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SPECIAL ARTICLE

Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

More than 1 million (1 089 103) new cases of gastric cancer were estimated globally in 2020, resulting in 768 793 deaths.[1] These burden estimates will continue to increase due to the ageing population and growth of high-risk groups. Of these global numbers, an estimated 136 038 cases and 96 997 deaths occurred in Europe.[1] Gastric cancer displays substantial global variation in incidence; the highest rates are observed in Eastern Asia, Central and Eastern Europe and South America.[1] A gradual decline in the incidence of gastric cancer has been observed in Western Europe and North America over the past 60 years, and more recent declines in high-risk countries have also become apparent.[2] This is epidemiologically distinct from the relative increase in oesophageal adenocarcinoma, including tumours of the oesophagogastric junction (OGJ), which are discussed in a separate guideline document.

Incidence in men is twice as high as in women. Risk factors vary by anatomical subsite of disease; non-cardia gastric cancer, which is more common in East Asia and Latin America, represents ∼80% of gastric tumours globally and has been associated with *Helicobacter pylori* (*H. pylori*) infection, alcohol use, high salt intake and low consumption of fruit and vegetables. Proximal (cardia) gastric cancer is associated with obesity and gastro-oesophageal reflux and is more common in North America and Western Europe.[3] Epstein-Barr virus (EBV)-positive gastric cancer is more prevalent in the fundus or body (62%) and its prevalence seems to be similar in Asia, Europe and the Americas.[4]

Recent studies report an increase in non-cardia gastric cancer among young individuals (<50 years), especially in low-incidence countries such as the UK and US — populations with a low prevalence of *H. pylori* infection. Dysbiosis of the gastric microbiome associated with modern lifestyles and an increase in autoimmune disorders in this age group have been postulated as potential explanations.[5]

Genetic predisposition

Gastric cancer demonstrates familial aggregation in ∼10% of cases, and an inherited genetic predisposition is identified in up to 3% of cases.[6] Genetic tumour risk syndromes are characterised by an increased risk of early-onset cancers in a familial context. High cancer risk is mostly driven by loss-of-function variants in a single cancer-associated gene. *CDH1* and *CTNNA1* germline variants predispose to hereditary diffuse gastric cancer (HDGC), while *APC promoter 1B* single nucleotide variants predispose to gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). Familial intestinal gastric cancer (FIGC), recognised as a gastric cancer-predisposing disease, remains understudied and genetically unsolved.[7] Gastric cancer can also occur within the spectrum of other genetic tumour risk syndromes, such as Lynch syndrome, familial adenomatous polyposis (FAP), Li—Fraumeni and Peutz—Jeghers

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syndromes (Table 1).[6] HDGC is the most studied hereditary gastric cancer risk syndrome and is estimated to have a population incidence rate of ~5-10/100 000 births.[8] The incidence rates for other gastric cancer risk syndromes are less well defined. HDGC is an autosomal dominant cancer syndrome that is characterised by a high prevalence of diffuse gastric cancer and lobular breast cancer. HDGC is caused by *CDH1*/E-cadherin germline single nucleotide variants and copy number variants, classified as pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology *CDH1* variant curation guidelines.[9] Pathogenic variants in *CTNNA1* occur in a minority of families with HDGC. The International Gastric Cancer Linkage Consortium provides updated practice guidelines for HDGC, recognising the emerging evidence of variability in gastric cancer risk between families, the growing capability of endoscopic and histological surveillance in HDGC and greater experience managing long-term sequelae following total gastrectomy in young patients.[8]

Prevention

There is consistent evidence that eradication of *H. pylori* substantially reduces the incidence of gastric cancer in healthy individuals, patients with gastric atrophy and people with a family history of gastric cancer.[10,11] Non-cardia intestinal-type cancer—the most common histological subtype of gastric cancer—follows a pattern of stepwise progression (known as the Correa Cascade) from normal mucosa to non-atrophic gastritis, atrophic gastritis with or without intestinal metaplasia (IM), dysplasia and finally cancer.[12] In high-risk East Asian countries (China, Japan and South Korea), population- and endoscopy-based screening programmes have been implemented.[13-15] These programmes have resulted in higher detection rates of early-stage gastric cancer, with substantially reduced mortality. In contrast, population-based endoscopic screening of asymptomatic individuals is not recommended in low incidence countries.[16,17] Since individuals with IM have an increased risk of gastric cancer, multidisciplinary European and UK endoscopy guidelines recommend that patients with IM as well as a family history of gastric cancer, incomplete-type IM or persistent *H. pylori*-associated gastritis should undergo endoscopic surveillance with guided biopsies every 3 years.

Table 1. Gene mutations associated with inherited predisposition to gastric cancer[6]

Gene mutation	Associated syndrome
APC	FAP
APC promoter 1B	GAPPS
CDH1, CTNNA1	HDGC
MLH1, MSH2, MSH6, PMS2	Lynch syndrome
SMAD4, BMPR1A	Juvenile polyposis syndrome
STK11	Peutz–Jeghers syndrome
TP53	Li–Fraumeni syndrome

FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; HDGC, hereditary diffuse gastric cancer.
Adapted with permission.[6]

Recommendations

- If a familial cancer syndrome is suspected, referral to a geneticist for assessment is recommended [V, A].
- Population-based endoscopic screening of asymptomatic individuals is only recommended in regions with a very high incidence of gastric cancer [V, B].

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Gastric cancer is often asymptomatic in the early stages. In advanced disease, common signs and symptoms include dysphagia, asthenia, indigestion, vomiting, weight loss, early satiety and/or iron deficiency anaemia. In many cases, however, these non-specific symptoms do not lead to urgent investigations. Overall, ~60% of people with gastric cancer are not eligible for curative treatment owing to late presentation or comorbidities.[18]

Endoscopic examination and forceps biopsies are the gold standard method for diagnosing gastric cancer. Multiple (5-8) biopsies should be carried out to provide adequately sized material for histological and molecular interpretation, especially in the setting of ulcerated lesions.[19,20] Details of the mucosal surface can be evaluated by narrow-band imaging or chromoendoscopy in combination with magnifying endoscopy. Endoscopic ultrasonography (EUS) is also a helpful tool to identify infiltrated regions of the gastric wall.[21] Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) may also be used for diagnosis. Both procedures can deliver reliable staging information and can also be used to treat superficial lesions such as dysplasia or intramucosal carcinoma.[22]

Pathology

Approximately 90% of gastric cancers are adenocarcinomas (ACs). This Clinical Practice Guideline (CPG) does not apply to rarer gastric malignancies such as gastrointestinal stromal tumours, lymphomas and neuroendocrine tumours.

Based on macroscopic features, early gastric carcinomas are sub-classified into three main types according to the Endoscopic Classification Review Group (Paris classification): 0-I (protruded); 0-II (superficial); and 0-III (excavated).[23] Locally advanced gastric carcinomas are macroscopically sub-classified according to the Borrmann classification as polypoid/fungating without ulceration (type I), ulcerated with elevated borders and sharp margins (type II), ulcerated with diffuse infiltration at the base (type III) and diffusely infiltrative with thickening of the wall (type IV).[24]

There are several gastric cancer histopathological classification schemes. The most commonly used are the World Health Organization (WHO)[25] and Japanese Gastric Cancer Association[26] classifications, which are very similar, as well

as those proposed by Nakamura and colleagues[27] and Laurén, the latter of which recognises three main subtypes: intestinal, diffuse and mixed.[28] The WHO classification is widely used in Western countries and recognises five main histological subtypes: tubular, papillary, poorly cohesive (including signet ring cell and other subtypes), mucinous and mixed ACs.

Molecular biology

The recently identified molecular profiles of gastric cancer are important for better understanding gastric cancer subtypes and may also be useful for identifying clinically relevant biomarkers and new therapeutic targets. Intratumoural and intertumoural heterogeneity is a feature of gastric carcinoma which leads to diagnostic and therapeutic challenges.

The Cancer Genome Atlas (TCGA) research network identified four molecularly distinct gastric cancer subtypes: EBV positive, microsatellite instability-high (MSI-H), genomically stable (GS) and tumours with chromosomal instability (CIN).[4] Each subtype is enriched for selected molecular abnormalities, with some overlap. The CIN subtype is enriched for copy number changes in key receptor tyrosine kinase oncogenes such as *human epidermal growth factor receptor 2* (*HER2*), *epidermal growth factor receptor* (*EGFR*), *fibroblast growth factor receptor 2 (FGFR2)* and *MET*. Other genomic classifications, such as the Asian Cancer Research Group subtyping, show some overlap with TCGA classification.[29]

Based on positive phase III trial data, HER2 status and programmed death-ligand 1 (PD-L1) combined positive score (CPS) should be evaluated in patients with metastatic gastric cancer to tailor first-line treatment in combination with chemotherapy (ChT) [see the table of ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) scores for further details, Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.07.004].[30,31] Patients with HER2-overexpressing gastric cancer [HER2 immunohistochemistry (IHC) score 3+ or HER2 IHC 2+ and FISH positive] benefit from treatment with the anti-HER2 antibody trastuzumab in addition to standard platinum–fluoropyrimidine ChT.[30,32] The prevalence of HER2 overexpression is 10%-20%, with higher prevalence in proximal/OGJ cancers and in the intestinal subtype according to Laurén.[30,32,33] Efficacy of HER2-targeted treatment is hampered by the intratumoural heterogeneity of HER2 expression. Therefore, quantitative reporting of the proportion of tumour cells staining positive for HER2 by IHC and the gene amplification ratio (if *in situ* hybridisation was carried out, especially in IHC 2+ patients) have been suggested.[33]

Emerging data from clinical trials suggest that immunotherapies such as programmed cell death protein 1 (PD-1) inhibitors demonstrate efficacy in gastric cancer. Evaluation of PD-L1 expression in patients with gastric cancer using CPS has been proposed, where a cut-off $\geq$1 would indicate positive PD-L1 expression; the prevalence of PD-L1 CPS $\geq$1 tumours is between 50% and 60%.[34,35] A CPS cut-off $\geq$5 represents a validated threshold for overall survival (OS) benefit of nivolumab given in addition to standard platinum–fluoropyrimidine first-line ChT.[31] Different antibodies for staining of PD-L1 in gastric cancer are used. In a recent study, PD-L1 22C3 and 28-8 pharmDx assays, both tested on the same platform (hardware), were highly comparable at CPS cut-offs of 1, 10 and 50, providing evidence for the potential interchangeability of the two PD-L1 assays in gastric cancer.[36] These results, however, were not confirmed in another study, which suggested that scoring PD-L1 CPS with the 28-8 assay may result in higher PD-L1 scores and a higher proportion of PD-L1 positivity compared with the 22C3 and other assays. Until stronger evidence of inter-assay concordance is found, caution should be taken when treating the assays as equivalent.[37]

MSI-H/mismatch repair deficiency (dMMR) are associated with better prognosis in localised stages of gastric cancer.[38] There is an ongoing debate on whether microsatellite instability (MSI)/mismatch repair (MMR) status should be used in order to tailor peri-operative ChT.[39,40] As MSI-H/dMMR are associated with a high response rate and improved benefit from immunotherapy compared with ChT in stage IV gastric cancer,[41] MSI/MMR status should be assessed for patients with locally advanced and unresectable or metastatic gastric cancer to tailor treatment accordingly.[32]

Other molecular markers, such as *FGFR2* amplification/overexpression, *MET* amplification, claudin-18.2 overexpression and EBV,[32] are being investigated and their validation as predictive biomarkers in randomised controlled trials (RCTs) is awaited.

Recommendations

- Diagnosis should be made from multiple (5-8) endoscopic biopsies to guarantee an adequate representation of the tumour [IV, B].
- The histological diagnosis should be reported according to WHO criteria [V, B].
- HER2 expression by IHC and/or amplification by *in situ* hybridisation [I, A; ESCAT score: I-A], PD-L1 by IHC according to CPS [I, A] and MSI-H/dMMR [II, A; ESCAT score: I-B] are validated predictive biomarkers for drug therapy.

STAGING AND RISK ASSESSMENT

Careful tumour staging is essential to ensure patients are appropriately selected for treatment interventions. The recommended initial staging investigations are detailed in Table 2.

The following characteristics are frequently demonstrated in malignant lymph nodes detected on computed tomography (CT)[42]:

- Short axis diameter 6-8 mm in perigastric lymph nodes
- Round shape
- Central necrosis

- Loss of the fatty hilum
- Heterogeneous or high enhancement

Nevertheless, the sensitivity of CT for lymph node staging is variable (62.5%-91.9% on systematic review[42]) and global consensus is lacking on specific diagnostic criteria.

EUS is more sensitive for N staging compared with CT (91% versus 77%, respectively). Additionally, for T1 staging, the sensitivity for EUS (82%) is higher than that for multidetector CT (41%); however, both EUS and CT show limited specificity (49% and 63%, respectively).[43] [^{18}F]2-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)—CT imaging may improve staging by detecting involved lymph nodes or metastatic disease; however, FDG—PET may not be informative in patients with mucinous or diffuse tumours due to lower tracer uptake.[44] Therefore, FDG—PET—CT is not routinely recommended for staging of gastric cancer.

Laparoscopy and peritoneal washings for malignant cells are recommended in all stage IB-III gastric cancers which are considered potentially resectable, to exclude radiologically and macroscopically occult peritoneal metastatic disease. The benefit is greater for patients with T3/T4 disease and poorly cohesive tumours.[44] The accuracy for detection of peritoneal metastases is good, with overall sensitivity of 84.6% and specificity of 100%.[45] Peritoneal metastases should be documented according to the Peritoneal Carcinomatosis Index (PCI).[46] A lower PCI score has been associated with better prognosis, and patients with limited peritoneal metastases might be appropriate candidates for cytoreductive surgery and hyperthermic intraperitoneal ChT (HIPEC); however, evidence is still limited and risks must be balanced carefully against uncertain benefits.[47-49] The prognosis of patients with positive lavage cytology (CY+) without gross peritoneal dissemination is poor. The survival benefit of gastrectomy for these patients has not been established.[50,51] A retrospective analysis, however, indicated a better prognosis if CY+ can be converted to negative lavage cytology during neoadjuvant ChT.[52] The additional value of HIPEC needs to be established in ongoing clinical trials. Cases involving CY+ should be discussed in a multidisciplinary tumour board, weighing up the risks and potential benefit of surgery. Patients with CY+ peritoneal lavage should ideally be treated within a clinical trial.

Gastric cancer should be staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) 8th edition staging manual (see Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.annonc.2022.07.004).[53,54]

Patients should be tested for dihydropyrimidine dehydrogenase enzyme deficiency before starting cancer treatment with 5-fluorouracil (5-FU) given by infusion, or with the related medicines capecitabine and tegafur.[55]

Table 2. Diagnostic and staging investigations in gastric cancer.

Procedure	Purpose
FBC	Assess for iron deficiency anaemia
Renal and liver function	Assess renal and liver function to determine appropriate therapeutic options
Endoscopy and biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. HER2 status
CT of thorax + abdomen ± pelvis	Staging of tumour — to detect local/distant lymphadenopathy and metastatic disease or ascites
EUS	Accurate assessment of T and N stage in potentially operable tumours Determine the proximal and distal extent of tumour
Laparoscopy + washings	Exclude occult metastatic disease involving peritoneum/diaphragm
PET, if available	May improve detection of occult metastatic disease in some cases. Often negative in diffuse-type gastric cancer
Assessment of nutritional status	May detect relevant dietary and nutritional deficiencies in both localised and advanced disease settings

CT, computed tomography; EUS, endoscopic ultrasound; FBC, full blood count; HER2, human epidermal growth factor receptor 2; N, node; PET, positron emission tomography; T, tumour.

Recommendations

- Initial staging and risk assessment should include physical examination, full and differential blood count, liver and renal function tests, endoscopy and contrast-enhanced CT scan of the thorax, abdomen ± pelvis (Table 2) [V, A].
- FDG—PET—CT is not routinely recommended [III, C].
- Diagnostic laparoscopy and peritoneal washings for cytology are recommended for patients with resectable gastric cancer who are also candidates for perioperative ChT [III, B]. Patients with CY+ are uncertain candidates for curatively-intended surgical resection.
- The TNM stage should be recorded according to the 8th edition of the AJCC/UICC staging manual [IV, A].

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Multidisciplinary treatment planning before any treatment decision is mandatory. The core membership of the multidisciplinary team should include surgeons, medical and radiation oncologists, gastroenterologists, radiologists and pathologists, with dieticians and nurse specialists if available.[18] A proposed algorithm for the treatment of localised gastric cancer is shown in Figure 1.

Resection

Surgical resection of operable gastric cancer is potentially curative; however, most patients relapse following resection; therefore, combined modality therapies are standard for stage ≥IB disease.

Endoscopic resection. Endoscopic resection is recommended for very early gastric cancers (T1a) if they are clearly (i) confined to the mucosa, (ii) well-differentiated G1-2, (iii) ≤2 cm and (iv) non-ulcerated.[56] Expanded endoscopic resection criteria concerning size, depth of submucosal

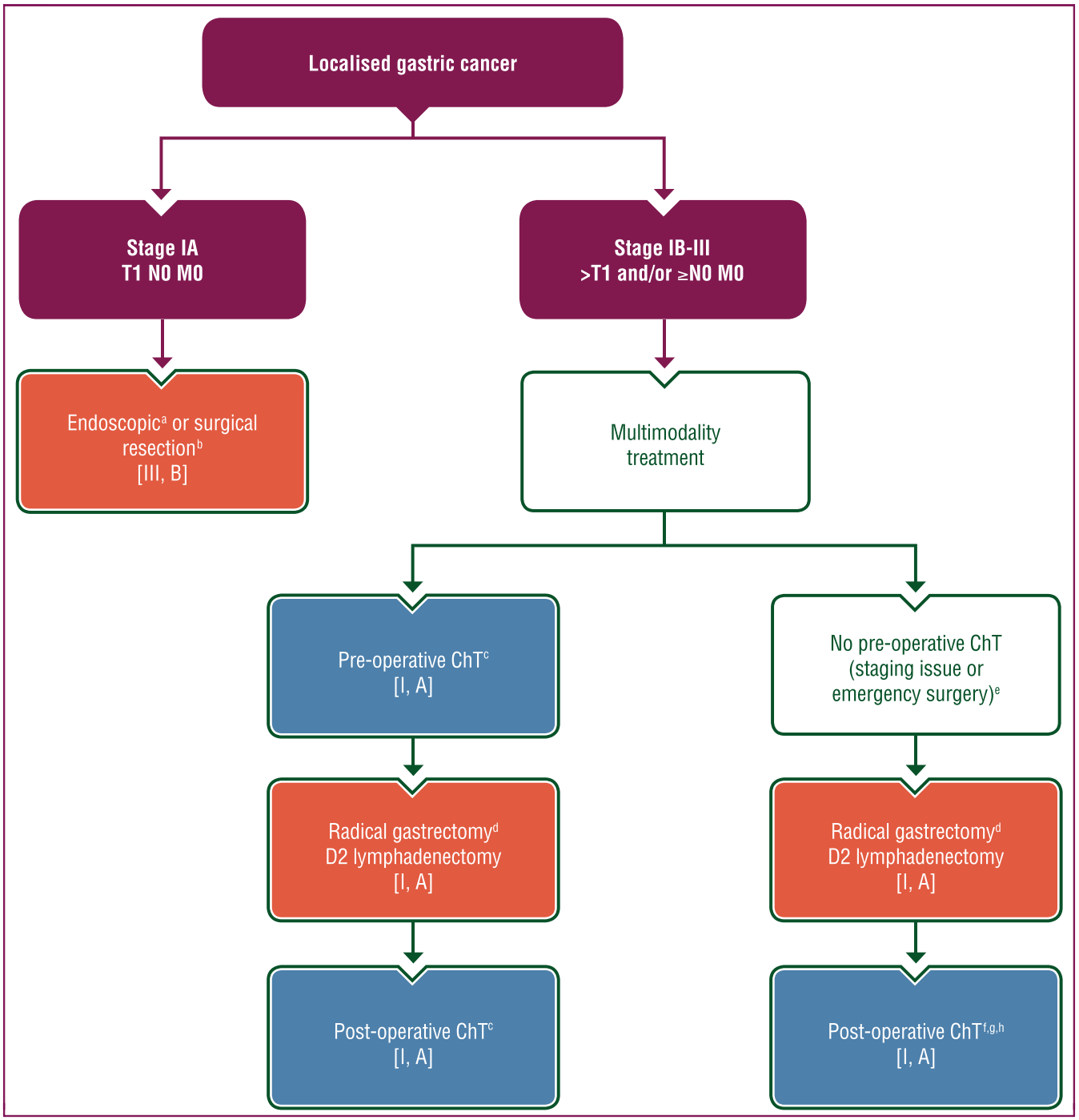

Figure 1. Treatment algorithm for localised gastric cancer.
Purple: general categories or stratification; red: surgery; white: other aspects of management; blue: systemic anticancer therapy.
ChT, chemotherapy; MSI-H, microsatellite instability-high; R1, microscopic tumour at the margin; RT, radiotherapy.
[a]Endoscopic resection indicated if: (i) confined to mucosa; (ii) well-differentiated G1-2; (iii) ≤2 cm; (iv) non-ulcerated. Endoscopic resection to be considered if no more than two expanded criteria are met according to Pimentel-Nunes et al.[56]
[b]Lymph node dissection for T1 tumours may be confined to perigastric lymph nodes and include local N2 nodes (D1+ lymphadenectomy, with variation in nodal groups dissected according to site of cancer).
[c]A triplet ChT regimen including a fluoropyrimidine, a platinum compound and docetaxel should be given when possible. Recommended treatment duration is 2-3 months pre- and post-operatively.
[d]Subtotal gastrectomy may be carried out if a macroscopic proximal margin of ≥3 cm can be achieved. For cancers of the poorly cohesive/diffuse subtype, a margin of ≥5 cm is advocated.
[e]For patients with stage ≥IB gastric cancer who have undergone surgery without administration of preoperative ChT. However, a peri-operative approach is preferred as adjuvant ChT is less well tolerated than neoadjuvant ChT and neoadjuvant therapy leads to tumour downsizing, allowing for more curative resections.
[f]A doublet ChT for a total duration of 6 months containing a fluoropyrimidine plus oxaliplatin or docetaxel is recommended.
[g]For patients with an R1 resection, adjuvant RT or ChT might be considered as an individual recommendation but is not standard.
[h]For patients with MSI-H gastric cancers who have undergone surgery, adjuvant ChT cannot be recommended.

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invasion and grade of differentiation [G1/G2-no ulceration, any diameter; G1/G2-ulceration, diameter ≤30 mm; G3-no ulceration, diameter ≤20 mm; SM1 tumours (<500 μm)] have been published and endoscopic resection might be considered for early gastric cancers with fewer than two expanded criteria.[57] As some of the criteria (grading, invasion of the submucosa) require an exact histopathological workup, endoscopic resection can primarily be carried out for diagnostic purposes and a resection with no tumour at the margin (R0) should be aimed for. Two forms of endoscopic resection are used in clinical practice: EMR is acceptable for lesions smaller than 10-15 mm with a very low probability of advanced histology (Paris 0-IIa)[23]; however, the European Society of Gastrointestinal Endoscopy (ESGE) recommends ESD as the treatment of choice for most gastric superficial neoplastic lesions.[56]

Endoscopic resection of early gastric cancer should be carried out *en bloc* and allow for a complete histological evaluation of the lateral and basal resection margins.

Surgery. The extent of surgical resection depends on tumour location, TNM category and histological subtype.

T1 tumours which do not meet the criteria for endoscopic resection require surgery, although less extensive surgery than other gastric cancers. Lymph node dissection for T1 tumours may be confined to perigastric lymph nodes and include local N2 nodes (D1+ lymphadenectomy, with variation in nodal groups dissected according to the site of cancer).

For stage IB-III disease, radical gastrectomy is indicated. A proximal margin of ≥3 cm is recommended for tumours with an expansive growth pattern (including intestinal histotypes) and ≥5 cm for those with an infiltrative growth pattern (including poorly cohesive/diffuse histotypes). When these rules cannot be satisfied, it is advisable to examine the whole thickness of proximal resection margin by frozen section. Subtotal gastrectomy can be selected when a satisfactory proximal resection margin can be obtained.[58-60]

The extent of nodal dissection accompanying radical gastrectomy has been extensively debated. D1 resection implies removal of the perigastric lymph nodes plus those along the left gastric artery. D1+ and D2 implies removal of additional lymph nodes along the proper or common hepatic artery, splenic artery or coeliac axis.[60] The current AJCC/UICC TNM (8th edition) classification recommends excision of a minimum of 15 lymph nodes for reliable staging.[53,54] In Asian countries, observational and randomised trials have demonstrated that D2 resection leads to superior outcomes compared with D1 resection.[60] In Western countries, patients with resectable disease should undergo D2 resection in specialised, high-volume centres with appropriate surgical expertise and post-operative care.[18] The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland has stated that an ideal oesophagogastric unit would consist of four to six surgeons each carrying out a minimum of 15-20 oesophagogastric resections per year, serving a population of 1-2 million. The German Cancer Society requires 30 gastric resections per year by two dedicated surgeons to qualify for certification as a gastric cancer centre.[18] The concept of 'enhanced recovery' encompasses all aspects of optimal peri-operative care for patients undergoing gastrectomy; guidance is provided by relevant Enhanced Recovery After Surgery® Society guidelines on this topic.[61]

Laparoscopic surgery has the potential benefits of decreased post-operative morbidity and reduced recovery time, with a lymph node yield comparable with open surgery.[62] Trials from East Asia in early and advanced (T2-T4a) gastric cancer have shown that laparoscopic distal gastrectomy is non-inferior with regard to oncological outcomes, with improved short-term outcomes. In Western countries, two small, randomised trials reported similar short-term outcomes between open versus laparoscopic gastrectomies, with non-inferior results regarding relapse-free survival. Today, laparotomy is an acceptable approach to achieve total or partial gastrectomy with D2 lymphadenectomy for gastric cancer. A laparoscopic approach may be selectively proposed in expert hands. Robot-assisted gastrectomy has shown similar oncological outcomes in terms of survival and lymph node yield compared with conventional laparoscopic gastrectomy. With technical advances, future gastric cancer surgery will most likely become increasingly minimally invasive and will probably take advantage of the rapidly developing robotic technologies.[32]

Peri-operative ChT

The UK-based phase III MAGIC trial demonstrated an improvement in 5-year survival from 23% to 36% [hazard ratio (HR) for death 0.75; 95% confidence interval (CI) 0.60-0.93; $P = 0.009$] in patients with resectable stage II and III gastric cancer treated with six cycles (three pre- and three post-operative) of epirubicin—cisplatin—5-FU (ECF) compared with surgery alone.[63] These data are supported by a similarly designed but smaller French phase III trial that evaluated a regimen of peri-operative cisplatin—5-FU, suggesting that anthracyclines may not be needed for optimal results.[64] Peri-operative ChT has therefore been adopted as the standard of care in Europe and many Western countries.

A German phase II-III study investigating eight cycles of peri-operative 5-FU—leucovorin—oxaliplatin—docetaxel (FLOT) versus six cycles ECF/epirubicin—cisplatin—capecitabine (ECX) reported a significant improvement in the primary endpoint of OS (median 50 months with FLOT versus 35 months with ECF/ECX; HR 0.77; 95% CI 0.63-0.94; $P = 0.012$), with no major concerns for toxicity.[65] Based on these data, the peri-operative use of FLOT (four cycles pre- and four cycles post-operative) should be regarded as standard of care for patients who are able to tolerate a triple cytotoxic drug regimen. For patients unfit for triplet ChT, a combination of a fluoropyrimidine with cisplatin or oxaliplatin is recommended.

In all relevant trials, the post-operative ChT regimen was the same as the preoperative regimen. Whether a different treatment regimen should be used after poor response to

neoadjuvant ChT is currently unknown. Also, the potential benefit of additional preoperative radiotherapy (RT) to peri-operative ChT is currently undefined and is being explored in clinical trials.

Adjuvant treatment

Adjuvant ChT. Historically, a greater benefit has been noted with adjuvant ChT in Asian studies, and uptake of adjuvant ChT in Europe for patients with resected gastric cancer remains limited due to a perceived lack of benefit and routine use of peri-operative ChT. Nevertheless, a large individual patient-level meta-analysis of adjuvant ChT in gastric cancer has confirmed a 6% absolute benefit in 5-year OS for 5-FU-based ChT compared with surgery alone (HR 0.82; 95% CI 0.76-0.90; $P < 0.001$) in all subgroups tested, including the group of Western patients.[66] A doublet ChT for a total duration of 6 months containing a fluoropyrimidine plus oxaliplatin or docetaxel is recommended. It is notable, however, that adjuvant ChT is less well tolerated than neoadjuvant ChT and neoadjuvant therapy leads to tumour downsizing, allowing for more curative resections; therefore, a peri-operative approach is preferred, if possible, so that more patients can benefit from systemic treatment even if the post-operative component of treatment is unable to be delivered.

Adjuvant chemoradiotherapy. Recently, the randomised phase III CRITICS trial concluded that patients undergoing ChT followed by surgery with curative intent have similar OS and progression-free survival (PFS), regardless of whether they receive ChT or chemoradiotherapy (CRT) after surgery.[67,68] Additionally, the Korean ARTIST and ARTIST II studies did not demonstrate a survival benefit for the addition of RT to adjuvant ChT in patients who had undergone gastrectomy with D2 lymphadenectomy.[69-71] Therefore, in patients who receive adequate surgery and have a high risk of relapse (e.g. positive nodal status), only adjuvant ChT should be given. The addition of post-operative CRT is not recommended following R0 resection, whereas for patients who have not received pre-operative ChT and have not undergone an appropriate D2 lymphadenectomy, adjuvant CRT can be considered.[72,73] In current post-operative CRT regimens, RT should preferably be given as a concomitant regimen of fluoropyrimidine-based CRT to a total dose of 45 Gy in 25 fractions of 1.8 Gy (five fractions per week) by intensity-modulated RT techniques.

In patients who have undergone gastrectomy with involved margins and are not candidates for more extended surgery, post-operative RT or CRT should be discussed by a multidisciplinary tumour board. Post-operative performance status, comorbidities and additional tumour risk factors, including nodal status, should be considered for decision making. A retrospective Dutch registry study suggested that adjuvant CRT was associated with a marginal improvement in survival compared with no further treatment in patients who had undergone a resection with microscopic tumour at the margin (R1).[74] As in the case of R0 resections, tumour recurrence after R1 resections is mainly systemic rather than local. The potential benefit of additive local post-operative therapies in R1-resected patients must be balanced against overall prognosis and therapy-specific morbidity and mortality. In conclusion, no specific and evidence-based recommendation can be made for patients with R1-resected gastric cancer.

MSI. Patients with MSI-H gastric cancers who have undergone radical resection have a better prognosis compared with patients with non-MSI-H subtypes of gastric cancer. There seems to be no added benefit of adjuvant ChT in this population, according to retrospective analyses of prospectively conducted RCTs.[38] Although evidence is limited, adjuvant (post-operative) ChT should be avoided in resected MSI-H gastric cancers.[38] Regarding peri-operative treatment of MSI-H disease, combinatorial results from older clinical trials that did not use taxanes did not show a benefit of peri-operative ChT for patients with MSI-H gastric cancer[38]; however, data from a small number of MSI-H patients treated with FLOT demonstrated better response rates than historical rates with platinum—5-FU.[75] Therefore, if a response is required to downstage an MSI-H tumour before surgery, FLOT is recommended. This does not, however, imply that FLOT is better than surgery alone as no control group was available to compare in the FLOT4 trial. In the future, it is likely that chemoimmunotherapy or immunotherapy alone[76] may be alternative treatment choices.

Recommendations

- Multidisciplinary treatment planning before any treatment decision is mandatory [IV, B].

Resection

- Endoscopic or surgical resection alone is appropriate for selected very early tumours (stage IA) [III, B].
- For stage IB-III gastric cancer, peri-operative therapy and radical gastrectomy is recommended [I, A].
- Patients should undergo D2 resection in a high-volume surgical centre [II, B].

Peri-operative ChT

- Peri-operative (pre- and post-operative) ChT is recommended for patients with stage $\geq$IB resectable gastric cancer [I, A].
- A triplet ChT regimen including a fluoropyrimidine, a platinum compound and docetaxel should be given when possible [I, A].
- Peri-operative use of FLOT is standard of care for patients who are able to tolerate a triple cytotoxic drug regimen [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A].
- For patients unfit for triplet ChT, a combination of a fluoropyrimidine with cisplatin or oxaliplatin is recommended [II, B].

Adjuvant treatment

- For patients with stage ≥IB gastric cancer who have undergone surgery without administration of preoperative ChT, adjuvant ChT is recommended [I, A].
- For patients who have undergone surgery with clear margins (R0), post-operative RT has no added benefit and should not be given [I, D].
- For patients undergoing peri- or post-operative ChT, the addition of post-operative RT has no added benefit and should not be given [I, E].
- For patients who have not received preoperative ChT and have not undergone an appropriate D2 lymphadenectomy, adjuvant CRT can be considered [I, C].
- For patients who have undergone surgery with involved margins (R1), adjuvant RT or CRT might be considered as an individual recommendation, but is not standard [IV, C].
- For patients with MSI-H gastric cancer who have undergone curative surgery, adjuvant ChT cannot be recommended [IV, D], but if a response is required to downstage a tumour before surgery, FLOT is recommended.

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

Locally advanced unresectable or metastatic gastric cancer has a poor prognosis; survival in clinical trials assessing the value of ChT has historically been <1 year in non-Asian countries.[32] ChT improves survival in comparison to best supportive care, and combination ChT improves survival compared with single-agent 5-FU.[77] Additionally, the use of nivolumab with ChT has recently improved survival for patients with advanced/metastatic disease[31] and trastuzumab—ChT has improved survival in patients with HER2-positive advanced/metastatic disease.[30]

First-line ChT, targeted therapy and immunotherapy

A proposed algorithm for the first-line treatment of advanced and metastatic gastric cancer is shown in Figure 2.

ChT. Standard first-line ChT for gastric cancer is a platinum—fluoropyrimidine doublet. Oxaliplatin and cisplatin are the most commonly used platinum drugs, whereas fluoropyrimidines may be administered as an infusion (5-FU) or as oral treatment [capecitabine or tegafur—gimeracil—oteracil (S-1)]. Cisplatin and oxaliplatin were shown to be equally effective in RCTs.[78,79] In older patients (aged >65 years), oxaliplatin has a superior safety profile and may be associated with improved survival.[79] Oral capecitabine is at least as effective as infused 5-FU. Infused 5-FU may be favoured when dysphagia is a problem. S-1 is commonly used in Asian patients.[80] In non-Asian populations, pharmacogenetic differences require altered dosing and reduce S-1 tolerability. For older or frail patients, results from the phase III GO-2 trial support dose-reduced oxaliplatin-based

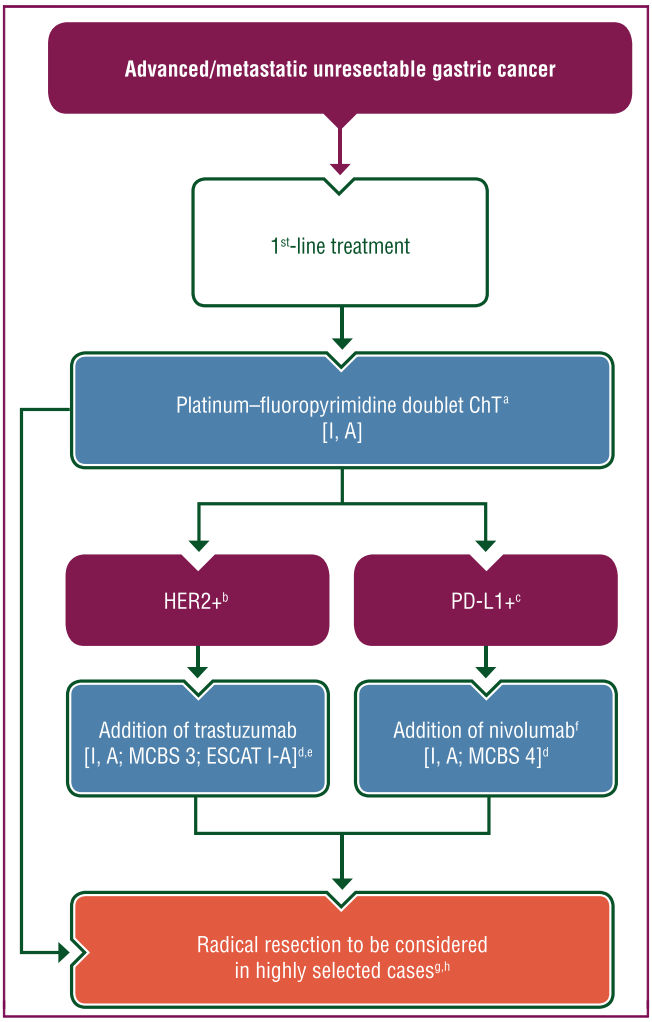

Figure 2. Treatment algorithm for first-line treatment of advanced/metastatic unresectable gastric cancer.
Purple: general categories or stratification; red: surgery; white: other aspects of management; blue: systemic anticancer therapy.
5-FU, 5-fluorouracil; ChT, chemotherapy; CPS, combined positive score; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PD-L1, programmed death-ligand 1; S-1, tegafur—gimeracil—oteracil.
[a]Recommended platinum compounds are oxaliplatin or cisplatin. Oxaliplatin is preferred, especially for older patients. Recommended fluoropyrimidines are intravenous 5-FU, oral capecitabine or oral S-1. Irinotecan—5-FU can be considered an alternative option for patients who do not tolerate platinum compounds.
[b]HER2 IHC 3+ or IHC 2+/FISH-positive.
[c]PD-L1 status should be reported according to the CPS.
[d]ESMO-MCBS v1.1[112] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[111]
[f]Nivolumab—ChT is recommended for advanced, untreated gastric cancer with a PD-L1 CPS score ≥5 (FDA approved without PD-L1 CPS restriction, EMA approved for PD-L1 CPS ≥5).
[g]Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms.
[h]Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT.

ChT, demonstrating lower toxicity and comparable survival outcomes versus standard dosing.[81]

The addition of a taxane to a platinum doublet increased radiological response rates and OS in one older phase III randomised trial, but was associated with substantially increased toxicity.[82] Phase II trials evaluating taxane-based triplets showed higher toxicity but did not provide level I evidence of higher efficacy.[83-85] In the large phase III JCOG1013 study, Japanese patients with advanced gastric cancer were randomly assigned to receive either cisplatin—S-1 or cisplatin—S-1—docetaxel.[86] No differences in radiological response rate, PFS or OS were demonstrated between the treatment groups. Due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens, first-line taxane-based triplet ChT is not recommended as a standard approach.

Irinotecan—5-FU has been evaluated in comparison to cisplatin—5-FU and to ECX in randomised phase III trials and demonstrated superior time to treatment failure compared with ECX (HR 0.77; 95% CI 0.63-0.93; log-rank $P = 0.008$). Irinotecan—5-FU can be considered an alternative option for patients who do not tolerate platinum compounds.[87,88]

HER2-positive tumours. Adding trastuzumab to ChT is recommended for patients with HER2-overexpressing (HER2 IHC 3+ or IHC 2+/FISH positive) gastric cancer, based on the phase III ToGA study, which demonstrated higher response rates and longer OS (HR 0.74; 95% CI 0.60-0.91; $P = 0.0046$) with trastuzumab—ChT compared with ChT alone; additional toxicity was low and manageable.[30]

Immunotherapy. The phase III CheckMate 649 study evaluated the addition of nivolumab to ChT (either capecitabine—oxaliplatin or 5-FU—leucovorin—oxaliplatin) in patients with treatment-naive gastric, OGJ or oesophageal cancer.[31] Nivolumab—ChT resulted in significant improvements in OS (HR 0.71; 98.4% CI 0.59-0.86; $P < 0.0001$) and PFS (HR 0.68; 98% CI 0.56-0.81; $P < 0.0001$) versus ChT alone in patients with a PD-L1 CPS $\geq$5 (minimum follow-up 12.1 months).

In the phase III KEYNOTE-062 trial, pembrolizumab monotherapy was non-inferior to cisplatin—fluoropyrimidine ChT for OS in patients with PD-L1 CPS $\geq$1, but was associated with lower response rates and inferior PFS, and is therefore not recommended.[89] Pembrolizumab is approved for patients with AC of the oesophagus and OGJ expressing PD-L1 CPS $\geq$10, based on the results of the phase III KEYNOTE-590 trial[90]; however, KEYNOTE-590 included relatively few patients with AC.

Patients with MSI-H gastric cancer have high response rates and excellent long-term outcomes when treated with anti-PD-1 monotherapy.[41,91]

Second- and later-line treatment

A proposed algorithm for the second-line treatment of advanced and metastatic gastric cancer is shown in Figure 3. In previously treated gastric cancer, treatment options often follow clinical trials which have enrolled patients with gastric and OGJ cancer. The standard ChT options are paclitaxel, docetaxel and irinotecan, which have equivalent efficacy but different toxicity profiles.[77,92] 5-FU—leucovorin—irinotecan (FOLFIRI) is also used, but there are limited data to support this regimen.[88] The addition of the anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, ramucirumab, to paclitaxel improves overall response rate (ORR), PFS and OS, based on the results of the phase III RAINBOW trial.[93] In the phase III REGARD trial, ramucirumab monotherapy demonstrated limited response rates but improved OS compared with placebo.[94] In the phase III KEYNOTE-061 trial, pembrolizumab monotherapy did not improve survival compared with ChT in second-line gastroesophageal cancer,[95] but an exploratory subgroup analysis suggested a benefit in advanced MSI-H gastric cancer.[41] In the phase II KEYNOTE-158 trial, pembrolizumab monotherapy was highly active in patients with previously treated advanced MSI-H gastric cancer, demonstrating an ORR of 45.8% and a median PFS of 11 months, with median OS and median duration of response not yet reached.[96] Such results have never been reported with ChT. If available, pembrolizumab should therefore be the preferred treatment in this setting.

Trials evaluating second-line trastuzumab combinations, lapatinib and trastuzumab emtansine have been negative in patients with HER2-positive gastric cancer who have progressed on trastuzumab[32]; however, a recent phase II Asian randomised trial evaluating the HER2-targeting antibody drug conjugate, trastuzumab deruxtecan, compared with ChT in HER2-positive pre-treated gastric cancer reported a survival benefit for trastuzumab deruxtecan-treated patients.[97] Confirmatory global trials have demonstrated comparable response rates in non-Asian populations.[98]

In the third-line setting for patients with gastric cancer, treatment with trifluridine—tipiracil has the strongest evidence base following the phase III TAGS trial.[99] Alternative treatments in chemorefractory gastric cancer include a taxane or irinotecan.[77] A proposed algorithm for the third-line treatment of advanced and metastatic gastric cancer is shown in Figure 4.

Surgery for metastatic gastric cancer

The randomised phase III REGATTA trial demonstrated that gastrectomy in addition to ChT without resection of metastases for oligometastatic gastric cancer did not improve survival compared with ChT alone.[100] The phase II AIO-FLOT3 trial reported favourable outcomes in patients with oligometastatic disease after FLOT induction followed by gastrectomy plus resection of the metastatic site, but this study was not randomised.[101] The potential benefit of surgery in oligometastatic gastric cancer is currently being explored in two ongoing randomised phase III trials [RENAISSANCE (NCT0257836) and SURGIGAST (NCT03042169)], but at the present time, data to support routine resection or ablation of oligometastases are limited.[102] In case of limited peritoneal carcinomatosis, addition of HIPEC to

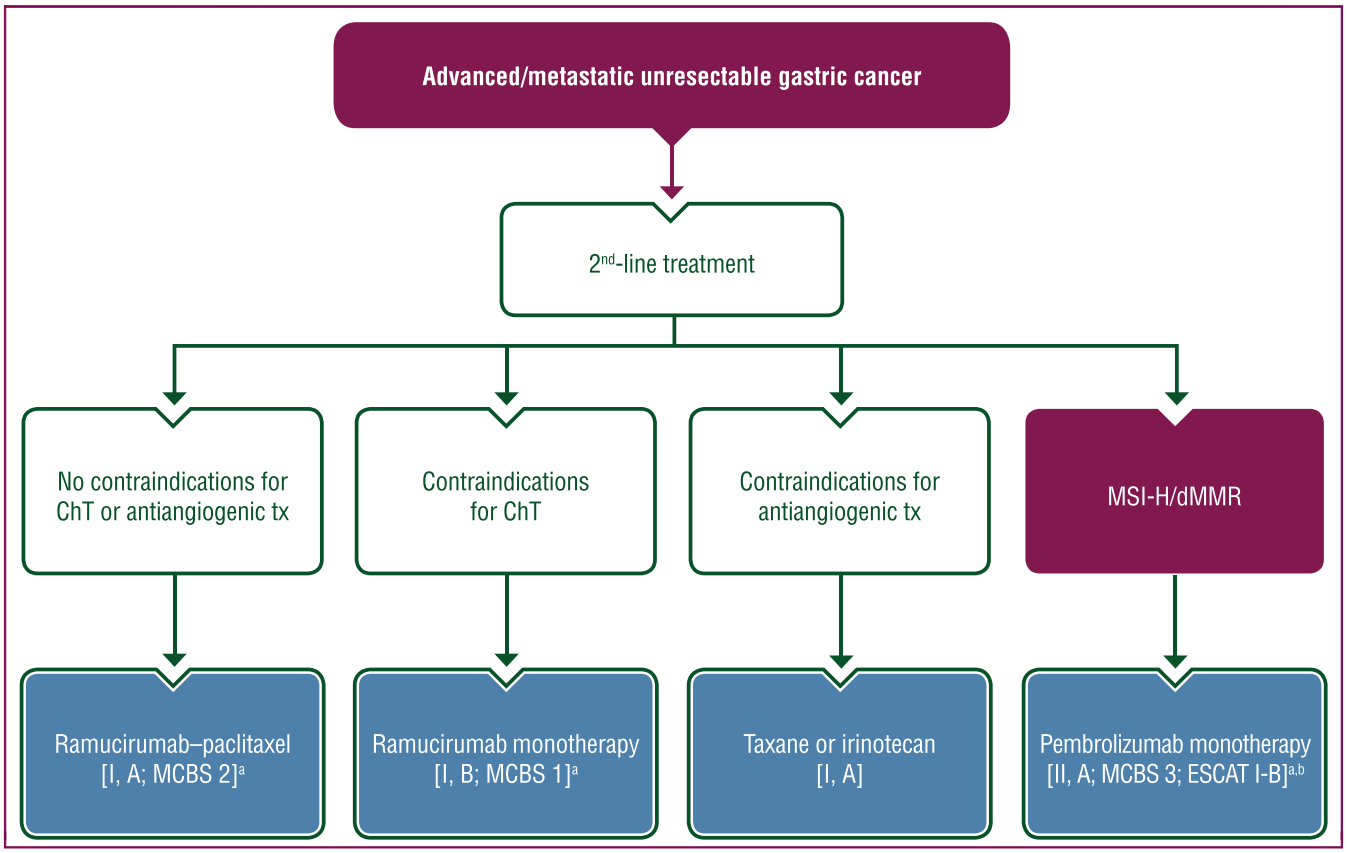

Figure 3. Treatment algorithm for second-line treatment of advanced/metastatic unresectable gastric cancer.
Purple: general categories or stratification; white: other aspects of management; blue: systemic anticancer therapy.
ChT, chemotherapy; dMMR, mismatch repair deficient; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high; tx, treatment.
[a]ESMO-MCBS v1.1[112] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[111]

cytoreduction has been reported to be safe and may be associated with some improved oncological outcomes, but is yet to be confirmed in larger trials.[47-49] Peri-operative ChT with or without HIPEC may also be a strategy for patients with CY+ without gross peritoneal metastases, but the prognostic benefit of gastrectomy in this situation is currently not established.[50-52]

Pressurised intraperitoneal aerosol ChT (PIPAC) is a recently developed technique that allows homogeneous locoregional application of intraperitoneal ChT during a laparoscopic procedure. This technique could offer a valuable alternative for patients with unresectable peritoneal disease. Results from the randomised, controlled, multicentre phase II PIPAC EstoK 01 trial evaluating PIPAC in addition to intravenous ChT are awaited.[103]

Supportive care and nutrition

Supportive care is critical for the well-being of patients with gastric cancer. A recent randomised phase III trial demonstrated an increase in survival of 3 months for patients who received multidisciplinary supportive care compared with those who received standard ChT.[104] Supportive care includes both palliation of symptoms and nutritional support.

Weight loss is multifactorial and may be due to obstruction of the gastrointestinal tract, anorexia, malabsorption or hypermetabolism. In clinical trial datasets, weight loss of $\geq$10% before treatment and $\geq$3% during the first cycle of treatment is associated with reduced OS.[105] Dysphagia due to proximal gastric tumours may be relieved by RT or stent placement.[106] Single-dose brachytherapy may be a preferred option even after external RT, since it provides better long-term relief of dysphagia with fewer complications than metal stent placement. Stenting is warranted in patients with severe dysphagia, especially with short life expectancy, since the effect on swallowing is immediate, whereas RT (both brachytherapy and external beam) takes around 4-6 weeks for relief of dysphagia.[107] Options for patients who are not suitable for RT or stent placement include enteral feeding using nasojejunal or nasogastric tubes, or placement of percutaneous feeding tubes. Distal gastric outlet obstruction may be treated by pyloric stenting or bypass surgery.

Recommendations

First-line ChT, targeted therapy and immunotherapy

- First-line ChT with a platinum and fluoropyrimidine is recommended. Oxaliplatin is preferred, especially for

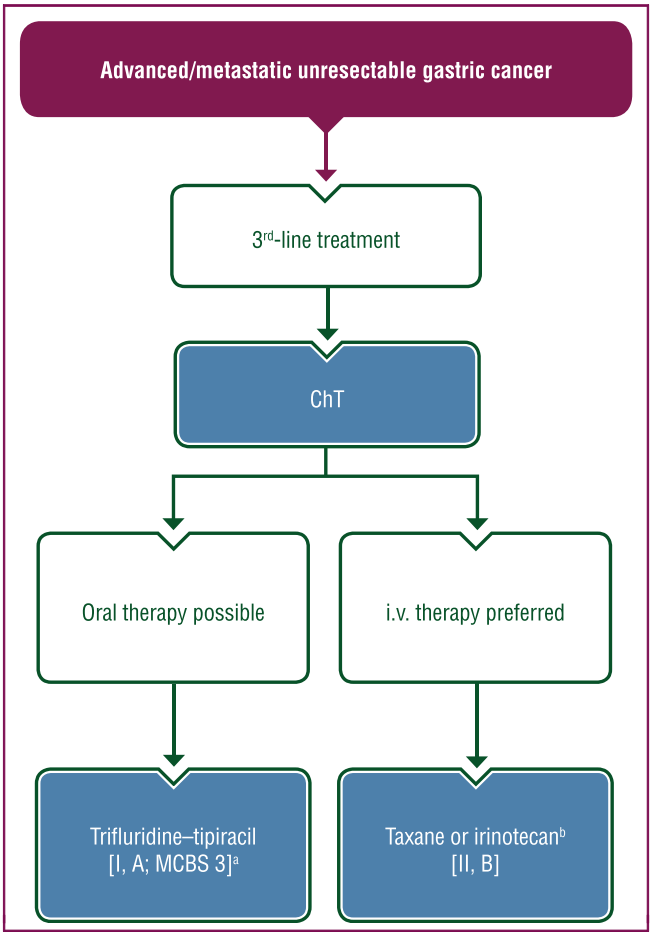

Figure 4. Treatment algorithm for third-line treatment of advanced/metastatic unresectable gastric cancer.
Purple: general categories or stratification; white: other aspects of management; blue: systemic anticancer therapy.
ChT, chemotherapy; i.v., intravenous; MCBS, ESMO-Magnitude of Clinical Benefit Scale.
[a]ESMO-MCBS v1.1[112] was used to calculate scores for therapies/indications approved by the European Medicines Agency or Food and Drug Administration. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]If not given previously for advanced/metastatic disease.

older patients [I, A]. S-1 is commonly used in Asian patients [I, A].

- Due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens, first-line taxane-based triplet ChT is not recommended as a standard approach [I, C].
- Irinotecan—5-FU can be considered an alternative option for patients who do not tolerate platinum compounds [II, B].
- Trastuzumab—ChT is recommended in patients with HER2-positive tumours [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A].
- Nivolumab—ChT is recommended for advanced, untreated gastric, OGJ and oesophageal cancer with a PD-L1 CPS $\geq$5 [I, A; ESMO-MCBS v1.1 score: 4].
- Pembrolizumab is approved for patients with AC of the oesophagus and OGJ expressing PD-L1 CPS $\geq$10 [II, C; ESMO-MCBS v1.1 score: 4].

Second- and later-line treatment

- Ramucirumab—paclitaxel is recommended for second-line treatment of gastric cancer [I, A; ESMO-MCBS v1.1 score: 2]. Ramucirumab monotherapy is also an option [I, B; ESMO-MCBS v1.1 score: 1].
- Where ramucirumab is not available, paclitaxel, docetaxel or irinotecan monotherapy [I, A] or FOLFIRI [II, B] are recommended.
- Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer [I, D], but trastuzumab deruxtecan may be considered [II, B; ESMO-MCBS v1.1 score: 4; Food and Drug Administration (FDA) approved, not EMA approved].
- Pembrolizumab is recommended for second-line treatment of patients with MSI-H/dMMR gastric cancer [II, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B].
- For patients previously treated with two lines of therapy, trifluridine—tipiracil is recommended [I, A; ESMO-MCBS v1.1 score: 3]. Alternative treatments include a taxane or irinotecan [II, B].

Surgery for metastatic gastric cancer

- Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms [I, D].
- Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT [V, C].

Supportive care and nutrition

- Care for patients with gastric cancer should include an early palliative care referral and nutritional support [I, A].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

In the setting of resectable gastric cancer, the complexity of treatment frequently induces symptoms that adversely affect health-related quality of life. Regular follow-up may allow investigation and treatment of symptoms, psychological support and early detection of recurrence, though there is no evidence that it improves survival outcomes. Follow-up should be tailored to the individual patient and stage of disease.[108] Dietary support is recommended, with attention to vitamin and mineral deficiencies.[109,110]

In the advanced disease setting, regular follow-up is recommended to detect symptoms of disease progression before significant clinical deterioration. If disease progression is suspected, then a clinical history, physical examination and directed blood tests should be carried out. Radiological investigations should be carried out in patients who are candidates for further cancer-specific therapies. For patients receiving cancer-specific therapies such as ChT, CT of the thorax/abdomen plus specific body regions of

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interest, if necessary, are typically recommended every 6-12 weeks in order to avoid futile therapy and to switch to alternative treatment options, if available.

The aggressive nature of gastric cancer and historically poor outcomes even in the setting of resectable disease mean that the concept of survivorship is only now beginning to evolve. Long-term implications, late effects of therapy and the psychosocial impact of treatment have been poorly studied to date.

Recommendations

- Regular follow-up is recommended for investigation and treatment of symptoms, psychological support and early detection of recurrence [III, B].
- Follow-up should be tailored to the individual patient and stage of disease [V, B].
- Dietary support is recommended with attention to vitamin and mineral deficiencies [V, B].
- In the advanced disease setting, regular follow-up is recommended to detect symptoms of disease progression before significant clinical deterioration [IV, B].
- Radiological investigations, specifically CT of the thorax and abdomen, should be carried out every 6-12 weeks in patients who are candidates for further cancer-specific therapies [IV, B].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESCAT table with ESCAT scores is included in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.07.004. ESCAT scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[111] An ESMO-MCBS table with ESMO-MCBS scores is included in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.07.004. ESMO-MCBS v1.1[112] was used to calculate scores for therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA or other regulatory body approval statuses of new therapies/indications are reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.07.004.[113,114] Statements without grading were considered justified standard clinical practice by the authors. Future updates to this CPG will be published on esmo.org as a Living Guideline version or an eUpdate, to be made available at: https://www.esmo.org/guidelines/gastrointestinal-cancers/gastric-cancer.

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