Advances in the management of gastric cancer

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ABSTRACT

Gastric cancer is a considerable global health burden, ranking as the fifth most common cancer and the third leading cause of mortality related to cancer worldwide. The disease often presents at advanced stages, which poses challenges to diagnosis and treatment. This review provides a comprehensive overview of gastric cancer, covering its epidemiology, clinical presentation, diagnostic approaches, staging, and classification. This review highlights recent advances in treatment, emphasizing the transition to multimodal strategies that combine surgery, chemotherapy, radiation therapy, and targeted therapies. The basis of this analysis is formed by a comprehensive review of the literature, including randomized controlled trials, meta-analyses, and landmark studies. Promising emerging therapies, including immunotherapy and molecular-targeted agents, are also explored.

Introduction

Gastric cancer remains a major global health concern, accounting for approximately 7.7% of deaths related to cancer worldwide and is the fifth most commonly diagnosed malignancy.[1] The aggressive nature of gastric cancer, coupled with its frequent late stage diagnosis, contributes to poor prognostic outcomes, which makes early detection and effective treatment strategies critical.

One of the greatest challenges in the management of gastric cancer is its tendency for early dissemination, often via peritoneal, hematogenous, and lymphatic spread, which noticeably impacts survival rates. Given the complexity of the disease, treatment approaches have evolved over the years, shifting from surgery alone to comprehensive, multimodality strategies, incorporating chemotherapy, radiation therapy, targeted therapies, and, more recently, immunotherapy. Advances in molecular profiling and precision medicine have also paved the way for more personalized therapeutic approaches, offering hope for improved patient outcomes.

This review will provide an in depth discussion of gastric cancer, including its epidemiology, risk factors, clinical presentation, diagnosis, staging, and classification. The main scope includes current treatment modalities and emerging therapeutic strategies. Ongoing research and future directions in the management of gastric cancer will be also highlighted.

Methods

We conducted a comprehensive literature search by using PubMed, Cochrane, and Clinical Trials.gov, covering publications from January 2000 to December 2024 with the search terms "gastric cancer" and "gastric adenocarcinoma." We gave priority to high quality evidence including randomized controlled trials, systematic reviews, meta-analyses, and international guidelines. Additionally, we included large retrospective cohort studies (n≥100) and influential landmark trials or studies published before 2000 based on their significance to the topic. To ensure the review reflected emerging evidence, selected literature published between 1 January and 31 October 2025 was incorporated during the editorial process.

Gastroesophageal junction cancer was excluded from this review because of its distinct pathophysiology and treatment paradigms. We focused on non-cardia gastric cancer. We excluded small, single center retrospective cohort studies, case series, and case reports owing to their limited generalizability. We only included literature published in English.

Epidemiology

Gastric cancer accounts for 7.7% of deaths related to cancer worldwide and is the fifth most commonly diagnosed cancer globally.[1] Eastern Asia and South Central Asia were responsible for up to 69% of cases in 2020, whereas the US is considered a country with low incidence of gastric cancer, with an overall age standardized incidence rate of 4.73 per 100 000 persons.[2 3] In the US, the median age of diagnosis is 68 years, with 59.6% of patients diagnosed after the age of 65.[4] Men show a higher incidence.[1 2 4] Racial and ethnic minorities, such as Hispanic and non-Hispanic Black patients, have a twofold higher incidence of gastric cancer compared with non-Hispanic white patients, while Asian Americans demonstrate a 6.6-fold higher incidence.[5 6]

Many cases (33.7%) are diagnosed at the metastatic stage, with regional disease accounting for 23.5%, localized disease for 31%, and 11.8%

remaining unstaged.[4] Owing to the high percentage of diagnoses at advanced stages, survival rates are poor, with a five year relative survival rate of 36.4% for all stages combined.[4] Gaps in survival rates are substantial, with localized disease having a five year overall survival rate of 75.4%, compared with just 7% for distant disease.[4] Asian Americans tend to have a better prognosis compared with Caucasian populations, likely due to distinct tumor biology and genetic polymorphisms.[2]

Globally, the incidence and mortality rates of gastric cancer have been declining steadily, driven by preventive and screening efforts, as well as advancements in management and therapeutics.[2 3 7] This decline is attributed to the decreased prevalence of *Helicobacter pylori* infection, improved food preservation and storage, dietary changes, and reduced tobacco use.[1 3 8] However, an increasing trend in gastric cancer incidence among younger populations (<50 years) has been observed, especially in the US and UK.[2 3 9] Although the exact causes are unclear, the rising prevalence of autoimmune gastritis and dysbiosis of the gastric microbiome due to increased use of antibiotics and proton pump inhibitors are believed to be contributing factors.[1]

Risk factors

The most well defined risk factor for gastric cancer is chronic *H pylori* infection. Virulent strains of *H pylori* producing VacA or CagA cause indirect inflammation of the gastric mucosa and direct epigenetic changes in the epithelial cells, promoting malignant transformation.[10] The seroprevalence of *H pylori* in the US is relatively low (around 9% in recent retrospective series).[11] Less than 5% of individuals with *H pylori* infection will develop gastric cancer, with other changes in the gastrointestinal microbiota recently pointed out as potential contributors.[2 12]

Along with *H pylori* infection, salt intake is a well studied risk factor for gastric cancer.[13] In particular, high consumption of salted fish is associated with increased risk of gastric cancer, where high consumption of sodium chloride may detrimentally alter the gastric mucosa or serve as a proxy of poor diet and higher carcinogen consumption.[14] Other dietary factors that can increase the risk of gastric cancer include low intake of fiber, high consumption of refined grains, and low consumption of antioxidant vitamins.[15] Mediterranean diets and the consumption of fresh fruits and white vegetables can have a protective effect.[15 16]

To better answer how medical, environmental, and lifestyle factors affect the risk of gastric cancer development, the Stomach Cancer Pooling Project developed an international consortium of harmonized patient level data, predominantly through case-control studies, which captured approximately 13 000 gastric cancer cases and 31 000 controls in their 2024 update.[17] The Stomach Cancer Pooling Project consortium confirmed a positive association with ever smoking, heavy alcohol consumption (>4 drinks/day), and red or processed meat consumption, but found no such association between type 2 diabetes and non-cardia gastric cancer.[18-21] A systematic review and meta-analysis also found no substantial association between obesity and risk of gastric cancer.[22] Epstein-Barr virus associated gastric cancer is a distinct molecular subtype, accounting for 2% to 20% of gastric cancers and is associated with a more favorable prognosis.[23 24] Recent reviews showed that a healthy lifestyle index (composed of body mass index and adherence to recommendations for healthy diet, smoking, alcohol consumption, and physical activity) had an inverse association with gastric cancer, with long term follow-up studies replicating these results.[14 25] Other factors have highly heterogenous evidence that supports association with gastric cancer incidence, including bile acid reflux, autoimmune disorders, non-alcoholic fatty liver disease, previous gastric surgery, long term proton pump inhibitor use, and aspirin use.[26-31]

Non-modifiable risk factors for gastric cancer are mostly genetic, with 10% of cases displaying a familial aggregation and less than 3% with true mendelian inheritance.[32] Among these, pathogenic CDH1 variants that underly hereditary diffuse gastric cancer confer substantially elevated lifetime risk, for which risk-reducing total gastrectomy and/or intensive endoscopic surveillance are recommended for appropriate carriers.[33 34] Lynch syndrome, familial adenomatous polyposis, gastric adenocarcinoma and proximal polyposis of the stomach, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome, as well as BRCA1/2 mutations, have all been related to the development of gastric cancer.[34]

Clinical presentation

Gastric cancer usually presents with nonspecific symptoms such as indigestion and dyspepsia.[35] However, dyspeptic symptoms alone are not sufficient to raise suspicion of gastric cancer, and healthcare providers rely on the presence of additional alarm symptoms such as dysphagia, weight loss, persistent vomiting, anemia, and/or signs and symptoms of upper gastrointestinal bleeding to consider gastric cancer.

More rarely, gastric cancer can present with a palpable mass or symptoms related to metastatic disease such as malignant ascites, bowel obstruction from peritoneal implants, or jaundice and clinical evidence of liver failure. Over 25 cutaneous paraneoplastic syndromes have been described in advanced gastric cancer, with acanthosis nigricans, acanthosis palmaris, eruptive seborrheic keratosis (Leser-Trélat sign), dermatomyositis, migratory thrombophlebitis (Trousseau's syndrome), cutaneous leukocytoclastic vasculitis, and polyarteritis nodosa being the most common.[36] Microangiopathic hemolytic anemia and membranous nephropathy have also been described. Up to 10% of women with gastric cancer develop a Krukenberg tumor, which is a metastatic implant to the ovary, most commonly of

gastric origin and signet ring cell adenocarcinoma in histology. These tumors can become symptomatic, causing pain, bloating, ascites, irregular vaginal bleeding, and dyspareunia, as well as hormone production due to changes within the ovarian stroma.[37 38]

Distant lymphatic spread can sometimes be identified by physical examination, with the detection of a left supraclavicular node (Virchow node) or left axillary node (Irish node). Peritoneal spread can lead to a periumbilical node (Sister Mary Joseph nodule) and palpable masses in the cul-de-sac (Blumer's shelf).

Diagnosis and staging

As with any cancer, histologic confirmation is essential for a definitive diagnosis of gastric cancer, which is obtained through esophagogastroduodenoscopy. The National Comprehensive Cancer Network guidelines recommend six to eight biopsies,[39] and endoscopy enables precise assessment of the tumor's location within the stomach, its relationship to the gastroesophageal junction for proximal tumors, and the treatment of some lesions.

After diagnosis, cancer staging utilizes multiple imaging modalities, including endoscopic ultrasonography; contrast-enhanced computed tomography of the chest, abdomen, and pelvis; and F-18 fluorodeoxyglucose positron emission tomography or computed tomography from the skull to the mid-thigh. Additional assessments, including genetic testing, evaluation of *H pylori* status, and biopsy of suspected metastatic disease, are performed as clinically indicated. Staging is based on the tumor, node, metastases classification (box 1), which informs treatment selection, prognostication, and helps to align patient expectations.[39 40]

Endoscopic ultrasonography is particularly valuable in distinguishing early stage gastric cancer from locally advanced gastric cancer. Its optimal indication is in cases of suspected early gastric cancer without evident bulky regional disease on cross sectional imaging, helping to identify tumors suitable for endoscopic intervention or upfront surgery. Furthermore, fine-needle aspiration during endoscopic ultrasonography can be used for cytologic assessment of accessible lymph nodes.[39] Multiphasic, contrast enhanced computed tomography with submillimeter axial sections from chest to pelvis is one of the most reliable staging methods, being both accessible and rapid, and it is particularly effective for liver metastasis, with a specificity reaching up to 99.8% in some studies.[41 42] However, identifying peritoneal metastasis by using computed tomography is challenging due to their variable and subtle appearance.[42] The addition of F-18 fluorodeoxyglucose positron emission tomography/computed tomography adds value by improving the accuracy of lymph node assessment, identifying distant metastasis, and offering metabolic insights into the tumor, though not all gastric cancers are F-18 fluorodeoxyglucose avid, and physiologic uptake can occur in the stomach.[39] Positron emission tomography/computed tomography is most commonly employed as a second line test when computed tomography reveals a suspicious finding.[39] Abdomen ultrasonography and magnetic resonance imaging have limited roles in gastric cancer staging.[43]

Staging laparoscopy combined with peritoneal washings is recommended for medically fit, potentially resectable patients with cT1b stage or above, as well as those scheduled for neoadjuvant therapy.[39] Staging laparoscopy shows high sensitivity (64% to 100%) and specificity (80% to 100%) for detecting visible metastasis, enabling precise staging and reducing unnecessary surgical morbidity, mortality, and costs in the treatment of gastric cancer when used selectively.[44 45] Peritoneal carcinomatosis detection by using staging laparoscopy ranges from 10.7% in early stage gastric cancer to 24% overall.[46 47]

Biomarker testing and tumor marker evaluation are essential during gastric cancer staging. National Comprehensive Cancer Network guidelines advise microsatellite instability testing (by using polymerase chain reaction, next-generation sequencing, or mismatch repair by immunohistochemistry) for all newly diagnosed cases. Human epidermal growth factor receptor 2 (HER2), Claudin18.2, and programmed cell death ligand 1 (PD-L1) testing are

Box 1: Stomach cancer tumor, node, metastases clinical staging criteria according to American Joint Committee on Cancer

Primary tumor (T) category
- TX—Primary tumor cannot be assessed
- T0—No evidence of primary tumor
- Tis—Carcinoma in situ: Intraepithelial tumor without invasion of the lamina propria; high grade dysplasia
- T1—Tumor invades the lamina propria, muscularis mucosae, or submucosa
  - T1a—Tumor invades the lamina propria or muscularis mucosae
  - T1b—Tumor invades the submucosa
- T2—Tumor invades the muscularis propria
- T3—Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures*
- T4—Tumor invades the serosa (visceral peritoneum) or adjacent structures*
  - T4a—Tumor invades the serosa (visceral peritoneum)
  - T4b—Tumor invades adjacent structures or organs*

Regional lymph nodes (N) category
- NX—Regional lymph node(s) cannot be assessed
- N0—No regional lymph node metastasis
- N1—Metastasis in 1-2 regional lymph nodes
- N2—Metastasis in 3-6 regional lymph nodes
- N3—Metastasis in ≥7 regional lymph nodes
  - N3a—Metastasis in 7-15 regional lymph nodes
  - N3b—Metastasis in ≥16 regional lymph nodes

Distant metastasis (M) category
- M0—No distant metastasis
- M1—Distant metastasis

*Considered adjacent structures: spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

recommended for suspected or confirmed metastatic disease to expand treatment options.[23 39] Additional mutations can be accessed via next generation sequencing, including tumor mutational burden, NTRK and RET gene fusions, and BRAF V600E mutation.[39] Tumor markers carcinoembryonic antigen and the carbohydrate antigen 19-9 are commonly linked with gastric cancer; a meta-analysis found carbohydrate antigen 19-9 sensitivity at 30%, ranging from 6.8% to 51.7%, with higher values linked to advanced disease stages and tumor burden.[48] Raised carbohydrate antigen 19-9 was associated with reduced overall survival (hazard ratio 1.83, 95% confidence interval 1.56 to 2.15), though optimal cutoff values and their predictive use for recurrences remain debated.[48]

Gastric cancer classifications

Adenocarcinomas constitute over 90% of gastric tumors. The World Health Organization classifies gastric adenocarcinomas into histologic subtypes such as tubular, parietal cell, mixed type, papillary, micropapillary, mucoepidermoid, mucinous, poorly cohesive (including signet ring cell histology), medullary, hepatoid, and Paneth cell adenocarcinoma.[49] One of the earliest classifications, the Lauren classification, categorizes gastric cancer into intestinal, diffuse, mixed, and unclassified types based on histopathology and clinical characteristics.[50] Intestinal type arises from precursor lesions related to chronic inflammation, predominantly affects older patients, and has been declining in incidence.[50 51] The diffuse type, arising from active inflammation, is more prevalent among younger patients, although survival differences between types remain debated.[51] For advanced gastric cancer, the Borrmann classification organizes tumors by morphology: type I polypoid, type II fungating, type III ulcerated, and type IV flat/diffusely infiltrative.[43 52] In a retrospective cohort study, incidences were reported as 18.7%, 39%, 32.4%, and 10% for each type, respectively.[53] Polypoid tumors commonly presented with systemic symptoms, were often of intestinal type, and were more likely to express human epidermal growth factor receptor 2+, while diffusely infiltrative tumors were more prevalent among younger patients, frequently classified as Lauren diffuse type, and had signet ring cells in up to 62.5% of cases.[53] Other systems are also used, such as the Paris classification for early gastric cancer and the Japanese classification combining the Paris and Borrmann classifications.[54 55]

The Cancer Genome Atlas Research Network recently introduced a molecular classification for gastric cancer, which aims to enhance targeted therapy and precision medicine. It identifies four molecular subtypes: Epstein-Barr virus associated, microsatellite unstable, chromosomal unstable, and genomically stable.[56 57] Epstein-Barr virus associated gastric cancer is more common in younger patients, has unique histological features, and accounts for up to 20% of all cases of gastric cancer.[23] Microsatellite unstable gastric cancer, which occurs in up to 22% of cases,[39 57] primarily affects older patients and the distal stomach, is associated with a high mutational load, and tends to have a better overall survival. Epstein-Barr virus associated and microsatellite unstable gastric cancer are mutually exclusive, not occurring in the same patient. Chromosomally unstable gastric cancer is more heterogeneous, often presents with an intestinal phenotype, and frequently harbors HER2 overexpression. Genomically stable gastric cancer typically aligns with diffuse gastric cancer and is linked to CDH1 mutations.[23]

Screening

Gastric cancer screening allows for secondary prevention by diagnosis of early gastric cancer, with survival rates exceeding 95%.[58] Asian countries with a high prevalence of gastric cancer have robust screening programs, where nearly 60% of all gastric cancers are diagnosed in early stages.[59] In the US, <25% of gastric cancer cases are diagnosed at an early stage.[60] The national gastric cancer screening program in South Korea, which started in 1999, has been covering almost all of its citizens. The program offers gastric cancer screening for persons aged 40 years and over on a biennial basis with upper gastrointestinal series or upper endoscopy.[61]

Similarly, in Japan, a gastric cancer screening program was initiated nationwide in 1983. In 2014, the Japanese guidelines recommended gastric cancer screening for individuals aged 50 years and over with upper gastrointestinal series and upper endoscopy every 2 years.[62] Anecdotally, these programs provide substantial value in reducing gastric cancer mortality, however, there is limited randomized control trial level data evaluating the benefit of these programs. A study using a synthetic control method estimated the effect of these screening programs on gastric cancer mortality.[63] It found that a nationwide gastric cancer screening program in South Korea was associated with a reduction in mortality related to gastric cancer of 41% in the 15th year of its inception. However, the impact of the screening program on gastric cancer mortality in Japan was uncertain.[63] It is important to note that in Japan, endoscopy screening was not recommended until 2014 and endoscopic screening has higher sensitivity compared with upper gastrointestinal series, so these results need to be interpreted with caution.

Standardized gastric cancer screening protocols in the US are lacking owing to low disease prevalence and concerns about cost effectiveness. However, evidence supports the implementation of a screening program in the US to target a higher risk population, including immigrants and their children that are born in the US, who retain their increased risk for gastric cancer despite relocation.[64-66]

For certain Asian groups in the US, a Markov model has shown that screening is cost effective.[67] This study found that a one time upper endoscopy with biopsies, followed by continued endoscopic surveillance if gastric intestinal metaplasia is

identified, is cost effective for Asian Americans aged 50 and over.[67] However, studies on the cost effectiveness of screening in Asia have yielded conflicting results.[68 69] Since cost effectiveness does not always translate to clinical effectiveness, more studies are needed before implementing such programs. At the same time, the health and economic burden of not screening for gastric cancer in the US is increasing because the at risk population is growing. Several European countries have already advocated for gastric cancer screening for groups at high risk.[70 71] These factors have led to efforts in the US to identify high risk individuals for gastric cancer screening. In 2020, a summit was convened at Stanford University to propose a framework for gastric cancer prevention in the US.[60] Based on discussions among experts, high risk groups in the US were defined as: individuals with a family history of gastric cancer; first generation immigrants from regions with a high incidence of gastric cancer; individuals belonging to racial or ethnic groups at increased risk for gastric cancer (African Americans, Alaska Natives, Native Americans, Asian Americans, and Hispanic Americans); and individuals with certain hereditary cancer syndromes.

Endoscopy

The use of endoscopy for screening could have some limitations but adverse events related to endoscopy are extremely rare in the US, and there are limited data about overdiagnosis.[60 72] Studies from Asia show that screening leads to the diagnosis of early stage cancers rather than the detection of indolent tumor.[60] Endoscopy remains the recommended method for screening because it allows for the direct examination of the gastric mucosa and biopsies.[73 74] Advanced imaging techniques, such as chromoendoscopy and narrow band imaging, further enhance accuracy. However, some challenges related to the use of endoscopy in the US include increased burden on endoscopy resources, patient acceptance, and cost.[68]

Alternative screening methods

Other screening methods for gastric cancer include upper gastrointestinal series, serum pepsinogen testing, and *H pylori* serology. *H pylori* serology has low sensitivity for gastric cancer screening and can often yield negative results in the presence of longstanding atrophic gastritis or gastric intestinal metaplasia, making it less useful.[68] The primary prevention of gastric cancer through *H pylori* eradication can reduce risk by up to 76%.[75-77]

Finally, surveillance of premalignant conditions for gastric cancer (including gastric intestinal metaplasia and atrophic gastritis) continues to be debated, as well as the incidental diagnosis of other diseases during screening. Gastric intestinal metaplasia is present in up to 15% of the population, with a slow progression rate to gastric cancer, accounting for only 10% of gastric cancer cases.[68 78-80]

The 2015 American Society for Gastrointestinal Endoscopy guidelines recommended screening in patients with gastric intestinal metaplasia who have certain ethnic backgrounds or family history of the disease, but the screening interval should be individualized.[81] The most recent American Gastroenterological Association guidelines, published in 2020, recommend considering surveillance for gastric intestinal metaplasia in patients with high risk of gastric cancer.[82] Patients with gastric intestinal metaplasia need to be risk stratified using the Sydney protocol for biopsies (minimum of five biopsies obtained from the antrum, incisura, and gastric body, with any suspicious areas biopsies separately).[83] After obtaining biopsies, gastric intestinal metaplasia needs to be further classified based on histology into complete versus incomplete, anatomical distribution of gastric intestinal metaplasia, and presence of *H pylori* infection.[84] In individuals with extensive gastric intestinal metaplasia (including the gastric body) and incomplete gastric intestinal metaplasia, endoscopic surveillance can be considered and recommended every three years.[85] This is based on the fact that patients with high risk features of gastric intestinal metaplasia are at higher risk of developing gastric cancer faster compared with patients with low risk gastric intestinal metaplasia.[86] Lastly, individuals with autoimmune gastritis should also be screened for type I gastric neuroendocrine tumors.[85 86]

Endoscopic management of early gastric cancer

Endoscopic resection for premalignant lesions and early gastric cancer is well established. Endoscopic resection techniques include endoscopic mucosal resection, endoscopic submucosal dissection, and endoscopic full thickness resection. The choice of proceeding with endoscopic resection versus surgery for early gastric cancer is dependent on the risk of lymph node metastasis. A large Japanese study including 5000 patients who underwent gastrectomy with lymph node dissection for early gastric cancer were evaluated for lymph node metastasis.[87] Factors associated with no risk of lymph node metastasis included: well differentiated intramucosal cancers <30 mm, regardless of ulceration; lesions without ulceration; and well differentiated cancer <30 mm without lymphovascular invasion and depth of submucosal invasion <500 µm. These findings set the foundation for endoscopic submucosal dissection for early gastric cancer. The Japanese Gastric Cancer Association initially recommended endoscopic submucosal dissection for early gastric cancers with differentiated-type histologic features, confined to the mucosa (T1a) and ≤20 mm.[88] However, given more data on identifying features that can predict lymph node metastasis, the indications for endoscopic submucosal dissection for early gastric cancer have now been expanded to include nonulcerated differentiated early gastric cancers of any size, ulcerated differentiated early gastric cancers <30 mm, or differentiated early gastric cancers <30 mm

with superficial submucosal invasion (SM1; depth of submucosal invasion <500 µm).[89]

Several studies have since evaluated the outcomes of endoscopic submucosal dissection for these indications. A meta-analysis found the incidence of lymph node metastasis in early gastric cancer according to the expanded criteria for endoscopic submucosal dissection by the Japanese Gastric Cancer Association to be 0.7%.[90] The American Gastroenterological Association has also published guidance in regard to endoscopic submucosal dissection in 2019.[91] According to the American Gastroenterological Association guidelines, the absolute indication for gastric endoscopic submucosal dissection was mucosal adenocarcinoma (and lesions with high grade dysplasia), intestinal type, G1 or G2 differentiation, size ≤2 cm, with no ulceration. This document also included expanded indications for gastric endoscopic submucosal dissection which included: adenocarcinoma, intestinal type, G1 or G2 differentiation, any size, without ulceration; adenocarcinoma, intestinal type, G1 or G2 differentiation, with submucosal invasion (<500 µm); adenocarcinoma, intestinal type, G1 or G2 differentiation, ≤3 cm, with ulceration; and adenocarcinoma, diffuse type, G3 or G4 differentiation, size ≤2 cm, without ulceration.

The challenge with endoscopic submucosal dissection in western countries lies in its reliance on histological assessment. Endoscopic ultrasonography often struggles to differentiate superficially invasive early gastric cancer from deeper submucosal invasion. Thus, decisions for endoscopic submucosal dissection rely on optical diagnosis via careful upper endoscopy with white light and narrow band imaging. After endoscopic submucosal dissection, perform a pathology review to assess differentiation, invasion, margins, and depth. Curative resection is determined based on these factors, followed by multidisciplinary or gastrointestinal tumor board review.[92 93] After an endoscopic submucosal dissection has been deemed curative, there is still a 5.9% risk of a metachronous cancer within three years.

Surgical treatment

Surgical indications

Surgically resectable gastric cancer includes both early stage and locally advanced diseases. In regard to locoregional disease, upfront surgery with adequate lymphadenectomy is recommended for cT1b tumors.[39] Upfront surgery is also appropriate for ≥cT2 tumors or node-positive disease; however these cases are increasingly being treated with a multimodal approach as this has been shown to improve outcomes.[94 95] Unresectability criteria include: infiltration of the disease into the root of the mesentery; para-aortic lymph nodes that are highly suspicious on imaging or confirmed by biopsy; invasion or encasement of major vascular structures (excluding the splenic vessels); distant metastasis; and peritoneal seeding, which includes positive peritoneal washings. Tumors classified as T4b might be considered resectable if en bloc resection can result in R0 margins. Cytoreductive surgery, with or without hyperthermic intraperitoneal chemotherapy, can be considered for patients with a limited burden of peritoneal metastasis (peritoneal cancer index <10), specifically in high volume, experienced centers.[39]

Extent of gastric resection

The National Comprehensive Cancer Network guidelines recommend that the type of resection can be total, subtotal, or proximal, provided that negative margins are achieved.[39] Total gastrectomy is usually reserved for proximal lesions, large mid-gastric tumors, linitis plastica, and as prophylaxis for hereditary cancer syndromes. By contrast, subtotal gastrectomies are usually performed for lesions located in the lower third of the stomach because they are associated with improved nutritional status and quality of life for patients. Previous studies have shown no noticeable survival benefit for total gastrectomy in cases of distal tumors.[96 97] Proximal gastrectomy involves the removal of the upper half to two-thirds of the stomach, along with the cardia. Although it is considered an acceptable alternative to total gastrectomy for treating early stage upper gastric cancer,[43] studies on its technical aspects and the optimal size of the gastric remnant remain limited. Furthermore, its oncological effectiveness continues to be debated.[98] Notably, this technique is not widely practiced in western countries owing to concerns about chronic bile reflux and quality of life studies.[98]

Treatment guidelines recommend a proximal margin of at least 2 cm for early gastric cancer (T1). For tumors classified as T2 or greater, the required margins vary based on the growth pattern: expansive tumors necessitate a minimum margin of 3 cm, infiltrative tumors require at least 5 cm.[43 99] A large multicenter cohort study reported an incidence of positive margins as high as 8.2%. Independent risk factors for positive margins included pT3-4 tumors, lymph node positive, and M1 disease.[100] Positive margins have been associated with a poorer five year overall survival (hazard ratio 2.06, 95% confidence interval 1.61 to 2.65; P<0.001).[101]

Lymphadenectomy and adjacent organ resection

Lymphadenectomy extension is one of the most debated topics in the treatment of gastric cancer. Lymphadenectomy should aim for at least a D2 level, encompassing the perigastric lymph nodes and those along the named vessels of the celiac axis, with a goal of retrieving at least 16 lymph nodes.[39]

Early randomized controlled trials in Europe indicated that D2 resections led to increased operative morbidity and mortality without a corresponding survival benefit.[102 103] However, critics argue that these trials were underpowered, and that they included pancreatosplenectomy as part of the D2 resections. The definition of D2 lymphadenectomy

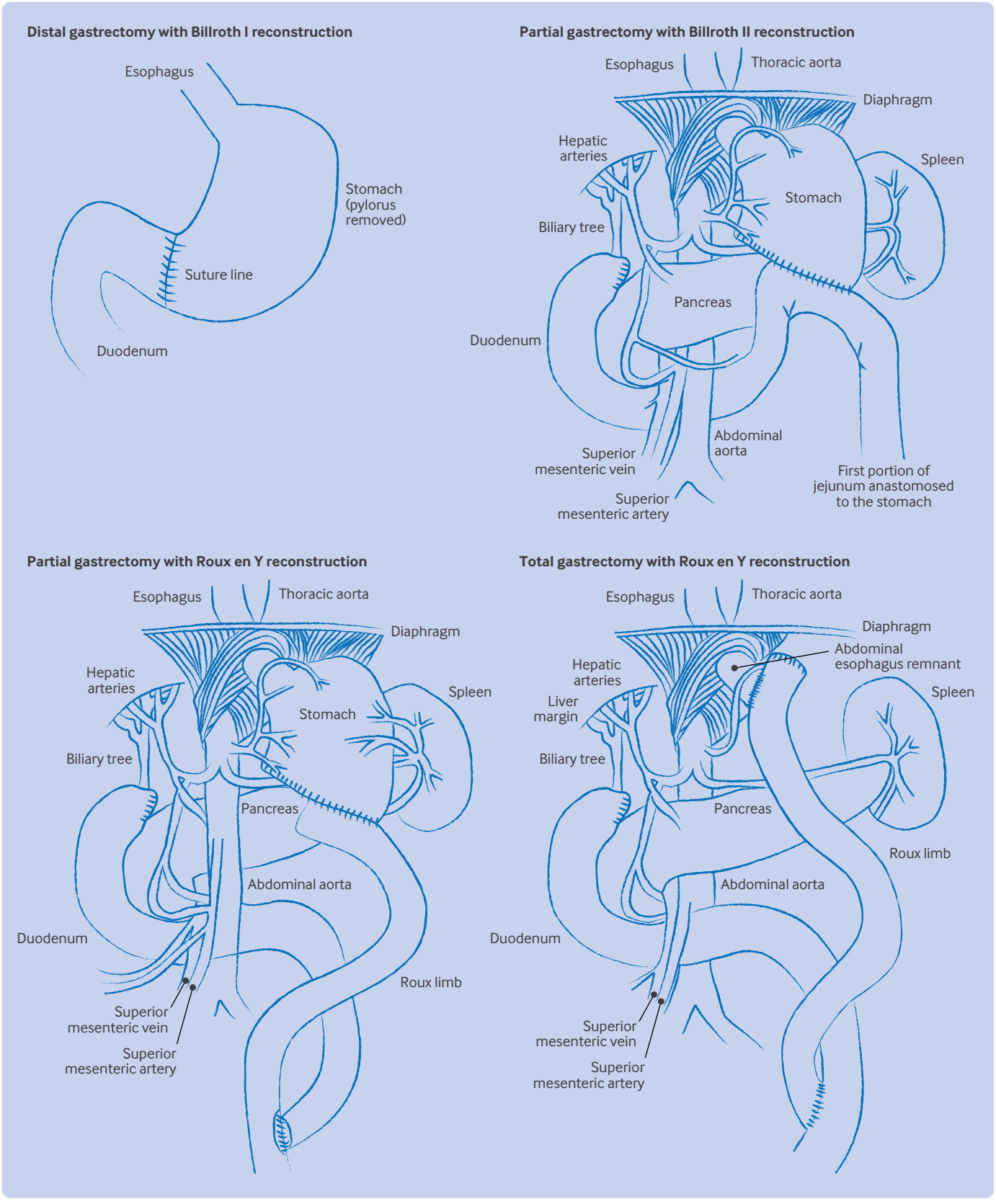

Fig 1 | Common reconstruction techniques after gastrectomy for gastric cancer

varies but typically includes the perigastric (D1) nodes, as well as those along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery.[39]

The definition of D3 lymphadenectomy is also variable, often referring to a D2 dissection with combined para-aortic nodal dissection.[104] The Japanese Gastric Cancer Association instead uses D2+ to define non-standard lymphadenectomies that include dissection of splenic hilar, superior mesenteric venous, posterior pancreatic head, or para-aortic lymph nodes based on specific scenarios.[99] In 2004, the Japan Clinical Oncology Group 9501 trial showed the safety of D2 dissection and periaortic nodal dissection, but long term follow-up failed to show improved overall survival or recurrence-free survival with periaortic nodal dissection.[105 106] The 15 year follow-up of the Dutch D1 versus D2 trial found no overall survival benefit (D1 21% *v* D2 29%; P=0.34), but reported higher mortality related to gastric cancer in the D1 group (48% *v* 37% in the D2 group; P=0.01).[107] When evaluating the patients who did not undergo pancreatosplenectomy, the overall survival was higher in the D2 group (35% *v* 22% in the D1 group; P=0.006). The authors concluded that D2 lymphadenectomy with a spleen preserving approach, when performed at a high volume center, might provide better locoregional control and survival specific to cancer compared with D1.[107]

Extended resections beyond lymphadenectomy, including bursectomy (resection of the peritoneal lining of the lesser sac), have been extensively studied, but substantial benefits have not been shown.[108] Regarding routine splenectomy, a meta-analysis of randomized controlled trials found no significant difference in overall survival between patients undergoing spleen preservation and those who had splenectomy. Moreover, splenectomy was associated with higher overall post-operative complications (risk ratio 1.66, 95% confidence interval 1.45 to 1.99; P<0.001).[109] Routine splenectomy is not recommended unless the spleen is directly involved or there is extensive hilar adenopathy present.[39]

Reconstruction of the digestive tract

The choice of reconstruction technique after gastrectomy depends on the extent of the procedure performed. In cases of partial gastrectomy, where some stomach remains, the available options include Billroth I (B1), Billroth II (B2), and Roux en Y (RY) techniques (fig 1). In a Billroth I reconstruction, an end-to-end anastomosis is created between the gastric remnant and the duodenum, thereby preserving duodenal continuity. The Billroth II technique maintains jejunal but not duodenal continuity; it involves a gastrojejunal anastomosis that can be isoperistaltic or antiperistaltic, as well as antecolic or retrocolic. A Braun enteroenterostomy can be added to the Billroth II to reduce the bile reflux into the gastric remnant. The Roux en Y technique can be used after both partial and total gastrectomies (fig 1). In partial gastrectomy, a distal loop of jejunum is anastomosed to the gastric remnant in an isoperistaltic configuration. In total gastrectomy, the jejunal loop is anastomosed to the esophagus. Other options for total gastrectomy reconstruction include the creation of a jejunal pouch, or a Hunt-Lawrence pouch combined with the Roux en Y technique. The Roux limb used for reconstruction after total gastrectomy is typically longer to minimize bile reflux and can be positioned antecolic or retrocolic. The jejunal pouch serves to mimic a reservoir and can vary in size and shape (J, omega, or S), being either proximal or distal.[110] For isolated proximal gastrectomy, a double tract reconstruction can be employed. This involves configuring two pathways for food passage: one where a distal jejunal limb is anastomosed to the esophagus in an end-to-side manner with a closed jejunal stump, and another that includes a side-to-side gastrojejunostomy with the remnant stomach.[111]

When comparing these techniques, a meta-analysis of randomized controlled trials assessed Billroth I, Billroth II, Billroth II with Braun, and Roux en Y techniques. It found no significant differences in overall complications, anastomotic leak rates, anastomotic strictures, or 30 day mortality.[112] However, in a 12 month follow-up, the Roux en Y technique significantly reduced the risk of remnant gastritis compared with Billroth I (risk ratio 0.56, 95% confidence interval 0.35 to 0.76) and Billroth II techniques (0.47, 0.22 to 0.97).[112] A meta-analysis comparing Roux en Y with Billroth I showed no noticeable differences in health related quality of life, and insufficient data to determine differences in anastomotic leak rates, although Roux en Y likely leads to a lower incidence of bile reflux.[113] A review of patients from the KLASS 07 study indicated that those who underwent a Roux en Y reconstruction had the lowest rates of bile reflux at one year when compared with those with Billroth II Braun and Billroth II techniques (3.0% *v* 67.8% *v* 84.4%; overall P<0.05), while exhibiting similar nutritional status and morbidity rates.[114]

Minimally invasive surgery

Minimally invasive surgery for gastric cancer treatment, encompassing both laparoscopic and robotic approaches, is regarded as oncologically equivalent to open surgery. The National Comprehensive Cancer Network guidelines recommend using minimally invasive surgery in high volume centers with considerable experience, advising against its use for T4b cancers or those with bulky lymph nodes.[39] Minimally invasive surgery offers several advantages, including faster recovery, reduced postoperative pain, and improved quality of life after surgery. It can also be safely performed after neoadjuvant therapy without substantially increasing the risk of complications.[115 116] However, challenges such as bleeding, the presence of adhesions, bulky tumors, unclear anatomy, and intraoperative identification of T4 stage tumors can contribute to the failure of minimally invasive

surgery.[117] A large retrospective cohort study of patients who required conversion to open surgery found that recurrence rates were comparable, with no noticeable differences in five year overall survival and disease-free survival.[117]

The LOGICA trial was one of the first studies in western countries to directly compare laparoscopic with open gastrectomy. The trial showed no significant differences in postoperative complications (44% *v* 42%; P=0.91), mortality in hospital (4% *v* 7%; P=0.40), median lymph node yield (29 *v* 29 nodes; P=0.49), and one year overall survival (76% *v* 78%; P=0.74).[115] Further evaluations within the trial compared distal versus total gastrectomy, showing similar conversion rates (2% *v* 6%; P=0.135), fewer complications for the distal group (34% *v* 57%; P=0.001), and faster postoperative recovery (length of stay 6 *v* 8 days; P<0.001), while maintaining similar nodal yield and one year overall survival.[118] Studies in Asian countries have also shown similar results for laparoscopic gastrectomy, including in cases of locally advanced gastric cancer, reaffirming oncologic equivalency.[119-124]

As minimally invasive surgery has progressed to include robotic surgery, numerous studies have reported its safety and efficacy. A large meta-analysis of 17 712 patients compared robotic with laparoscopic gastrectomy, finding that robotic procedures had longer operative times (267 *v* 220 min; P<0.001), lower estimated blood loss (98 *v* 115 mL; P<0.001), and faster time to resume oral intake (4.25 *v* 4.43 days; P=0.0001).[125] No substantial differences were observed in conversion rates, reoperation rates, or mortality. Length of hospital stay was similar (8.67 *v* 9.29 days; P<0.11), and overall complication rates were comparable, supporting the efficacy, safety, and feasibility of robotic gastrectomy. However, the costs of robotic procedures were significantly higher than those of laparoscopic surgeries ($12 224.54 (£9100; €10 500) *v* $8292.78; P<0.001).[125]

Surgical management of metastatic disease

Peritoneal carcinomatosis is highly prevalent in gastric cancer, frequently becoming the primary metastatic site at stage 4 diagnosis; around 50% of patients develop it during their disease course.[126-128] Peritoneal involvement results in poor survival outcomes, not only owing to tumor progression but also because of associated complications such as bowel obstruction.[129]

Peritoneal washings detect intraperitoneal free cancer cells, with positivity found in 10.9% of patients with early stage gastric cancer.[44 47] Positive peritoneal washings, defined as pM1 disease, correlates with lower overall survival (hazard ratio 3.46, 95% confidence interval 2.77 to 4.31; P<0.001), and an increased risk of peritoneal recurrence.[130-132] Positive cytology is considered modifiable, and conversion to negative post-neoadjuvant therapy is associated with improved overall survival (0.42, 0.31 to 0.57; P<0.001).[130 133]

Surgical treatment in cases of limited peritoneal carcinomatosis or positive peritoneal washings (both considered pM1 disease) has recently gained momentum. The primary aim of cytoreductive surgery is to resect all visible disease, often in combination with intraperitoneal chemotherapy (commonly hyperthermic intraperitoneal chemotherapy) to target micrometastasis and free cancer cells. According to National Comprehensive Cancer Network guidelines, cytoreductive surgery could be considered for selected patients with a peritoneal cancer index ≤10, after at least three months of systemic therapy and restaging demonstrating stable or improving disease. This decision should be made within the context of a multidisciplinary team.[39]

The French CYTO-CHIP study, one of the largest retrospective studies, reported improved survival with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy compared with cytoreductive surgery alone (16.7 *v* 11.3 months, P=0.018) and identified hyperthermic intraperitoneal chemotherapy as an independent predictor of improved survival (hazard ratio 0.52, 95% confidence interval 0.38 to 0.71; P<0.001).[134] Additionally, a recent meta-analysis of 1700 patients found that hyperthermic intraperitoneal chemotherapy is associated with improved overall survival at three years (odds ratio 1.89, 95% confidence interval 1.17 to 3.05) and five years (1.87, 1.29 to 2.71), along with reduced overall recurrence (0.49, 0.31 to 0.80), and peritoneal recurrence (0.22, 0.11 to 0.47).[135] Although large randomized controlled trials are lacking, a small phase 2 trial validated the promising findings of earlier studies, reporting an initial one year overall survival of 90%.[136] A recent updated analysis revealed a five year overall survival of 18%.[137]

In managing oligometastatic disease in gastric cancer, such as isolated liver metastasis, National Comprehensive Cancer Network guidelines do not recommend surgery outside of clinical trials because these cases are considered unresectable.[39] Although Japanese guidelines weakly recommend liver resection for highly selected patients with limited metastatic burden and absence of other non-curable factors, no prospective randomized trials support this approach.[99]

Palliative gastrectomy is recommended only for cases involving obstruction or uncontrollable bleeding, with endoluminal stenting preferred for obstruction when feasible.[39] Gastric resection in the context of uncurable or metastatic disease is generally considered futile. The 2016 REGATTA trial, which compared gastrectomy with D1 lymphadenectomy followed by chemotherapy versus chemotherapy alone for patients with a single non-curable factor was closed prematurely. Its interim analysis revealed a two year overall survival of 31.7% for the chemotherapy alone group versus 25.1% in the surgery group, with a higher incidence of severe (grades 3 and 4) adverse events in the surgical group.[138] A recent meta-analysis of over 50 000

Table 1 | Summary of key completed studies (phase; line of therapy; tumor target; population; location) of medical treatment in gastric or gastroesophageal junction adenocarcinoma grouped by setting

Arms	Outcome	Hazard ratio (95% CI)	Objective response rate (%)
Adjuvant			
SWOG/INT 0116 (III; Adjuvant; NA; ≥T3 and/or N+ gastric/GEJ; US)			
Surgery alone *v* postoperative chemoradiation (5-FU/LV)	5y OS 43% *v* 28%	1.32 (1.10 to 1.60)	NA
CLASSIC (III; Adjuvant; NA; II-IIIB gastric cancer; South Korea, China, Taiwan)			
CAPOX x 6mo *v* surgery alone	3y DFS 74% *v* 59%; 5y OS 78% *v* 69%	0.56 (0.44 to 0.72); 0.66 (0.51 to 0.85)	NA
ARTIST (III; Adjuvant; NA; II-III gastric cancer; South Korea)			
XP/radiation/XP *v* XP alone	3y DFS 78% *v* 74%	NA	NA
ARTIST 2 (III; Adjuvant; NA; II-III gastric cancer; South Korea)			
Oral S-1 x 1y *v* SOX x 6mo *v* SOX+chemoradiation	3y DFS 65% *v* 74% *v* 73%	0.97 (0.66 to 1.42) between SOX *v* SOX+chemoradiation	NA
CRITICS (III; Adjuvant; NA; IB-Iva gastric/GEJ; Netherlands, Sweden, Denmark)[145]			
Preop EOX/ECX followed by D2 surgery and postoperative EOX/ECX or chemoradiation with XP	5y OS 58% *v* 46%	1.62 (1.24 to 2.12)	NA
ATTRACTION-5 (III; Adjuvant; NA; Pathologic stage III gastric/GEJ; Japan, South Korea, Taiwan, China)			
Chemotherapy+nivolumab *v* chemotherapy+placebo	3y RFS 68% *v* 65%	0.90 (0.69 to 1.18)	NA
Perioperative			
MAGIC (III; Perioperative; NA; ≥ Stage II gastric/ GEJ/distal esophagus; UK)			
Perioperative ECF *v* surgery alone	5 y OS 36% *v* 23%	0.75 (0.60 to 0.93)	NA
FLOT4-AIO (II/III; Perioperative; NA; ≥cT2 or cN+ gastric/GEJ; Germany)			
Perioperative FLOT *v* perioperative ECF	mOS 50 *v* 35 mo; pCR 16% *v* 8%	0.77 (0.63 to 0.94); NA	NA
KEYNOTE 585 (III; Perioperative; PD-L1; ≥cT3 or cN+ gastric/GEJ; Global)			
Main cohort: Chemotherapy+pembrolizumab *v* chemotherapy+placebo	EFS 44.4 *v* 25.5 mo; mOS 71.8 *v* 55.7 mo; pCR 14.2% *v* 2.8%	0.81 (0.67 to 0.99); 0.86 (0.71 to 1.06); NA	NA
FLOT cohort: FLOT+pembrolizumab *v* FLOT+placebo	mEFS NR *v* 30.9 mo; OS 72% *v* 73%; pCR 17% *v* 7%	0.79 (0.52 to 1.22); NA; NA	NA
MATTERHORN (III; Perioperative; PD-L1; II- IVA; Global)			
Perioperative FLOT+durvalumab *v* FLOT+placebo	mEFS 32.8 mo *v* NR; pCR 19.2% *v* 7.2%	0.71 (0.58 to 0.86) P<0.001; NA	
TOPGEAR (III; Perioperative; NA; T3/T4, Nany gastric/GEJ; Australasia, Canada, Europe)[146]			
Perioperative chemotherapy+preoperative chemoradiation *v* perioperative chemotherapy alone	mOS 46 *v* 49 mo	1.05 (0.83 to 1.31)	NA
ESOPEC (III; Perioperative; NA; cT1cN+ or cT2-4a cNany EAC; Germany)			
Perioperative FLOT *v* CROSS	mOS 66 *v* 37 mo; pCR 19.3% *v* 13.5%	0.70 (0.53 to 0.92); NA	NA
NEONIPIGA (II, single arm; Perioperative; Microsatellite high/deficient mismatch repair; cT2-4, Nany gastric/GEJ; France)			
Neoadjuvant nivolumab/ ipilimumab, surgery, adjuvant nivolumab	pCR 58.6%	NA	NA
Neoadjuvant			
INFINITY (II; Neoadjuvant; Microsatellite high/deficient mismatch repair; cT2-4, Nany gastric/GEJ; Italy)			
Cohort 1: durvalumab+tremelimumab followed by surgery	pCR 60%	NA	NA
Cohort 2: durvalumab+tremelimumab followed by surgery or observation based on restaging	NA	NA	NA
Metastatic			
CheckMate 649 (III; 1L; PD-L1; Advanced/metastatic gastric/GEJ; Global)			
Chemotherapy+nivolumab *v* chemotherapy	PD-L1 CPS≥5: mOS 14.4 *v* 11.1 mo; mPFS 8.3 *v* 6.1 mo	0.70 (0.61 to 0.81); 0.71 (0.61 to 0.82)	60 *v* 45
	ITT: mOS 13.7 *v* 11.6 mo; mPFS 7.7 *v* 6.9 mo	0.79 (0.71 to 0.88); 0.80 (0.71 to 0.89)	58 *v* 46
KEYNOTE 859 (III; 1L; PD-L1; Advanced/metastatic gastric/GEJ; Global)			
Chemotherapy+pembrolizumab *v* chemotherapy	PD-L1 CPS≥10: mOS 15.8 *v* 11.8 mo; mPFS 7.8 *v* 5.6 mo	0.64 (0.53 to 0.78); 0.63 (0.51 to 0.77)	60.0 *v* 43.2
	PD-L1 CPS≥1: mOS 13.0 *v* 11.4 mo; mPFS 6.9 mo *v* 5.6 mo	0.75 (0.66 to 0.85); 0.73 (0.64 to 0.83)	51.8 *v* 42.6
	ITT: mOS 12.9 *v* 11.5 mo; mPFS 6.9 *v* 5.6 mo	0.79 (0.71to 0.88); 0.76 (0.68 to 0.85)	51.0 *v* 42.0
KEYNOTE 811 (III; 1L; HER2; Advanced/metastatic; Global)			
Chemotherapy+trastuzumab+ pembrolizumab+placebo *v* Chemotherapy+trastuzumab+placebo	PD-L1 CPS≥1: mOS 20.1 *v* 15.7 mo; mPFS 10.9 *v* 7.3 mo	0.79 (0.66 to 0.95); 0.72 (0.60 to 0.87)	72.6 *v* 60.1
ToGA (III; 1L; HER2; Advanced/metastatic; Global)			
Trastuzumab+ chemotherapy *v* chemotherapy	mOS 13.8 *v* 11.1 mo; mPFS 6.7 *v* 5.5 mo	0.74 (0.60 to 0.91); 0.71 (0.59 to 0.85)	
DESTINY Gastric01 (II, randomized; 3L+; HER2; Advanced/metastatic; South Korea, Japan)			
Trastuzumab deruxtecan 6.4 mg q3w *v* irinotecan or paclitaxel chemotherapy	mOS 12.5 *v* 8.9 mo; PFS 5.6 *v* 3.5 mo	0.60 (0.42 to 0.86); 0.47 (0.31 to 0.71)	42.0 *v* 12.5
DESTINY Gastric02 (II, single arm; 2L+; HER2; Advanced/metastatic; US, Europe)			
Trastuzumab deruxtecan 6.4 mg q3w	mOS 12.1 mo; 12 mo OS 50.6%; mPFS 5.6 mo	NA	42
NCT03929666 (II, single arm; 1L; HER2; Advanced/metastatic; North America)			
Zanidatamab+chemotherapy	mPFS 15.2 mo; 30 mo OS 59%	NA	84
SPOTLIGHT (III; 1L; Claudin 18.2; Advanced/metastatic; Global (31% Asian))			
Zolbetuximab+FOLFOX *v* FOLFOX	mOS 18.2 *v* 15.6 mo; mPFS 11.0 vs 8.9 mo	0.78 (0.64 to 0.95); 0.73 (0.59 to 0.91)	48.1 *v* 47.5

(Continued)

Table 1 | (Continued)

Arms	Outcome	Hazard ratio (95% CI)	Objective response rate (%)
GLOW (III; 1L; Claudin 18.2; Advanced/metastatic; Global (62% Asian))			
Zolbetuximab+CAPOX *v* CAPOX	mOS 14.4 *v* 12.2 mo; mPFS 8.2 *v* 6.8 mo	0.77 (0.62 to 0.97); 0.69 (0.54 to 0.87)	42.5 *v* 40.3
RAINBOW (III; 2L; VEGFR2; Advanced/metastatic; Global)			
Ramucirumab/paclitaxel *v* paclitaxel	mOS 9.6 *v* 7.4 mo; mPFS 4.4 *v* 2.9 mo	0·81 (0·68 to 0·96); 0.64 (0.54 to 0.75)	28 *v* 16
TAGS (III; 3L+; NA; Advanced/metastatic; Global)			
Trifluridine/tipiracil *v* placebo+best supportive care	mOS 5.7 *v* 3.6 mo	0.69 (0.56 to 0.85)	4 *v* 2
DisTinGuish (II, Part A, single arm; 1L; Dickkopf-1; Advanced/metastatic; Global)			
DKN-01+tislelizumab+chemotherapy	mOS 19.5 mo; 12 mo PFS 33%	NA	73
FIGHT (II, randomized; 1L; FGFR2b; Advanced/metastatic; Global)			
Bemarituzumab+mFOLFOX *v* placebo+mFOLFOX	ITT: mOS 19.2 *v* 13.5 mo; mPFS 9.5 *v* 7.4 mo	0.77 (0.52 to 1.14); 0.72 (0.49 to 1.08)	48.1 *v* 33.3
	≥ FGFR2b in 10% of tumor cells: mOS 24.7 *v* 11.1 mo; mPFS 14.0 *v* 7.3 mo	0.52 (0.31 to 0.85); 0.43 (0.26 to 0.73)	56.5 *v* 36.5
FORTITUDE 101 (III; 1L; FGFR2b; Advanced/metastatic; Global)			
Bemarituzumab+nivolumab+chemotherapy *v* nivolumab+chemotherapy	≥ FGFR2b in 10% of tumor cells: mOS 14.5 *v* 13.2 mo	0.82 (0.62 to 1.08)	NA

1L=first line; 5-FU/LV=fluorouracil and folinic acid; CAPOX=capecitabine and oxaliplatin; CPS=combined positive score; CROSS=(Chemoradiotherapy for Resectable Oesophageal Cancer with Surgery); DFS=disease-free survival; EAC=esophageal adenocarcinoma; ECF=epirubicin, cisplatin, fluorouracil; ECX=epirubicin, cisplatin, xeloda; EFS=event-free survival; EOX=epirubicin, oxaliplatin, xeloda; FGFR2b=fibroblast growth factor receptor 2b; FLOT=fluorouracil, oxaliplatin, docetaxel; FOLFOX=fluorouracil, leucovorin, oxaliplatin; GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; ITT=intention to treat; mEFS=median event-free survival; mOS= median overall survival; mPFS=median progression free survival; NA=not applicable; NR=not reached; OS=overall survival; PD-L1=programmed death ligand 1; pCR=pathologic complete response; q3w=every 3 weeks; RFS=recurrence-free survival; SOX=S-1 and oxaliplatin; TIGIT=T cell immunoreceptor with Ig and ITIM domains; VEGFR2=vascular endothelial growth factor receptor 2; XP=capecitabine and cisplatin.

patients highlighted significant morbidity associated with palliative gastrectomy (odds ratio 2.14, 95% confidence interval 1.34 to 3.46; P<0.001) compared with non-resectional approaches, such as bypass or feeding jejunostomy, or no intervention.[139]

Systemic therapy in resectable gastric adenocarcinoma

The use of systemic therapy combined with surgical resection has become integral in optimizing survival from resectable gastric cancer. SWOG/INT0116 was a seminal phase 3 study conducted in the US that demonstrated a median overall survival benefit of adjuvant chemoradiation with 5-FU and leucovorin after surgery compared with surgery alone (36 *v* 27 months).[94] However, a criticism of the study was suboptimal surgical resection and problems with gastrointestinal side effects.[140] Although trials of adjuvant chemotherapy have shown benefit primarily in Asian populations,[141 142] those results were not replicated in studies with non-Asian populations.[143]

Perioperative therapy underwent extensive trial evaluation with the goal of eliminating micrometastatic disease, improving symptoms related to tumors, assessing tumor biology, and downstaging tumors. The UK MAGIC trial of 503 patients with predominantly gastric cancer (74%) randomized participants to surgery alone versus surgery with perioperative epirubicin, cisplatin, and 5-FU (ECF).[95] Both progression-free survival and five year survival were noticeably improved in the perioperative group compared with surgery alone (36% *v* 23%). Subsequently, the phase II/III FLOT4-AIO trial showed that perioperative docetaxel, oxaliplatin, infusional 5-FU, and leucovorin (FLOT) improved survival over ECF in 716 patients with resectable gastric and gastroesophageal junction adenocarcinoma.[144] Noticeable benefit in pathologic complete response rate (16% *v* 8%) and median overall survival (50 *v* 35 months) were seen. However, grade 3 and 4 toxicities such as diarrhea, neutropenia, infection, and neuropathy were an issue. In addition, only 50% of patients were able to complete adjuvant therapy owing to serious side effects.

Perioperative chemoimmunotherapy

In an effort to improve perioperative therapy with agents beyond chemotherapy, a series of studies have been completed (table 1), or are ongoing (table 2), to evaluate the role of perioperative chemotherapy with immune checkpoint inhibition.

The ATTRACTION-5 study, which evaluated adjuvant nivolumab, a PD-1 inhibitor, with chemotherapy compared with chemotherapy plus placebo, did not show a benefit for recurrence free survival. Similarly, the global randomized phase 3 KEYNOTE 585 trial, which compared perioperative pembrolizumab plus cisplatin-based chemotherapy versus perioperative placebo plus chemotherapy did not show a statistically significant event-free survival benefit despite a numerical improvement and improvement in pathologic complete response rate of 10% to 11% in both the doublet and triplet chemotherapy backbones.[147 148] However, the global phase 3 MATTERHORN trial, which fully incorporated a modern chemotherapy backbone, showed that perioperative FLOT plus durvalumab demonstrated an event-free survival and an overall survival benefit over FLOT plus placebo.[149-152]

Refining systemic therapy for resectable microsatellite instability high or deficient mismatch repair gastric adenocarcinoma

Up to 10% of gastric cancer or gastroesophageal junction cancer harbors defects in the mismatch repair system which is responsible for the detection

Table 2 | Summary of key ongoing studies (phase; line of therapy; tumor target, population, drug class) of medical treatment in gastric or gastroesophageal junction adenocarcinoma grouped by setting

Arms	Primary endpoint(s)	Secondary endpoint(s)
Perioperative		
DANTE (II/III; Perioperative; PD-L1; ≥cT2 or cN+ gastric/GEJ; Monoclonal antibody)		
Perioperative FLOT+atezolizumab *v* perioperative FLOT	EFS	pCR, mOS in ITT and subgroups (CPS ≥5, CPS ≥10, MSI), R0 resection rate, safety/tolerability
Metastatic		
DESTINY GASTRIC04 (III; 2L; HER2; Advanced/metastatic; Antibody-drug conjugate)		
Trastuzumab deruxtecan *v* ramucirumab/paclitaxel	OS	PFS, ORR, DoR, DCR, safety
HERIZON-GEA-01 (III; 1L; HER2, (IHC3+or IHC2+/ISH+); Advanced/metastatic; Bispecific antibodies)		
Zanidatamab+tislelizumab+chemotherapy *v* zanidatamab+chemotherapy *v* trastuzumab+chemotherapy	PFS, OS	ORR, DoR, safety, HRQOL
DisTinGuish Part C (II, randomized; 1L; Dickkopf-1; Advanced/metastatic; Monoclonal antibody)		
DKN-01+tislelizumab+chemotherapy *v* tislelizumab+chemotherapy	PFS in Dickkopf-1 high and all patients	OS, ORR
FORTITUDE 102 (III; 1L; FGFR2b, ≥10% of tumor cells; Advanced/metastatic; Monoclonal antibody)		
Bemarituzumab+nivolumab+chemotherapy *v* nivolumab+chemotherapy	OS	PFS, ORR, safety
STAR-221 (III; 1L; TIGIT; Advanced/metastatic; Monoclonal antibody)		
Arm A: domvanalimab+zimberelimad+FOLFOX or domvanalimab+zimberelimad+CAPOX *v* Arm B: nivolumab+FOLFOX or nivolumab+CAPOX	OS in IIT and in PD-L1 TAP ≥5%	PFS, ORR, DoR, safety
EDGE-gastric (II; 1L; TIGIT; Advanced/metastatic; Monoclonal antibody)		
Arm A1: domvanalimab+zimberelimab+chemotherapy	ORR, safety	ORR by PD-L1, PFS

1L=first line; 2L=second line; CAPOX=capecitabine and oxaliplatin; CPS=combined positive score; DCR=disease control rate; DoR=duration of response; EFS=event free survival; FGFR2b=fibroblast growth factor receptor 2b; FLOT=fluorouracil, oxaliplatin, docetaxel; FOLFOX=fluorouracil, leuvocorin, oxaliplatin; GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; HRQOL=heath related quality of life; ITT=intention to treat; mOS=median overall survival; MSI=microsatellite instability; ORR=objective response rate; OS=overall survival; pCR=pathologic complete response; PD-L1=programmed death ligand 1; PFS=progression-free survival; TAP=tumor area positivity; TIGIT=T cell immunoreceptor with Ig and ITIM domains.

and correction of base mismatches, insertions, and deletions that occur during DNA replication.[153-155] Post replicative DNA mismatch repair involves the protein complexes MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and PMS1 homolog 2 (PMS2).[156] Defects in mismatch repair are associated with genome-wide instability and the progressive accumulation of mutations, especially regions of simple repetitive DNA sequences known as microsatellites, resulting in microsatellite instability, which is associated with enhanced recognition by the immune system. In reanalyses of microsatellite high or deficient mismatch repair cohorts of MAGIC, CLASSIC, ARTIST and ITACA-S trials, deficient mismatch repair resectable gastric or gastroesophageal junction adenocarcinoma did not benefit from chemotherapy alongside surgery.[154] Cytotoxic chemotherapy might impair immunosurveillance in deficient mismatch repair or microsatellite high tumors, resulting in poorer outcomes when chemotherapy is incorporated into curative therapy.[157] As a result, perioperative immune checkpoint inhibition is being investigated for resectable microsatellite high or deficient mismatch repair.[158 159] NEONIPIGA is a phase 2 trial of 32 patients with microsatellite instability high or deficient mismatch repair resectable gastric or gastroesophageal junction adenocarcinoma, who received neoadjuvant nivolumab plus ipilimumab followed by surgery and adjuvant nivolumab for nine months.[158] Interim analysis showed a pathologic complete response rate of 58.6%. With a median follow-up of 14.9 months, no patient had relapsed. Similarly, the phase 2 multicohort, single arm INFINITY trial of 18 patients evaluated the role of single dose of durvalumab (a PD-L1 inhibitor) and tremelimumab (a CTLA-4 inhibitor) in patients with microsatellite high resectable gastric or gastroesophageal junction adenocarcinoma.[159] Of the 15 evaluable patients with median follow-up 13.4 months, 60% had pathologic complete response. Although these findings were seen in a relatively small cohort of patients, owing to its impressive results, perioperative nivolumab and ipilimumab, pembrolizumab, and neoadjuvant durvalumab plus tremelimumab are now recommended in National Comprehensive Cancer Network guidelines for microsatellite high or deficient mismatch repair gastric cancer.[39]

Limited role of radiation for resectable gastric cancers

Although SWOG/INT 0116 showed a median overall survival benefit with adjuvant chemoradiation, subsequent studies did not show a benefit with adding radiation to modern chemotherapy regimens. The ARTIST trial conducted in South Korea compared two cycles of capecitabine and cisplatin followed by radiotherapy and two additional cycles of capecitabine and cisplatin versus capecitabine and cisplatin alone. The radiotherapy group did not prolong disease-free survival, however, a subset analysis showed that a superior disease-free survival was seen in patients with lymph node positive disease.[160] Despite this promising signal, the subsequent ARTIST 2 trial, which compared concurrent chemoradiotherapy with two chemotherapy arms in resected node positive gastric cancer, showed no overall survival or progression-free survival benefit with radiation.[161] Similarly, the CRITICS and TOPGEAR trials did not show an overall survival benefit with the addition of radiation

to adjuvant or neoadjuvant therapies, respectively; in fact, CRITICS showed that the five year overall survival of adjuvant chemotherapy was superior to chemoradiation (58% *v* 46%, hazard ratio 1.62; P=0.0004).[145 146]

The importance of optimal systemic therapy for resectable gastric cancer is magnified by these negative trials. The recent ESOPEC trial also showed superiority of perioperative triplet chemotherapy with FLOT compared with neoadjuvant chemoradiation in resectable gastroesophageal junction adenocarcinoma (median overall survival of 66 *v* 37 months).[162]

Systemic therapy for advanced gastric adenocarcinoma

Progress to treat advanced, unresectable gastric and gastroesophageal junction adenocarcinoma has been driven by new tumor specific targets such as HER2, PD-L1, and Claudin 18.2. There are rarer subtypes such as microsatellite high or deficient mismatch repair (5% to 10%),[163-165] Epstein Barr virus associated (5%),[166] epidermal growth factor receptor amplified (6%),[167] neurotrophic tyrosine receptor kinase fusion (<1%),[168 169] B-Raf proto-oncogene (<1%),[170] and receptor tyrosine kinase fusions (<1%) that can be effectively targeted.[171]

HER2

HER2 or ERBB2 is overexpressed or amplified in 20% to 30% of gastric or gastroesophageal junction adenocarcinoma.[172] The phase 3 ToGA trial demonstrated a substantial median overall survival benefit with trastuzumab, a HER2 directed monoclonal antibody, combined with fluoropyrimidine/cisplatin doublet compared with chemotherapy alone in HER2 overexpressed gastric or gastroesophageal junction adenocarcinoma.[173] However, subsequent trials failed to show a benefit from other HER2 directed agents such as pertuzumab or trastuzumab,[174] TDM-1,[175] and lapatinib.[176] Success would come with the phase 3 randomized KEYNOTE 811 trial of chemotherapy, trastuzumab, and pembrolizumab showing both a median progression-free survival (10.9 *v* 7.3 months) and median overall survival benefit (20.1 *v* 15.7 months) compared with chemotherapy, trastuzumab, and placebo in first line PD-L1+gastric or gastroesophageal junction cancer.[177] Anti-HER2 therapy after trastuzumab in gastric cancer has historically shown disappointing results in part due to loss of HER2 overexpression after trastuzumab (35%).[178] DESTINY Gastric01 was a randomized, phase 2 trial conducted in East Asia evaluating trastuzumab deruxtecan, an HER2 directed antibody drug conjugate with a topoisomerase payload, compared with chemotherapy in HER2-positive (IHC: 3+or IHC 2+/ISH^{+}) 3L+gastric cancer. Trastuzumab deruxtecan significantly improved the objective response rate compared with physician choice of chemotherapy (42.0% *v* 12.5% and median overall survival (12.5 *v* 8.9 months).[179] DESTINY Gastric02, a single arm, phase 2 study conducted in the US and Europe evaluated trastuzumab deruxtecan after first line trastuzumab-based therapy, and showed an objective response rate of 42% and median overall survival of 12.1 months.[180]

PD-L1 and immune checkpoint inhibition

With the success of immune checkpoint inhibitors to CTLA-4, PD-1, and PD-L1 in other cancers, there was intense interest in understanding their effects in gastric adenocarcinoma. In monotherapy trials and later line settings of PD-1 inhibition, there were modest objective response rates (10% to 15%) without clear survival benefit.[181-185] When evaluated in the first line setting combined with fluoropyrimidine/platinum doublet, benefit was more clearly seen. Three phase 3 trials, CheckMate 649, KEYNOTE 859, and RATIONALE 305 confirmed that doublet chemotherapy with PD-1 inhibition provide meaningful clinical benefit in the first line setting.[186-188] Four year follow-up of CheckMate 649 continued to show a median overall survival benefit in the overall population (13.7 *v* 11.6 months) with increasing benefit with higher PD-L1 combined positive score of 13.8 versus 11.4 months in PD-L1 combined positive score ≥1 and 14.4 versus 11.1 months in PD-L1 combined positive score ≥5. With its initial approval, the US Food and Drug Administration did not restrict use of a PD-1 inhibitor based on PD-L1 combined positive score for either CheckMate 649 or KEYNOTE 859.[189 190] FDA's Oncologic Drugs Advisory Committee convened in September 2024 to reassess combined positive score cutoffs for the use of PD-1 inhibitors nivolumab, pembrolizumab, and tislelizumab in combination with first line chemotherapy. By a vote of 10 to 2 with one abstention, the Oncologic Drugs Advisory Committee, after reviewing PD-L1 combined positive score subgroup analyses, recommended against the use of PD-1 inhibitors in the first line treatment of patients with advanced HER2-negative, microsatellite stable gastric adenocarcinoma with a PD-L1 combined positive score <1.[191]

Claudin 18.2

Claudin 18.2 is a tight junction protein and a biomarker unique to gastric adenocarcinoma and is overexpressed in 20% to 30% of cases.[192] It is normally expressed on gastric mucosa cells but in states of malignancy, it becomes overexpressed and exposed on the cell surface, making it an ideal target for drug development.[192] Zolbetuximab is a first in class monoclonal antibody that binds to CLDN18.2.[193] Initial studies from earlier phase 2 MONO and FAST studies showed promising efficacy leading to two global phase 3 trials,[194 195] SPOTLIGHT and GLOW, which compared zolbetuximab plus fluoropyrimidine/platinum combination compared with chemotherapy alone in high CLDN18.2 expressing gastric adenocarcinoma (IHC 2/3+, ≥75% of tumor cells).[196 197] SPOTLIGHT evaluated zolbetuximab with 5-FU, leuvocorin, and oxaliplatin

in a primarily non-Asian population. GLOW evaluated zolbetuximab with capecitabine and oxaliplatin in a primarily Asian population. SPOTLIGHT and GLOW demonstrated a median overall survival benefit of the addition of zolbetuximab to chemotherapy over chemotherapy alone (18.2 *v* 15.6 months and 14.4 *v* 12.2 months, respectively), leading to regulatory approvals.

Guidelines

The rapidly evolving landscape of gastroesophageal cancer treatment requires clinicians to lean heavily on evidence based guidelines for decision making. In the US, the National Comprehensive Cancer Network guidelines routinely update recommendations for the workup and treatment of early, locally advanced and metastatic disease, primarily through detailed algorithms.[39] By contrast, the European Society of Medical Oncology Clinical Practice Guidelines are more narrative based in reviewing the current literature and provide concise recommendations for the diagnosis, workup and treatment of gastroesophageal cancer.[43] In East Asia, given the high incidence of gastric cancer, multiple well established guidelines are available such as the Japanese Gastric Cancer Association and Korean Gastric Cancer Association guidelines, which remain authoritative on surgical strategy, including the extent of lymphadenectomy, resection margins, and indications for endoscopic or function-preserving procedures.[55 198]

Emerging treatments

Several biomarker directed therapies are being investigated in clinical trials (tables 1 and 2).

FGFR2b

The fibroblast growth factor and its receptor (FGF/FGFR) pathway is integral to cancer growth.[199] The IIIb splice isoform of FGFR2 (FGFR2b) was observed to be overexpressed in approximately 30% of HER2 negative gastric cancer.[200] The phase 2 FIGHT trial of 155 patients evaluated the addition of bemarituzumab (an FGFR2b directed IgG monoclonal antibody) to first line chemotherapy versus chemotherapy alone in FGFR2b overexpressed gastric or gastroesophageal junction adenocarcinoma. Bemarituzumab combined with mFOLFOX6 (FIGHT trial) showed meaningful clinical benefit compared with chemotherapy alone with improvements in median progression-free survival (9.5 *v* 7.4 months) and median overall survival (19.2 *v* 13.5 months).[200] Highest improvement was seen in tumors with FGFR2b hyperexpression (>10% of tumor cells). Despite the promising results from the earlier phase 2 trial, the phase 3 FORTITUDE 101 trial, which compared bemarituzumab plus chemotherapy with chemotherapy alone, did not show a statistically significant median overall survival benefit with longer follow-up (table 1).[201] Results of the ongoing phase 3 FORTITUDE 102 trial, which compare bemarituzumab, nivolumab, plus chemotherapy with nivolumab plus chemotherapy are awaited (table 2).

Dickkopf-1

Dickkopf-1 modulates Wnt signaling and promotes tumor angiogenesis, proliferation, and metastasis.[202] It also has immunomodulatory effects such as down regulating natural killer cell function and enhancing myeloid-derived suppressor cell activity. Part A of the phase 2 DisTinGuish trial evaluated DKN-01 (a monoclonal antibody that neutralizes Dickkopf-1) in combination with tislelizumab and doublet chemotherapy for 1L gastric adenocarcinoma. The objective response rate was 73% with a disease control rate of 95%. In Dickkopf-1 high tumors, the objective response rate was 90% and in Dickkopf-1 low tumors, it was 67% (median overall survival of 19.5 months).[203] DisTinGuish Part C, which randomized 170 patients to chemotherapy plus tislelizumab with or without DKN-01, has completed enrollment and is awaiting read out (table 2).

T cell immunoreceptor with Ig and ITIM domains (TIGIT)

TIGIT is an immune checkpoint on T and NK cells that is overexpressed in multiple tumor types, including gastric adenocarcinoma. Combined PD-1 and TIGIT blockade has shown to increase the expansion of tumor antigen specific CD8+T cells, which supports its combined use.[204] Initial data from the ongoing EDGE-gastric trial showed that doublet chemotherapy, with anti-TIGIT domvanalimab and PD-1 inhibitor zimberelimab, showed an objective response rate of 59% with objective response rates noticeably higher in PD-L1 high tumors compared with those with PD-L1 low tumors (80% *v* 46%).[177] Six month progression-free survival was 75%, again higher with the PD-L1 high tumors compared with with PD-L1 low tumors (93% *v* 66%). There is an ongoing phase 3 STAR-221 trial, which is randomizing patients to receive domvanalimab, zimberelimab, and chemotherapy versus nivolumab and chemotherapy for first line advanced gastric and gastroesophageal junction adenocarcinoma (table 2).

Future of drug development and other technologies

Bispecific antibodies

Bispecific antibodies are designed for simultaneous binding of two antigens on cancer cells and/or immune cells (fig 2).[205] Zanidatamab is a biparatropic bispecific antibody targeted against two distinct HER2 epitopes, which results in HER2 receptor cluster internalization and receptor down regulation.[206] A phase 2 study of 42 patients evaluated first line zanidatamab in combination with chemotherapy for HER2 positive advanced gastroesophageal adenocarcinoma.[207] The 18 month overall survival rate was 84% and the median overall survival had not yet been reached with 26.5 months of median follow-up. HERIZON-GEA-01 is an ongoing phase 3 study of zanidatamab with tislelizumab

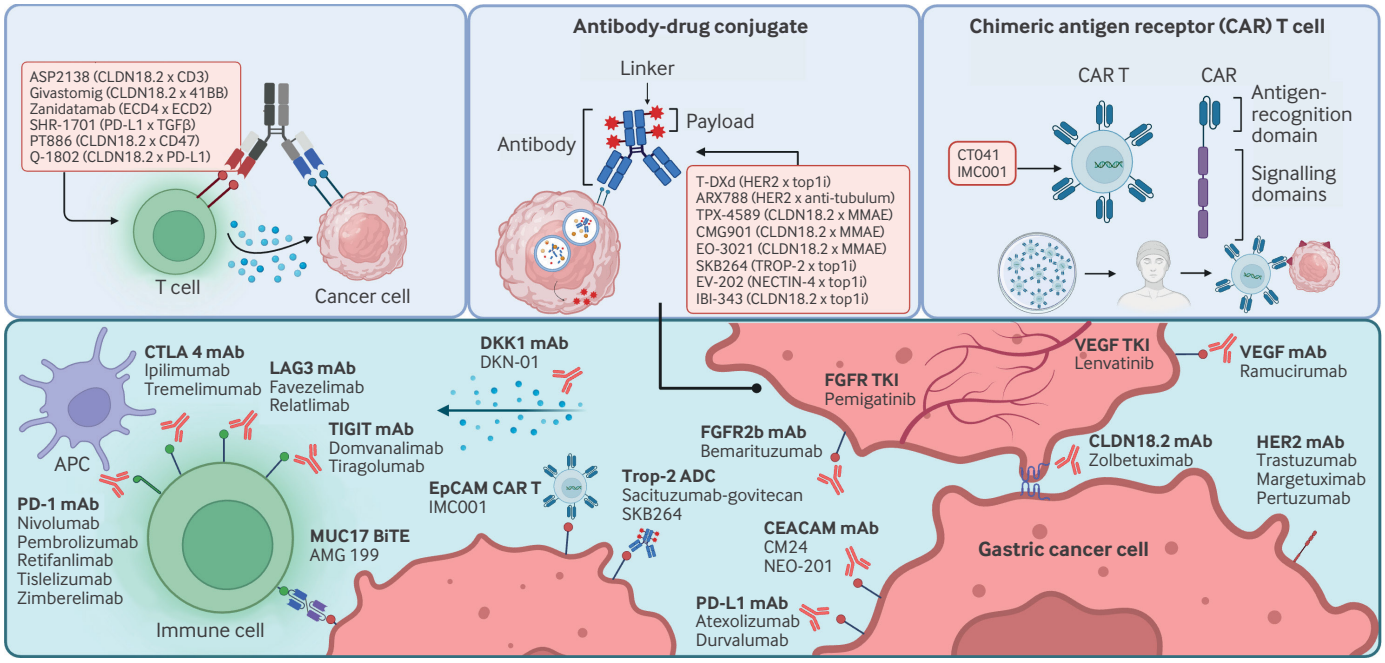

Fig 2 | Landscape of gastric cancer associated targets with novel drug platforms and updated therapies

and chemotherapy compared with tislelizumab and chemotherapy for first line treatment of HER2-positive gastroesophageal adenocarcinoma (table 2).

Antibody-drug conjugates

Antibody-drug conjugates are composed of an antibody directed to a tumor specific antigen with a cleavable linker to a cytotoxic payload.[208] There is interest in developing this class of drugs because they can combine the tumor targeting properties of an antibody and the potency of cytotoxic agents (fig 2).[208] The purported bystander effect, which allows the released payload to induce an anti-tumor effect in neighboring cancer cells, was seen in an exploratory cohort of HER2 low (IHC 2+/FISH– and IHC 1+) gastric cancer in the DESTINY Gastric 02 trial.[209] Other tumor specific antigen-antibody-drug conjugates are being actively developed against gastric cancer associated biomarkers (fig 2). Toxicity associated with antibody-drug conjugates, such as corneal and lung toxicity, will require continued investigation especially as these therapies move into the curative setting.

Chimeric antigen receptor (CAR) T cell therapy

There is increasing interest in evaluating CAR T cell therapy for gastric adenocarcinoma (fig 2).[210] CAR-engineered T cells contain an antibody fragment linked to an activation and costimulatory domain allowing for T cell activation inducing cancer cell apoptosis.[210] In a phase 2 study of CT041, a CLDN18.2 CAR T cell, 14 evaluable patients with refractory CLDN18.2+gastric cancer achieved an objective response rate of 57.1% with one patient achieving a complete response and two with a partial response and disease control rate of 78.6%.[211] With CAR T cell therapy and its potential for robust anti-tumor immune response, symptoms of cytokine release syndrome or immune effector cell-associated neurogenic syndrome are closely monitored.

Conclusion

Gastric cancer remains a leading cause of global cancer mortality, yet outcomes have improved with the evolution of multimodal treatment strategies. Standards of care have been redefined through evidence based advances in targeted screening, refined surgical techniques, and personalized systemic therapies. The integration of molecular profiling now enables approaches that are directed by biomarkers and based on immunotherapy that individualize treatment and extend survival. Continued international collaboration, equitable access to diagnostic and therapeutic advances, in addition to randomized trials that are well designed are essential to further improve outcomes for patients with this complex disease.

QUESTIONS FOR FUTURE RESEARCH

- In patients with well differentiated T1b gastric cancer, which histopathological features predict the suitability of curative endoscopic resection?
- What is the optimal role of surgery in patients with mismatch repair-deficient gastric cancers who exhibit a strong response to neoadjuvant therapy?
- For patients with multiple actionable biomarkers, what is the optimal sequence or combination strategy for targeted treatments?

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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;71:209-49. doi:10.3322/caac.21660
2 Yang WJ, Zhao HP, Yu Y, et al. Updates on global epidemiology, risk and prognostic factors of gastric cancer. *World J Gastroenterol* 2023;29:2452-68. doi:10.3748/wjg.v29.i16.2452
3 Rustgi SD, McKinley M, McBay B, et al. Epidemiology of gastric malignancies 2000-2018 according to histology: a population-based analysis of incidence and temporal trends. *Clin Gastroenterol Hepatol* 2023;21:3285-3295.e8. doi:10.1016/j.cgh.2023.01.037
4 National Institutes of Health. Surveillance Epidemiology, and End Results Program (SEER) - National Cancer Institute: An interactive website for SEER cancer statistics. https://seer.cancer.gov/statistics-network/explorer/application.html?site=1&data_type=1&graph_type=2&compareBy=sex&chk_sex_3=3&chk_sex_2=2&rate_type=2&race=1&age_range=1&hdn_stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_show_apc=on&advopt_display=2#resultsRegion0
5 Mok JW, Oh YH, Magge D, Padmanabhan S. Racial disparities of gastric cancer in the USA: an overview of epidemiology, global screening guidelines, and targeted screening in a heterogeneous population. *Gastric Cancer* 2024;27:426-38. doi:10.1007/s10120-024-01475-9
6 GBD US Health Disparities Collaborators. The burden of stomach cancer mortality by county, race, and ethnicity in the USA, 2000-2019: a systematic analysis of health disparities. *Lancet Reg Health Am* 2023;24:100547. doi:10.1016/j.lana.2023.100547
7 van Velzen MJM, Braemer M, Nieuwenhuijzen GAP, et al. Incidence, stage, treatment, and survival of noncardia gastric Cancer. *JAMA Netw Open* 2023;6:e2330018. doi:10.1001/jamanetworkopen.2023.30018
8 Yan S, Gan Y, Song X, et al. Association between refrigerator use and the risk of gastric cancer: A systematic review and meta-analysis of observational studies. *PLoS One* 2018;13:e0203120. doi:10.1371/journal.pone.0203120
9 Torrejon NV, Deshpande S, Wei W, Tullio K, Kamath SD. Proportion of early-onset gastric and esophagus cancers has changed over time with disproportionate impact on black and hispanic patients. *JCO Oncol Pract* 2022;18:e759-69. doi:10.1200/OP.21.00692
10 Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. *Int J Mol Sci* 2020;21:4012. doi:10.3390/ijms21114012
11 Sonnenberg A, Turner KO, Genta RM. low prevalence of helicobacter pylori-positive peptic ulcers in private outpatient endoscopy centers in the United States. *Am J Gastroenterol* 2020;115:244-50. doi:10.14309/ajg.0000000000000517
12 Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, et al. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. *Gut* 2018;67:226-36. doi:10.1136/gutjnl-2017-314205
13 Morais S, Costa A, Albuquerque G, et al. Salt intake and gastric cancer: a pooled analysis within the Stomach cancer Pooling (StoP) Project. *Cancer Causes Control* 2022;33:779-91. doi:10.1007/s10552-022-01565-y
14 Bouras E, Tsilidis KK, Triggi M, Siargkas A, Chourdakis M, Haidich AB. Diet and risk of gastric cancer: an umbrella review. *Nutrients* 2022;14:1764. doi:10.3390/nu14091764
15 Hui Y, Tu C, Liu D, Zhang H, Gong X. Risk factors for gastric cancer: A comprehensive analysis of observational studies. *Front Public Health* 2023;10:892468. doi:10.3389/fpubh.2022.892468
16 Fang X, Wei J, He X, et al. Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. *Eur J Cancer* 2015;51:2820-32. doi:10.1016/j.ejca.2015.09.010
17 Pelucchi C, La Vecchia C, Bonzi R, et al, StoP Project Working Group. The global gastric cancer consortium: an update from the Stomach cancer Pooling (StoP) project. *Eur J Cancer Prev* 2024;33:433-7. doi:10.1097/CEJ.0000000000000874
18 Ferro A, Morais S, Rota M, et al. Tobacco smoking and gastric cancer: meta-analyses of published data versus pooled analyses of individual participant data (StoP Project). *Eur J Cancer Prev* 2018;27:197-204. doi:10.1097/CEJ.0000000000000401
19 Rota M, Pelucchi C, Bertuccio P, et al. Alcohol consumption and gastric cancer risk-A pooled analysis within the StoP project consortium. *Int J Cancer* 2017;141:1950-62. doi:10.1002/ijc.30891
20 Dabo B, Pelucchi C, Rota M, et al. The association between diabetes and gastric cancer: results from the Stomach Cancer Pooling Project Consortium. *Eur J Cancer Prev* 2022;31:260-9. doi:10.1097/CEJ.0000000000000703
21 Ferro A, Rosato V, Rota M, et al. Meat intake and risk of gastric cancer in the Stomach cancer Pooling (StoP) project. *Int J Cancer* 2020;147:45-55. doi:10.1002/ijc.32707
22 Du X, Hidayat K, Shi BM. Abdominal obesity and gastroesophageal cancer risk: systematic review and meta-analysis of prospective studies. *Biosci Rep* 2017;37:BSR20160474. doi:10.1042/BSR20160474
23 Röcken C. Predictive biomarkers in gastric cancer. *J Cancer Res Clin Oncol* 2023;149:467-81. doi:10.1007/s00432-022-04408-0
24 Liu X, Liu J, Qiu H, et al. Prognostic significance of Epstein-Barr virus infection in gastric cancer: a meta-analysis. *BMC Cancer* 2015;15:782. doi:10.1186/s12885-015-1813-9
25 van den Brandt PA. The impact of a healthy lifestyle on the risk of esophageal and gastric cancer subtypes. *Eur J Epidemiol* 2022;37:931-45. doi:10.1007/s10654-022-00899-w
26 Zhang LY, Zhang J, Li D, et al. Bile reflux is an independent risk factor for precancerous gastric lesions and gastric cancer: An observational cross-sectional study. *J Dig Dis* 2021;22:282-90. doi:10.1111/1751-2980.12986
27 Song M, Latorre G, Ivanovic-Zuvic D, Camargo MC, Rabkin CS. Autoimmune diseases and gastric cancer risk: A systematic review and meta-analysis. *Cancer Res Treat* 2019;51:841-50. doi:10.4143/crt.2019.151
28 Liu SS, Ma XF, Zhao J, et al. Association between nonalcoholic fatty liver disease and extrahepatic cancers: a systematic review and meta-analysis. *Lipids Health Dis* 2020;19:118. doi:10.1186/s12944-020-01288-6
29 Mak TK, Guan B, Peng J, et al. Prevalence and characteristics of gastric remnant cancer: A systematic review and meta-analysis. *Asian J Surg* 2021;44:11-7. doi:10.1016/j.asjsur.2020.03.012
30 Weltermann T, Schulz C, Macke L. Effect of frequently prescribed drugs on gastric cancer risk. *Best Pract Res Clin Gastroenterol* 2021;50-51:101741. doi:10.1016/j.bpg.2021.101741
31 Niikura R, Hirata Y, Hayakawa Y, Kawahara T, Yamada A, Koike K. Effect of aspirin use on gastric cancer incidence and survival: A systematic review and meta-analysis. *JGH Open* 2019;4:117-25. doi:10.1002/jgh3.12226
32 Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. *Int J Mol Sci* 2020;21:4012. doi:10.3390/ijms21114012
33 Setia N, Clark JW, Duda DG, et al. Familial Gastric Cancers. *Oncologist* 2015;20:1365-77. doi:10.1634/theoncologist.2015-0205
34 Kim W, Kidambi T, Lin J, Idos G. Genetic syndromes associated with gastric cancer. *Gastrointest Endosc Clin N Am* 2022;32:147-62. doi:10.1016/j.giec.2021.08.004
35 Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 2020;396:635-48. doi:10.1016/S0140-6736(20)31288-5
36 Hejna M, Wöll E, Tschandl P, Raderer M. Cutaneous paraneoplastic disorders in stomach cancer: Collaboration between oncologically active dermatologists and clinical oncologists. *Crit Rev Oncol Hematol* 2016;103:78-85. doi:10.1016/j.critrevonc.2016.04.013
37 Lin X, Han T, Zhuo M, et al. A retrospective study of clinicopathological characteristics and prognostic factors of

Krukenberg tumor with gastric origin[Internet]. *J Gastrointest Oncol* 2022;13:1022-34. https://jgo.amegroups.org/article/view/65869. doi:10.21037/jgo-22-464
38 Lionetti R, DE Luca M, Raffone A, et al. Clinics and pathology of Krukenberg tumor: a systematic review and meta-analysis. *Minerva Obstet Gynecol* 2022;74:356-63. doi:10.23736/S2724-606X.21.04797-7
39 National Comprehensive Cancer Network. Gastric Cancer (v.4.2024) https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
40 Ajani J, In H, Sano T, et al. Stomach. In: AJCC Cancer Staging Manual. 8th ed. Springer, 2017.
41 Kwee RM, Kwee TC. Modern imaging techniques for preoperative detection of distant metastases in gastric cancer. *World J Gastroenterol* 2015;21:10502-9. doi:10.3748/wjg.v21.i37.10502
42 Tham E, Sestito M, Markovich B, Garland-Kledzik M. Current and future imaging modalities in gastric cancer. *J Surg Oncol* 2022;125:1123-34. doi:10.1002/jso.26875
43 Lordick F, Carneiro F, Cascinu S, et al, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022;33:1005-20. doi:10.1016/j.annonc.2022.07.004
44 Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer* 2012;15(Suppl 1):S38-47. doi:10.1007/s10120-011-0047-z
45 Li K, Cannon JGD, Jiang SY, et al. Diagnostic staging laparoscopy in gastric cancer treatment: A cost-effectiveness analysis. *J Surg Oncol* 2018;117:1288-96. doi:10.1002/jso.24942
46 Allen CJ, Newhook TE, Vreeland TJ, et al. Yield of peritoneal cytology in staging patients with gastric and gastroesophageal cancer. *J Surg Oncol* 2019;120:1350-7. doi:10.1002/jso.25729
47 Allen CJ, Blumenthaler AN, Das P, et al. Staging laparoscopy and peritoneal cytology in patients with early stage gastric adenocarcinoma. *World J Surg Oncol* 2020;18:39. doi:10.1186/s12957-020-01813-y
48 Song YX, Huang XZ, Gao P, et al. Clinicopathologic and Prognostic value of serum carbohydrate antigen 19-9 in gastric cancer: A meta-analysis. *Dis Markers* 2015;2015:549843. doi:10.1155/2015/549843
49 Kushima R. The updated WHO classification of digestive system tumours-gastric adenocarcinoma and dysplasia. *Pathologe* 2022;43:8-15. doi:10.1007/s00292-021-01023-7
50 Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31-49. doi:10.1111/apm.1965.64.1.31
51 Tang CT, Zeng L, Yang J, Zeng C, Chen Y. Analysis of the incidence and survival of gastric cancer based on the lauren classification: A large population-based study using SEER. *Front Oncol* 2020;10:1212. doi:10.3389/fonc.2020.01212
52 Luo Y, Gao P, Song Y, et al. Clinicopathologic characteristics and prognosis of Borrmann type IV gastric cancer: a meta-analysis. *World J Surg Oncol* 2016;14:49. doi:10.1186/s12957-016-0805-9
53 Díaz del Arco C, Ortega Medina L, Estrada Muñoz L, et al. Are Borrmann's types of advanced gastric cancer distinct clinicopathological and molecular entities? A western study. *Cancers (Basel)* 2021;13:3081. doi:10.3390/cancers13123081
54 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003;58(Suppl):S3-43. doi:10.1016/S0016-5107(03)02159-X
55 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011;14:101-12. doi:10.1007/s10120-011-0041-5
56 Felismino TC, Coimbra FJF. Lessons in gastric adenocarcinoma from TCGA. *Nat Rev Cancer* 2023;23:655. doi:10.1038/s41568-023-00606-1
57 Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;513:202-9. doi:10.1038/nature13480
58 González CA, Sanz-Anquela JM, Gisbert JP, Correa P. Utility of subtyping intestinal metaplasia as marker of gastric cancer risk. A review of the evidence. *Int J Cancer* 2013;133:1023-32. doi:10.1002/ijc.28003
59 Akintoye E, Obaitan I, Muthusamy A, Akanbi O, Olusunmade M, Levine D. Endoscopic submucosal dissection of gastric tumors: A systematic review and meta-analysis. *World J Gastrointest Endosc* 2016;8:517-32. doi:10.4253/wjge.v8.i15.517
60 Huang RJ, Epplein M, Hamashima C, et al. An approach to the primary and secondary prevention of gastric cancer in the United States. *Clin Gastroenterol Hepatol* 2022;20:2218-2228.e2. doi:10.1016/j.cgh.2021.09.039
61 Lee S, Jun JK, Suh M, et al. Gastric cancer screening uptake trends in Korea: results for the National Cancer Screening Program from 2002 to 2011: a prospective cross-sectional study. *Medicine (Baltimore)* 2015;94:e533. doi:10.1097/MD.0000000000000533
62 Hamashima C. Cancer screening guidelines and policy making: 15 years of experience in cancer screening guideline development in Japan. *Jpn J Clin Oncol* 2018;48:278-86. doi:10.1093/jjco/hyx190
63 Sun D, Mülder DT, Li Y, et al. The effect of nationwide organized cancer screening programs on gastric cancer mortality: a synthetic control study. *Gastroenterology* 2024;166:503-14. doi:10.1053/j.gastro.2023.11.286
64 Hallowell BD, Endeshaw M, McKenna MT, Senkomago V, Razzaghi H, Saraiya M. Cancer mortality rates among US and foreign-born individuals: United States 2005-2014. *Prev Med* 2019;126:105755. doi:10.1016/j.ypmed.2019.105755
65 Pabla BS, Shah SC, Corral JE, Morgan DR. increased incidence and mortality of gastric cancer in immigrant populations from high to low regions of incidence: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020;18:347-359.e5. doi:10.1016/j.cgh.2019.05.032
66 Maskarinec G, Noh JJ. The effect of migration on cancer incidence among Japanese in Hawaii. *Ethn Dis* 2004;14:431-9.
67 Shah SC, Canakis A, Peek RMJr, Saumoy M. Endoscopy for gastric cancer screening is cost effective for Asian Americans in the United States. *Clin Gastroenterol Hepatol* 2020;18:3026-39. doi:10.1016/j.cgh.2020.07.031
68 Kim GH, Liang PS, Bang SJ, Hwang JH. Screening and surveillance for gastric cancer in the United States: Is it needed?*Gastrointest Endosc* 2016;84:18-28. doi:10.1016/j.gie.2016.02.028
69 Suh YS, Lee J, Woo H, et al. National cancer screening program for gastric cancer in Korea: Nationwide treatment benefit and cost. *Cancer* 2020;126:1929-39. doi:10.1002/cncr.32753
70 Cubiella J, Pérez Aisa Á, Cuatrecasas M, et al, en representación de la Asociación Española de Gastroenterología, la Sociedad Española de Endoscopia Digestiva y la Sociedad Española de Anatomía Patológica. Gastric cancer screening in low incidence populations: Position statement of AEG, SEED and SEAP. *Gastroenterol Hepatol* 2021;44:67-86. doi:10.1016/j.gastrohep.2020.08.004
71 Banks M, Graham D, Jansen M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut* 2019;68:1545-75. doi:10.1136/gutjnl-2018-318126
72 Wolfsen HC, Hemminger LL, Achem SR, et al. Complications of endoscopy of the upper gastrointestinal tract: a single-center experience. *Mayo Clin Proc* 2004;79:1264-7. doi:10.4065/79.10.1264
73 Tashiro A, Sano M, Kinameri K, Fujita K, Takeuchi Y. Comparing mass screening techniques for gastric cancer in Japan. *World J Gastroenterol* 2006;12:4873-4.
74 Cho E, Kang MH, Choi KS, Suh M, Jun JK, Park EC. Cost-effectiveness outcomes of the national gastric cancer screening program in South Korea. *Asian Pac J Cancer Prev* 2013;14:2533-40. doi:10.7314/APJCP.2013.14.5.2533
75 Lee YC, Chiang TH, Chou CK, et al. Association between helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. *Gastroenterology* 2016;150:1113-1124.e5. doi:10.1053/j.gastro.2016.01.028
76 Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut* 2020;69:2113-21. doi:10.1136/gutjnl-2020-320839
77 Kumar S, Metz DC, Ellenberg S, Kaplan DE, Goldberg DS. Risk factors and incidence of gastric cancer after detection of helicobacter pylori infection: a large cohort study. *Gastroenterology* 2020;158:527-536.e7. doi:10.1053/j.gastro.2019.10.019
78 Sonnenberg A, Genta RM. Changes in the gastric mucosa with aging. *Clin Gastroenterol Hepatol* 2015;13:2276-81. doi:10.1016/j.cgh.2015.02.020
79 Li D, Bautista MC, Jiang SF, et al. Risks and predictors of gastric adenocarcinoma in patients with gastric intestinal metaplasia and dysplasia: a population-based study. *Am J Gastroenterol* 2016;111:1104-13. doi:10.1038/ajg.2016.188
80 Reddy KM, Chang JI, Shi JM, Wu BU. Risk of gastric cancer among patients with intestinal metaplasia of the stomach in a US integrated health care system. *Clin Gastroenterol Hepatol* 2016;14:1420-5. doi:10.1016/j.cgh.2016.05.045
81 Evans JA, Chandrasekhara V, Chathadi KV, et al, ASGE Standards of Practice Committee. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. *Gastrointest Endosc* 2015;82:1-8. doi:10.1016/j.gie.2015.03.1967
82 Gupta S, Li D, El Serag HB, et al. AGA Clinical Practice Guidelines on management of gastric intestinal metaplasia. *Gastroenterology* 2020;158:693-702. doi:10.1053/j.gastro.2019.12.003

83 Rugge M, Genta RM, Malfertheiner P, et al, RE GA IN. RE.GA. IN.: the Real-world Gastritis Initiative-updating the updates. *Gut* 2024;73:407-41. doi:10.1136/gutjnl-2023-331164
84 Trieu JA, Bilal M, Saraireh H, Wang AY. Update on the diagnosis and management of gastric intestinal metaplasia in the USA. *Dig Dis Sci* 2019;64:1079-88. doi:10.1007/s10620-019-05526-5
85 Shah SC, Piazuelo MB, Kuipers EJ, Li D. AGA clinical practice update on the diagnosis and management of atrophic gastritis: expert review. *Gastroenterology* 2021;161:1325-1332.e7. doi:10.1053/j.gastro.2021.06.078
86 Lee JWJ, Zhu F, Srivastava S, et al. Severity of gastric intestinal metaplasia predicts the risk of gastric cancer: a prospective multicentre cohort study (GCEP). *Gut* 2022;71:854-63. doi:10.1136/gutjnl-2021-324057
87 Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219-25. doi:10.1007/PL00011720
88 Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017;20:1-19. doi:10.1007/s10120-016-0622-4
89 Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 2016;28:3-15. doi:10.1111/den.12518
90 Abdelfatah MM, Barakat M, Lee H, et al. The incidence of lymph node metastasis in early gastric cancer according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association: a systematic review of the literature and meta-analysis. *Gastrointest Endosc* 2018;87:338-47. doi:10.1016/j.gie.2017.09.025
91 Draganov PV, Wang AY, Othman MO, Fukami N. AGA institute clinical practice update: endoscopic submucosal dissection in the United States. *Clin Gastroenterol Hepatol* 2019;17:16-25.e1. doi:10.1016/j.cgh.2018.07.041
92 Nakajima T, Oda I, Gotoda T, et al. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance?*Gastric Cancer* 2006;9:93-8. doi:10.1007/s10120-006-0372-9
93 Wang AY, Hwang JH, Bhatt A, Draganov PV. AGA clinical practice update on surveillance after pathologically curative endoscopic submucosal dissection of early gastrointestinal neoplasia in the United States: commentary. *Gastroenterology* 2021;161:2030-2040.e1. doi:10.1053/j.gastro.2021.08.058
94 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;30:2327-33. doi:10.1200/JCO.2011.36.7136
95 Cunningham D, Allum WH, Stenning SP, et al, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20. doi:10.1056/NEJMoa055531
96 Gouzi JL, Huguier M, Fagniez PL, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 1989;209:162-6. doi:10.1097/00000658-198902000-00005
97 Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L, Italian Gastrointestinal Tumor Study Group. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. *Ann Surg* 1999;230:170-8. doi:10.1097/00000658-199908000-00006
98 Hipp J, Hillebrecht HC, Kalkum E, et al. Systematic review and meta-analysis comparing proximal gastrectomy with double-tract-reconstruction and total gastrectomy in gastric and gastroesophageal junction cancer patients: Still no sufficient evidence for clinical decision-making. *Surgery* 2023;173:957-67. doi:10.1016/j.surg.2022.11.018
99 Japanese Gastric Cancer Association. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). *Gastric Cancer* 2023;26:1-25. doi:10.1007/s10120-022-01331-8.
100 Tu RH, Lin JX, Wang W, et al. Pathological features and survival analysis of gastric cancer patients with positive surgical margins: A large multicenter cohort study. *Eur J Surg Oncol* 2019;45:2457-64. doi:10.1016/j.ejso.2019.06.026
101 Jiang Z, Liu C, Cai Z, et al. Impact of surgical margin status on survival in gastric cancer: a systematic review and meta-analysis. *Cancer Control* 2021;28:10732748211043665. doi:10.1177/10732748211043665
102 Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;345:745-8. doi:10.1016/S0140-6736(95)90637-1
103 Cuschieri A, Fayers P, Fielding J, et al, The Surgical Cooperative Group. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. *Lancet* 1996;347:995-9. doi:10.1016/S0140-6736(96)90144-0
104 Douridas GN, Pierrakakis SK. Is There Any Role for D3 Lymphadenectomy in Gastric Cancer?*Front Surg* 2018;5:27. doi:10.3389/fsurg.2018.00027
105 Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy--Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004;22:2767-73. doi:10.1200/JCO.2004.10.184
106 Sasako M, Sano T, Yamamoto S, et al, Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453-62. doi:10.1056/NEJMoa0707035
107 Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;11:439-49. doi:10.1016/S1470-2045(10)70070-X
108 Kurokawa Y, Doki Y, Mizusawa J, et al. Five-year follow-up of a randomized clinical trial comparing bursectomy and omentectomy alone for resectable gastric cancer (JCOG1001). *Br J Surg* 2022;110:50-6. doi:10.1093/bjs/znac373
109 Wang D, Ren J, Wang Y, et al. Splenectomy versus splenic preservation in total gastrectomy for gastric cancer: a systematic review and meta-analysis comparing survival benefits and short-term complications. *Postgrad Med* 2024;136:266-77. doi:10.1080/00325481.2024.2333233
110 Shen J, Ma X, Yang J, Zhang JP. Digestive tract reconstruction options after laparoscopic gastrectomy for gastric cancer. *World J Gastrointest Oncol* 2020;12:21-36. doi:10.4251/wjgo.v12.i1.21
111 Lewis TS, Feng Y. A review on double tract reconstruction after proximal gastrectomy for proximal gastric cancer. *Ann Med Surg (Lond)* 2022;79:103879. doi:10.1016/j.amsu.2022.103879
112 Lombardo F, Aiolfi A, Cavalli M, et al. Techniques for reconstruction after distal gastrectomy for cancer: updated network meta-analysis of randomized controlled trials. *Langenbecks Arch Surg* 2022;407:75-86. doi:10.1007/s00423-021-02411-6
113 Nishizaki D, Ganeko R, Hoshino N, et al. Roux-en-Y versus Billroth-I reconstruction after distal gastrectomy for gastric cancer. *Cochrane Database Syst Rev* 2021;9:CD012998.
114 Park SH, Hur H, Park JH, et al. Reappraisal of optimal reconstruction after distal gastrectomy - a study based on the KLASS-07 database. *Int J Surg* 2024;110:32-44. doi:10.1097/JS9.0000000000000796
115 van der Veen A, Brenkman HJF, Seesing MFJ, et al, LOGICA Study Group. Laparoscopic Versus Open Gastrectomy for Gastric Cancer (LOGICA): a multicenter randomized clinical trial. *J Clin Oncol* 2021;39:978-89. doi:10.1200/JCO.20.01540
116 Yan Y, Yang A, Lu L, et al. Impact of neoadjuvant therapy on minimally invasive surgical outcomes in advanced gastric cancer: an international propensity score-matched study. *Ann Surg Oncol* 2021;28:1428-36. doi:10.1245/s10434-020-09070-9
117 Ding Z, Jiang L, Zhang K, Huang R. Short- and long-term outcomes of conversion in laparoscopic gastrectomy for gastric cancer. *J BUON* 2018;23:1004-12.
118 de Jongh C, van der Veen A, Brosens LAA, et al, LOGICA Study Group. Distal versus total D2-gastrectomy for gastric cancer: a secondary analysis of surgical and oncological outcomes including quality of life in the multicenter randomized LOGICA-trial. *J Gastrointest Surg* 2023;27:1812-24. doi:10.1007/s11605-023-05683-z
119 Shi Y, Xu X, Zhao Y, et al. Short-term surgical outcomes of a randomized controlled trial comparing laparoscopic versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer. *Surg Endosc* 2018;32:2427-33. doi:10.1007/s00464-017-5942-x
120 Kim HH, Han SU, Kim MC, et al, Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) Group. Effect of laparoscopic distal gastrectomy vs open distal gastrectomy on long-term survival among patients with stage I gastric cancer: The KLASS-01 randomized clinical trial. *JAMA Oncol* 2019;5:506-13. doi:10.1001/jamaoncol.2018.6727
121 Huang C, Liu H, Hu Y, et al, Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Laparoscopic vs open distal gastrectomy for locally advanced gastric cancer: five-year outcomes from the CLASS-01 randomized clinical trial. *JAMA Surg* 2022;157:9-17. doi:10.1001/jamasurg.2021.5104
122 Katai H, Mizusawa J, Katayama H, et al. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. *Lancet Gastroenterol Hepatol* 2020;5:142-51. doi:10.1016/S2468-1253(19)30332-2
123 Liu F, Huang C, Xu Z, et al, Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. morbidity and mortality of laparoscopic vs open total gastrectomy for clinical stage I gastric

cancer: the CLASS02 multicenter randomized clinical trial. *JAMA Oncol* 2020;6:1590-7. doi:10.1001/jamaoncol.2020.3152
124 Son SY, Hur H, Hyung WJ, et al, Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) Group. laparoscopic vs open distal gastrectomy for locally advanced gastric cancer: 5-year outcomes of the KLASS-02 randomized clinical trial. *JAMA Surg* 2022;157:879-86. doi:10.1001/jamasurg.2022.2749
125 Guerrini GP, Esposito G, Magistri P, et al. Robotic versus laparoscopic gastrectomy for gastric cancer: The largest meta-analysis. *Int J Surg* 2020;82:210-28. doi:10.1016/j.ijsu.2020.07.053
126 Foster JM, Zhang C, Rehman S, Sharma P, Alexander HR. The contemporary management of peritoneal metastasis: A journey from the cold past of treatment futility to a warm present and a bright future. *CA Cancer J Clin* 2023;73:49-71. doi:10.3322/caac.21749
127 Thomassen I, van Gestel YR, van Ramshorst B, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. *Int J Cancer* 2014;134:622-8. doi:10.1002/ijc.28373
128 Badgwell B, Das P, Ajani J. Treatment of localized gastric and gastroesophageal adenocarcinoma: the role of accurate staging and preoperative therapy. *J Hematol Oncol* 2017;10:149. doi:10.1186/s13045-017-0517-9
129 Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000;88:358-63. doi:10.1002/(SICI)1097-0142(20000115)88:2<358::AID-CNCR16>3.0.CO;2-O
130 Jamel S, Markar SR, Malietzis G, Acharya A, Athanasiou T, Hanna GB. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. *Gastric Cancer* 2018;21:10-8. doi:10.1007/s10120-017-0749-y
131 Pecqueux M, Fritzmann J, Adamu M, et al. Free intraperitoneal tumor cells and outcome in gastric cancer patients: a systematic review and meta-analysis. *Oncotarget* 2015;6:35564-78. doi:10.18632/oncotarget.5595
132 Yepuri N, Bahary N, Jain A, Dhir M. Review and update on the role of peritoneal cytology in the treatment of gastric cancer. *J Surg Res* 2019;235:607-14. doi:10.1016/j.jss.2018.10.049
133 Valletti M, Eshmuminov D, Gnecco N, Gutschow CA, Schneider PM, Lehmann K. Gastric cancer with positive peritoneal cytology: survival benefit after induction chemotherapy and conversion to negative peritoneal cytology. *World J Surg Oncol* 2021;19:245. doi:10.1186/s12957-021-02351-x
134 Bonnot PE, Lintis A, Mercier F, et al, FREGAT and BIG-RENAPE Networks. Prognosis of poorly cohesive gastric cancer after complete cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (CYTO-CHIP study). *Br J Surg* 2021;108:1225-35. doi:10.1093/bjs/znab200
135 Patel M, Arora A, Mukherjee D, Mukherjee S. Effect of hyperthermic intraperitoneal chemotherapy on survival and recurrence rates in advanced gastric cancer: a systematic review and meta-analysis. *Int J Surg* 2023;109:2435-50. doi:10.1097/JS9.0000000000000457
136 Badgwell B, Ikoma N, Murphy MB, et al. A Phase II trial of cytoreduction, gastrectomy, and hyperthermic intraperitoneal perfusion with chemotherapy for patients with gastric cancer and carcinomatosis or positive cytology. *Ann Surg Oncol* 2021;28:258-64. doi:10.1245/s10434-020-08739-5
137 Badgwell B, Estrella J, Roy-Chowdhuri S, et al. Updated analysis of a phase 2 trial of cytoreduction, gastrectomy, and hyperthermic intraperitoneal perfusion with chemotherapy for patients with peritoneal carcinoma from gastric cancer. *Ann Surg Oncol* 2024;31:2824-5. doi:10.1245/s10434-024-14953-2
138 Fujitani K, Yang HK, Mizusawa J, et al, REGATTA study investigators. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol* 2016;17:309-18. doi:10.1016/S1470-2045(15)00553-7
139 Cowling J, Gorman B, Riaz A, et al. Peri-operative outcomes and survival following palliative gastrectomy for gastric cancer: a systematic review and meta-analysis. *J Gastrointest Cancer* 2021;52:41-56. doi:10.1007/s12029-020-00519-4
140 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;345:725-30. doi:10.1056/NEJMoa010187
141 Noh SH, Park SR, Yang HK, et al, CLASSIC trial investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:1389-96. doi:10.1016/S1470-2045(14)70473-5
142 Sakuramoto S, Sasako M, Yamaguchi T, et al, ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810-20. doi:10.1056/NEJMoa072252
143 Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999;35:1059-64. doi:10.1016/S0959-8049(99)00076-3
144 Al-Batran SE, Homann N, Pauligk C, et al, FLOT4-AIO Investigators. 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;393:1948-57. doi:10.1016/S0140-6736(18)32557-1
145 Cats A, Jansen EPM, van Grieken NCT, et al, CRITICS investigators. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:616-28. doi:10.1016/S1470-2045(18)30132-3
146 Leong T, Smithers BM, Michael M, et al, Australasian Gastro-Intestinal Trials Group, National Health and Medical Research Council Clinical Trials Centre, Trans-Tasman Radiation Oncology Group, European Organisation for Research and Treatment of Cancer, and Canadian Cancer Trials Group. Preoperative chemoradiotherapy for resectable gastric cancer. *N Engl J Med* 2024;391:1810-21. doi:10.1056/NEJMoa2405195
147 Shitara K, Rha SY, Wyrwicz LS, et al, KEYNOTE-585 investigators. 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* 2024;25:212-24. doi:10.1016/S1470-2045(23)00541-7
148 Shitara K, Rha SY, Wyrwicz LS, et al. LBA3 Final analysis of the phase III KEYNOTE-585 study of pembrolizumab plus chemotherapy vs chemotherapy as perioperative therapy in locally-advanced gastric and gastroesophageal junction cancer. *Ann Oncol* 2024;35:S213doi:10.1016/j.annonc.2024.06.007
149 AstraZeneca. Imfinzi-based regimen demonstrated statistically significant and clinically meaningful improvement in event-free survival in resectable early-stage gastric and gastroesophageal junction cancers [press release]. 2025 Mar 7. https://www.astrazeneca.com/media-centre/press-releases/2025/imfinzi-improved-efs-in-early-stage-gastric-cancer.html
150 Janjigian YY, Al-Batran S-E, Wainberg ZA, et al. Pathological complete response (pCR) to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab (D) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): Subgroup analysis by region from the phase 3, randomized, double-blind MATTERHORN study. *J Clin Oncol* 2024;42(suppl):LBA246doi:10.1200/JCO.2024.42.3_suppl.LBA246 .
151 Janjigian YY, Al-Batran SE, Wainberg ZA, et al, MATTERHORN Investigators. Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer. *N Engl J Med* 2025;393:217-30. doi:10.1056/NEJMoa2503701
152 Tabernero J, Al-Batran SE, Wainberg ZA, et al. Final overall survival and the association of pathological outcomes with event free survival in MATTERHORN: a randomised, Phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel in resectable gastric/gastroesophageal junction adenocarcinoma. In: Proceedings from the European Society of Medical Oncology; October 17 – 21, 2025; Berlin, Germany. Abstract LBA81
153 Tran-Minh ML, Lehmann-Che J, Lambert J, et al, for NORDICAP. Prevalence and prognosis of microsatellite instability in oesogastric adenocarcinoma, NORDICAP 16-01. *Clin Res Hepatol Gastroenterol* 2021;45:101691. doi:10.1016/j.clinre.2021.101691
154 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;37:3392-400. doi:10.1200/JCO.19.01124
155 Nie RC, Chen GM, Yuan SQ, et al. Adjuvant chemotherapy for gastric cancer patients with mismatch repair deficiency or microsatellite instability: systematic review and meta-analysis. *Ann Surg Oncol* 2022;29:2324-31. doi:10.1245/s10434-021-11050-6
156 Germano G, Amirouchene-Angelozzi N, Rospo G, Bardelli A. The clinical impact of the genomic landscape of mismatch repair-deficient cancers. *Cancer Discov* 2018;8:1518-28. doi:10.1158/2159-8290.CD-18-0150
157 Smyth EC, Wotherspoon A, Peckitt C, et al. mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the medical research council adjuvant gastric infusional chemotherapy (MAGIC) trial. *JAMA Oncol* 2017;3:1197-203. doi:10.1001/jamaoncol.2016.6762
158 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;41:255-65. doi:10.1200/JCO.22.00686

159 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(suppl):358doi:10.1200/JCO.2023.41.4_suppl.358 .

160 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;30:268-73. doi:10.1200/JCO.2011.39.1953

161 Park SH, Lim DH, Sohn TS, et al, ARTIST 2 investigators. 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;32:368-74. doi:10.1016/j.annonc.2020.11.017

162 Hoeppner J, Brunner T, Schmoor C, et al. Perioperative chemotherapy or preoperative chemoradiotherapy in esophageal cancer. *N Engl J Med* 2025;392:323-35. doi:10.1056/NEJMoa2409408

163 Maio M, Ascierto PA, Manzyuk L, et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. *Ann Oncol* 2022;33:929-38. doi:10.1016/j.annonc.2022.05.519

164 Chao J, Fuchs CS, Shitara K, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol* 2021;7:895-902. doi:10.1001/jamaoncol.2021.0275

165 U.S. Food and Drug Administration. FDA grants accelerated approval to dostarlimab-gxly for dMMR advanced solid tumors [press release]. 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors

166 Derks S, Liao X, Chiaravalli AM, et al. Abundant PD-L1 expression in Epstein-Barr Virus-infected gastric cancers. *Oncotarget* 2016;7:32925-32. doi:10.18632/oncotarget.9076

167 Maron SB, Moya S, Morano F, et al. epidermal growth factor receptor inhibition in epidermal growth factor receptor-amplified gastroesophageal cancer: retrospective global experience. *J Clin Oncol* 2022;40:2458-67. doi:10.1200/JCO.21.02453

168 Doebele RC, Drilon A, Paz-Ares L, et al, trial investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:271-82. doi:10.1016/S1470-2045(19)30691-6

169 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018;378:731-9. doi:10.1056/NEJMoa1714448

170 Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with *BRAF*^{V600E} mutations: results of the NCI-MATCH trial subprotocol H. *J Clin Oncol* 2020;38:3895-904. doi:10.1200/JCO.20.00762

171 Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol* 2022;23:1261-73. doi:10.1016/S1470-2045(22)00541-1

172 Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008;19:1523-9. doi:10.1093/annonc/mdn169

173 Bang YJ, Van Cutsem E, Feyereislova A, et al, ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-97. doi:10.1016/S0140-6736(10)61121-X

174 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;19:1372-84. doi:10.1016/S1470-2045(18)30481-9

175 Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol* 2017;18:640-53. doi:10.1016/S1470-2045(17)30111-0

176 Hecht JR, Bang YJ, Qin SK, et al. lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC--a randomized phase III trial. *J Clin Oncol* 2016;34:443-51. doi:10.1200/JCO.2015.62.6598

177 Janjigian YY, Kawazoe A, Bai Y, et al. 1400O Final overall survival for the phase III, KEYNOTE-811 study of pembrolizumab plus trastuzumab and chemotherapy for HER2+ advanced, unresectable or metastatic G/GEJ adenocarcinoma. *Ann Oncol* 2024;35:S877-8doi:10.1016/j.annonc.2024.08.1466 .

178 Pietrantonio F, Caporale M, Morano F, et al. HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: Implication for further clinical research. *Int J Cancer* 2016;139:2859-64. doi:10.1002/ijc.30408

179 Yamaguchi K, Bang Y-J, Iwasa S, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2–positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: Final overall survival (OS) results from a randomized, multicenter, open-label, phase 2 study (DESTINY-Gastric01). *J Clin Oncol* 2022;40(suppl):242doi:10.1200/JCO.2022.40.4_suppl.242 .

180 Van Cutsem E, di Bartolomeo M, Smyth E, et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. *Lancet Oncol* 2023;24:744-56. doi:10.1016/S1470-2045(23)00215-2

181 Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2016;17:717-26. doi:10.1016/S1470-2045(16)00175-3

182 Fuchs CS, Doi T, Jang RW, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. *JAMA Oncol* 2018;4:e180013. doi:10.1001/jamaoncol.2018.0013

183 Shitara K, Özgüroğlu M, Bang YJ, et al, KEYNOTE-061 investigators. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2018;392:123-33. doi:10.1016/S0140-6736(18)31257-1

184 Chung HC, Kang YK, Chen Z, et al. Pembrolizumab versus paclitaxel for previously treated advanced gastric or gastroesophageal junction cancer (KEYNOTE-063): A randomized, open-label, phase 3 trial in Asian patients. *Cancer* 2022;128:995-1003. doi:10.1002/cncr.34019

185 Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;390:2461-71. doi:10.1016/S0140-6736(17)31827-5

186 Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;398:27-40. doi:10.1016/S0140-6736(21)00797-2

187 Tabernero J, Bang YJ, Van Cutsem E, et al. KEYNOTE-859: a Phase III study of pembrolizumab plus chemotherapy in gastric/gastroesophageal junction adenocarcinoma. *Future Oncol* 2021;17:2847-55. doi:10.2217/fon-2021-0176

188 Qiu MZ, Oh DY, Kato K, et al, RATIONALE-305 Investigators. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ* 2024;385:e078876. doi:10.1136/bmj-2023-078876

189 U.S. Food and Drug Administration. FDA approves pembrolizumab with chemotherapy for HER2-negative gastric or gastroesophageal junction adenocarcinoma [press release]. 2023 https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemotherapy-her2-negative-gastric-or-gastroesophageal-junction

190 U.S. Food and Drug Administration. FDA approves nivolumab in combination with chemotherapy for metastatic gastric cancer and esophageal adenocarcinoma [press release]. 2021 https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal#:~:text=On%20April%2016%2C%202021%2C%20the,junction%20cancer%2C%20and%20esophageal%20adenocarcinoma

191 U.S. Food and Drug Administration. Meeting of the Oncologic Drugs Advisory Committee (ODAC). 2024 Sept 26 https://www.youtube.com/live/ELA3JDqtcFw

192 Niimi T, Nagashima K, Ward JM, et al. claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing. *Mol Cell Biol* 2001;21:7380-90. doi:10.1128/MCB.21.21.7380-7390.2001

193 Sahin U, Schuler M, Richly H, et al. A phase I dose-escalation study of IMAB362 (Zolbetuximab) in patients with advanced gastric and gastro-oesophageal junction cancer. *Eur J Cancer* 2018;100:17-26. doi:10.1016/j.ejca.2018.05.007
194 Türeci O, Sahin U, Schulze-Bergkamen H, et al. A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study. *Ann Oncol* 2019;30:1487-95. doi:10.1093/annonc/mdz199
195 Sahin U, Türeci Ö, Manikhas G, et al. FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. *Ann Oncol* 2021;32:609-19. doi:10.1016/j.annonc.2021.02.005
196 Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2023;401:1655-68. doi:10.1016/S0140-6736(23)00620-7
197 Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* 2023;29:2133-41. doi:10.1038/s41591-023-02465-7
198 Kim TH, Kim IH, Kang SJ, et al, Development Working Groups for the Korean Practice Guidelines for Gastric Cancer 2022 Task Force Team. Korean practice guidelines for gastric cancer 2022: an evidence-based, multidisciplinary approach. *J Gastric Cancer* 2023;23:3-106. doi:10.5230/jgc.2023.23.e11
199 Dieci MV, Arnedos M, Andre F, Soria JC. Fibroblast growth factor receptor inhibitors as a cancer treatment: from a biologic rationale to medical perspectives. *Cancer Discov* 2013;3:264-79. doi:10.1158/2159-8290.CD-12-0362
200 Wainberg ZA, Enzinger PC, Kang YK, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Oncol* 2022;23:1430-40. doi:10.1016/S1470-2045(22)00603-9
201 Rha SY, Pazo Cid R, Montes AF, et al. Bemarituzumab (BEMA) plus chemotherapy for advanced or metastatic FGF2b-overexpressing gastric or gastroesophageal junction cancer (G/GEJC): FORTITUDE-101 phase 3 study results. In: Proceedings from the European Society of Medical Oncology; October 17-21, 2025; Berlin, Germany. Abstract LBA10.
202 Kagey MH, He X. Rationale for targeting the Wnt signalling modulator Dickkopf-1 for oncology. *Br J Pharmacol* 2017;174:4637-50. doi:10.1111/bph.13894
203 Klempner SJ, Sonbol MB, Wainberg ZA, et al. DKN-01 in combination with tislelizumab and chemotherapy as first-line therapy in advanced gastric or gastroesophageal junction adenocarcinoma: DisTinGuish. *J Clin Oncol* 2025;43:339-49. doi:10.1200/JCO.24.00410
204 Chu X, Tian W, Wang Z, Zhang J, Zhou R. Co-inhibition of TIGIT and PD-1/PD-L1 in cancer immunotherapy: mechanisms and clinical trials. *Mol Cancer* 2023;22:93. doi:10.1186/s12943-023-01800-3
205 Goebeler ME, Stuhler G, Bargou R. Bispecific and multispecific antibodies in oncology: opportunities and challenges. *Nat Rev Clin Oncol* 2024;21:539-60. doi:10.1038/s41571-024-00905-y
206 Weisser NE, Sanches M, Escobar-Cabrera E, et al. An anti-HER2 biparatopic antibody that induces unique HER2 clustering and complement-dependent cytotoxicity. *Nat Commun* 2023;14:1394. doi:10.1038/s41467-023-37029-3
207 Elimova E, Ajani JA, Burris III HA, et al. Zanidatamab + chemotherapy as first-line treatment for HER2-expressing metastatic gastroesophageal adenocarcinoma (mGEA). *J Clin Oncol* 2023;41(suppl):347doi:10.1200/JCO.2023.41.4_suppl.347 .
208 Dumontet C, Reichert JM, Senter PD, Lambert JM, Beck A. Antibody-drug conjugates come of age in oncology. *Nat Rev Drug Discov* 2023;22:641-61. doi:10.1038/s41573-023-00709-2
209 Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in HER2-positive advanced gastric cancer: exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial. *Nat Med* 2024;30:1933-42. doi:10.1038/s41591-024-02992-x
210 Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. *Nat Rev Clin Oncol* 2016;13:370-83. doi:10.1038/nrclinonc.2016.36
211 Qi C, Gong J, Li J, et al. Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. *Nat Med* 2022;28:1189-98. doi:10.1038/s41591-022-01800-8