). Though there is no standard first-line therapy, a two-drug regimen of fluoropyrimidine and platinum is usually the selected regimen for most patients, with oxaliplatin mostly preferred over cisplatin due to lesser toxicity and similar effectiveness (96). A three-drug regimen is usually reserved for patients with good performance status who are medically fit. Docetaxel-bases triplet was shown to provide a higher response rate and longer PFS, which was counterbalanced by increased toxicity (97). ToGA (Trastuzumab for Gastric Cancer) demonstrated moderately but significantly improved outcomes for patients with advanced GC who are HER2-positive. Trastuzumab added to platinum-based chemotherapy (capecitabine plus cisplatin or fluorouracil plus cisplatin) resulted in a median OS of 13.8 months as compared to 11.1 months with chemotherapy alone (66). In the CheckMate 649 trial, nivolumab (a monoclonal antibody to PD-1) and ipilimumab (a recombinant antibody to CTLA4) were studied for patients with HER2 negative advanced GC (85). A total of 1,581 patients with gastric, GEJ or esophageal cancer, previously untreated, advanced non-resectable and HER2-negative were randomized to

Table 2 Selected perioperative targeted therapies and biomarkers clinical trials in resectable gastric cancer

Trial	Population/target	Investigational arm	Control arm	Results
INNOVATION (ongoing phase II)	HER2-positive resectable gastric or GEJ ADC	Arm I: perioperative chemotherapy + trastuzumab; Arm II: perioperative chemotherapy + trastuzumab+ pertuzumab (chemotherapy of choice: FLOT, FOLFOX, CapOx)	Perioperative chemotherapy	Pending
NEONIPIGA (phase II)	Locally-advanced resectable dMMR/MSI-H gastric or GEJ ADC	Neoadjuvant nivolumab and ipilimumab followed by surgery and adjuvant nivolumab	Single arm	59% pCR
IMHOTEP (ongoing phase II)	Resectable dMMR/MSI-H gastric adenocarcinomas (colorectal, endometrial, other*) or EBV$^+$ gastric cancers	Neoadjuvant single dose pembrolizumab followed by surgery and adjuvant pembrolizumab for 1 year in the absence of disease progression	Single arm	Pending
KEYNOTE-585 (ongoing phase III)	Immunotherapy in the perioperative treatment for patients with resectable gastric or GEJ ADC	Pembrolizumab plus chemotherapy as neoadjuvant treatment; pembrolizumab plus chemotherapy as adjuvant treatment followed by pembrolizumab monotherapy (chemotherapy of choice: XP, FP, FLOT)	Placebo plus chemotherapy as neoadjuvant treatment; placebo plus chemotherapy as adjuvant treatment followed by placebo monotherapy (chemotherapy of choice: XP, FP, FLOT)	Pending
MATTERHORN (ongoing phase III)	Immunotherapy in the perioperative treatment for patients with resectable gastric or GEJ ADC	Durvalumab and FLOT chemotherapy, followed by adjuvant durvalumab monotherapy	Placebo plus chemotherapy followed by adjuvant placebo monotherapy	Pending

other*, biliary tract or pancreas adenocarcinoma and small bowel adenocarcinoma. HER2, human epidermal growth factor receptor 2; GEJ, gastroesophageal junction; ADC, adenocarcinoma; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; FOLFOX, 5-fluorouracil/leucovorin, oxaliplatin; CapOx, capecitabine, oxaliplatin; dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high; ADC, adenocarcinoma; pathological complete response; EBV, Epstein-Barr virus; XP, capecitabine, cisplatin; FP, fluorouracil, cisplatin; pCR, pathological complete response.

either nivolumab plus chemotherapy (capecitabine with oxaliplatin or fluorouracil with leucovorin with oxaliplatin), chemotherapy alone, or nivolumab plus ipilimumab. At 13.1-month follow-up, a statistically significant improvement in OS was observed when nivolumab was added to standard chemotherapy (13.8 *vs.* 11.6 months). The largest OS benefits were observed in patients with a Combined Positive Score (CPS) score of ≥5 and ≥1 (14.4 *vs.* 11.1 months and 14 *vs.* 11.3 months, respectively). In patients with advanced HER2-negative GC and CPS ≥5, the treatment of choice in first line is nivolumab combined with chemotherapy (fluoropyrimidine and oxaliplatin) (12).

In the 2nd line therapy, the preferred treatment is depended upon prior therapy and performance status, and to test regimens that haven't yet been tried as a first line of treatment. Ramucirumab as monotherapy or combined with paclitaxel has been investigated as a second-line therapy. In the phase 3 REGARD trial, ramucirumab was superior to placebo as a second-line treatment for advanced GC and provided a modest but significant 1.4-month survival benefit (98). Patients who progressed on first-line chemotherapy were randomized to either paclitaxel and ramucirumab or placebo in the RAINBOW trial (68). The combination of ramucirumab and paclitaxel significantly improved PFS and OS (4.4 *vs.* 2.9 months and 9.6 *vs.* 7.4 months, respectively). Among patients who have good performance status, this combination therapy is the second-line treatment of choice for those who progressed on a fluoropyrimidine and platinum. A third-line regimen that is now approved is the orally fluoropyrimidine combination Trifluridine/tipiracil, that showed a survival benefit compared with placebo in the TAGS phase III trial (5.7 *vs.* 3.6 months) (99). In spite of a high rate of serious adverse events (43%), the addition of this drug has allowed for prolongation of life for patients who otherwise received supportive care only. For patients with MSI-H GC who

progressed on previous therapies, pembrolizumab is a valid option who demonstrated 45.8% objective response rate and 11 months of PFS in the KEYNOTE-158 trial (100).

An emerging promising target for advanced GC is the fibroblast growth factor receptor (FGFR). In a recent phase II trial investigating bemarituzumab, a monoclonal antibody for FGFR2b receptor, patients were screened for the FGFR2b status and randomized to either bemarituzumab or placebo; all patients received chemotherapy (oxaliplatin, leucovorin, 5-FU) (101). Patients treated with the combination of chemotherapy plus bemarituzumab had favorable PFS (9.5 *vs.* 7.4 months, P=0.073) compared to chemotherapy alone. In spite the lack of significant statistical difference in PFS, bemarituzumab showed encouraging clinical effect and a phase 3 trial is underway.

Novel approaches to guide treatment

Clinical and pathological response are not always good surrogates for long-term outcomes, and various emerging other techniques are under investigation to guide pre- and postoperative therapy. Following therapy, circulating tumor DNA (ctDNA) can be measured in the blood and used to diagnose minimal residual disease (MRD). The persistence of ctDNA after surgical resection was shown to predict survival outcomes in various solid malignancies (51,102). In locoregional GC patients treated with curative intent, ctDNA identified patients at high risk for recurrence before the radiographic recurrence occurred (103). In a cohort of 1,630 gastroesophageal adenocarcinoma patients, ctDNA characterized genomic alterations that correlated with clinicopathologic characteristics and outcomes (104).

Conclusions

Despite recent advancements in systemic therapy and improvements in outcomes, gastric adenocarcinoma remains a leading cause of death worldwide. Early detection offers the best chances of survival, with continued research needed at developing novel less invasive tools for early detection. The combination of surgical resection and perioperative systemic therapy improves long-term outcomes in patients with locally advanced gastric adenocarcinoma. Ongoing studies are aimed at optimizing perioperative and systemic therapies, as well as incorporating checkpoint inhibitors and biomarker-directed therapy.

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Footnote

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