Annals of Oncology 27 (Supplement 5): v38–v49, 2016
doi:10.1093/annonc/mdw350

Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Almost one million (951 600) new cases of gastric cancer were diagnosed globally in 2012, resulting in ~723 100 deaths [1]. Of these ~140 000 cases and ~107 000 deaths occurred in Europe [2]. Gastric cancer displays significant global variation in incidence; the highest rates are seen in Eastern Asia, Eastern Europe and South America, with lower rates in North America and Western Europe. 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-prevalence countries have also become apparent. This is epidemiologically distinct from the relative increase in tumours of the gastroesophageal junction, which are discussed in a separate guideline document.

Risk factors for gastric cancer include male gender (incidence is twice as high), *Helicobacter pylori* infection, tobacco use, atrophic gastritis, partial gastrectomy and Ménétrier's disease [3]. Regional variation in gastric cancer risk factors influences the most common anatomical subsites of disease. Distal or antral gastric cancers that are associated with *H. pylori* infection, alcohol use, high-salt diet, processed meat and low fruit and vegetable intake are more common in East Asia. Tumours of the proximal stomach (cardia) are associated with obesity, and tumours of the gastroesophageal junction are associated with reflux and Barrett's oesophagus and are more common in non-Asian countries [4]. Gastric cancer demonstrates familial aggregation in ~10% of cases, and an inherited genetic predisposition is found in a small proportion of cases (~1%–3%); relevant syndromes include hereditary non-polyposis colorectal cancer, familial adenomatous polyposis colorectal cancer, hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) and Peutz Jegher's syndrome [5, 6]. If a familial cancer syndrome such as HDGC is suspected, referral to a geneticist for assessment is recommended based on international clinical guidelines [V, B] [7].

diagnosis and pathology

Recommendation: Diagnosis should be made from a gastroscopic or surgical biopsy reviewed by an experienced pathologist, and histology should be reported according to the World Health Organisation (WHO) criteria [IV, C].

Patients in Asian countries are frequently diagnosed with gastric cancer at an earlier stage than in non-Asian countries. In Japan and Korea, where the incidence of gastric cancer is much higher than in Western countries, screening for gastric cancer is routine. In patients who develop symptoms from an underlying gastric cancer, these commonly include weight loss, dysphagia, dyspepsia, vomiting, early satiety and/or iron deficiency anaemia.

Ninety per cent of gastric cancers are adenocarcinomas (ACs), and these are subdivided according to histological appearances into diffuse (undifferentiated) and intestinal (well-differentiated) types (Lauren classification). Recent large-scale studies in molecular subtyping have defined four subtypes of gastric cancer across genomic, transcriptomic and proteomic levels; however, these subtypes do not yet have any impact on treatment [8]. These Clinical Practice Guidelines do not apply to rarer gastric malignancies such as gastrointestinal stromal tumours (GISTs), lymphomas and neuroendocrine tumours.

If a diagnosis of gastric cancer is suspected, diagnosis should be made from a gastroscopic or surgical biopsy reviewed by an experienced pathologist, and histology should be reported according to the WHO criteria [IV, C].

staging and risk assessment

Recommendation: Initial staging and risk assessment should include physical examination, blood count and differential, liver and renal function tests, endoscopy and contrast-enhanced computed tomography (CT) scan of the thorax, abdomen ± pelvis (Table 1) *[V, A]. Laparoscopy is recommended for patients with*

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†Approved by the ESMO Guidelines Committee: August 2016.

Table 1. Diagnostic and staging investigations in gastric cancer

Procedure	Purpose
Full blood count	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 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

CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography

resectable gastric cancer [III, B]. Multidisciplinary treatment planning before any treatment is mandatory [IV, C].

Careful tumour staging is essential to ensure that patients are appropriately selected for treatment interventions. The recommended initial staging investigations are detailed in Table 1.

Identification of malignant lymph nodes on CT: The following characteristics are frequently demonstrated in malignant lymph nodes detected on CT:

1) Short-axis diameter 6–8 mm in perigastric lymph nodes;
2) round shape;
3) central necrosis and
4) heterogeneous or high enhancement [9–11].

However, the sensitivity of CT for lymph node staging is variable (62.5%–91.9% on systematic review), and global consensus is lacking on specific diagnostic criteria [12].

Endoscopic ultrasound (EUS) is helpful in determining the proximal and distal extent of the tumour and provides further assessment of the T and N stage; however, it is less useful in antral tumours [III, B]. EUS is more consistently accurate than CT for the diagnosis of malignant lymph nodes: patterns associated with malignancy on EUS include hypoechogenicity, round shape, smooth, distinct margin and size >1 cm [13, 14]. Positron emission tomography (PET)-CT imaging may improve staging by detecting involved lymph nodes or metastatic disease. However, PET may not be informative in patients with mucinous or diffuse tumours [III, B].

Laparoscopy ± peritoneal washings for malignant cells is recommended in all stage IB–III gastric cancers which are considered potentially resectable, to exclude radiologically occult metastatic disease; the benefit may be greater for patients with T3/T4 disease [III, B] [15, 16].

The TNM stage should be recorded according to the latest edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) guidelines and staging manual [17, 18] (Tables 2 and 3).

treatment planning

Multidisciplinary treatment planning before any treatment decision is mandatory. The core membership of the multidisciplinary team should include surgeons, medical and radiation oncologists, radiologists and pathologists, with other members as available [IV, C].

management of local/locoregional disease

Recommendation: Endoscopic resection is appropriate for selected very early tumours [III, B]. For stage IB–III gastric cancer, radical gastrectomy is indicated and perioperative therapy is recommended for these patients [I, A]. Medically fit patients should undergo D2 resections in high-volume surgical centres [I, B].

surgery

Surgical resection of gastric cancer, specifically at early stages, is potentially curative. However, the majority of patients still relapse following resection, and therefore, combined modality therapies are standard for ≥ Stage IB disease.

The extent of resection is determined by the preoperative stage.

Endoscopic resection may be carried out for very early gastric cancers (T1a) if they are clearly confined to the mucosa, well-differentiated, ≤2 cm and non-ulcerated [III, B]. The associated lymph node metastatic risk in this group is virtually zero. Two forms of endoscopic resection are practised; endoscopic mucosal resection (EMR) is acceptable for lesions smaller than 10–15 mm with a very low probability of advanced histology (Paris 0–IIa) [19]. However, European Society of Gastrointestinal Endoscopy Guidelines recommend endoscopic submucosal dissection (ESD) as the treatment of choice for most gastric superficial neoplastic lesions [IV, B] [19].

T1 tumours that do not meet the above mentioned criteria for endoscopic resection require surgery, although less extensive surgery than other gastric cancers (see below). Lymph node dissection for T1 tumours may be confined to perigastric lymph nodes and include local N2 nodes (D1+, with variation in nodal groups dissected according to the site of cancer). Sentinel lymph node mapping may further modify these approaches.

For stage IB–III gastric cancer, radical gastrectomy is indicated. Subtotal gastrectomy may be carried out if a macroscopic proximal margin of 5 cm can be achieved between the tumour and the gastroesophageal junction. For diffuse cancers, a margin of 8 cm is advocated. Otherwise, a total gastrectomy is indicated [III, A]. Perioperative therapy is recommended for these patients.

The extent of nodal dissection accompanying radical gastrectomy has been extensively debated. D1 resection implies the removal of the perigastric lymph nodes and D2 implies removal of perigastric lymph nodes plus those along the left gastric, common hepatic and splenic arteries and the coeliac axis (see

Table 2. TNM staging of gastric cancer as per AJCC, 7th edition [17, 18]

Primary tumour (T)		Regional lymph nodes (N)		Distant metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph node(s) cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M1	Distant metastasis or positive peritoneal cytology
Tis	Carcinoma *in situ*: intraepithelial tumour without invasion of the lamina propria	N1	Metastasis in 1–2 regional lymph nodes		
T1a	Tumour invades the lamina propria or the muscularis mucosae	N2	Metastasis in 3–6 regional lymph nodes		
T1b	Tumour invades the submucosa	N3	Metastasis in 7 or more regional lymph nodes		
T2	Tumour invades the muscularis propria	N3a	Metastasis in 7–15 regional lymph nodes		
T3	Tumour penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures[a]	N3b	Metastasis in 16 or more regional lymph nodes		
T4	Tumour invades the serosa (visceral peritoneum) or adjacent structures[b]				
T4a	Tumour invades the serosa (visceral peritoneum)				
T4b	Tumour invades adjacent structures[b]				

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[a]T3 tumours also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures.

[b]Adjacent structures include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum.

Table 3. Anatomic stage/prognostic groups as per AJCC, 7th edition [17, 18]

Stage grouping	T stage	N stage	M stage
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0–1	M0
	T4a	N2	M0
	T3a	N3	M0
Stage IIIC	T4b	N2–3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

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Figure 1) [20]. The current UICC/AJCC TNM (seventh edition) classification recommends excision of a minimum of 15 lymph nodes to allow reliable staging. In Asian countries, experience from observational and randomised trials demonstrates that D2 dissection leads to superior outcomes compared with D1 resection [II, B]. In Western countries, a Dutch [21], an MRC [22] and a recent Italian [23] trial failed to demonstrate any initial survival advantage with D2 resection, although the Italian study suggested a trend towards a benefit in disease-specific survival for patients with T2–T4 lymph node-positive cancers treated with D2 resection [23]. Long-term (15-year) follow-up from the Dutch trial demonstrated fewer locoregional recurrences and gastric cancer-related deaths with D2 resection; however, this was offset slightly by an increase in postoperative mortality and morbidity [24]. A recent review of the quality of lymph node dissection in the same study also suggests that non-compliance in the D2 resection group may have obscured a significant difference in survival between the randomised groups; this has also been suggested for the recent Italian study [23].

Consensus opinion is that, in Western countries, medically fit patients should undergo D2 dissection that is carried out in specialised, high-volume centres with appropriate surgical expertise and postoperative care [I, B] [25–27]. As a result, perioperative outcome has become standardised with morbidity and mortality rates of 15% and 3.0%, respectively [23, 28]. The concept of 'enhanced recovery' encompasses all aspects of optimal perioperative care for the patient undergoing gastrectomy; guidance is provided by relevant Enhanced Recovery After Surgery (ERAS®) Society guidelines on this topic [29].

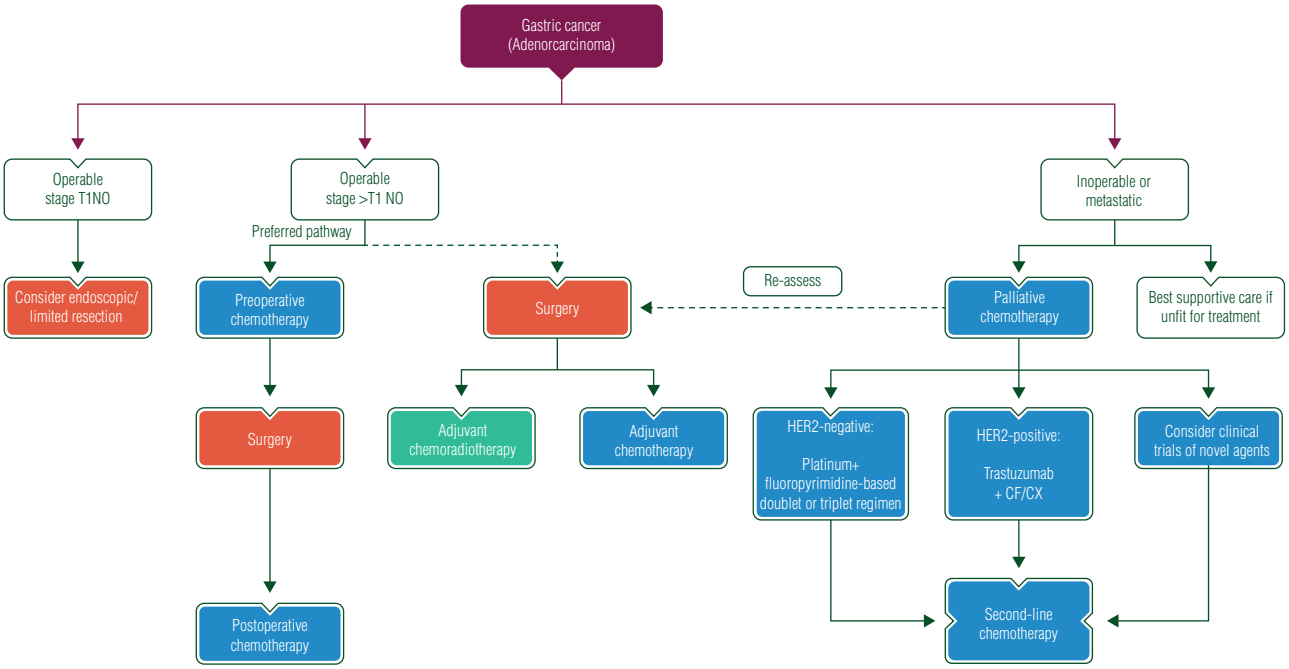

Figure 1. Gastric cancer treatment algorithm.
HER2, human epidermal growth factor receptor 2; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine

Laparoscopic surgery has the potential benefit of decreased postoperative morbidity and reduced recovery time. Although concerns existed regarding the possibility of a reduced nodal harvest with a laparoscopic approach, a recent meta-analysis suggests that lymph node yields are comparable for both approaches [30]. Trials from the Far East have reported equivalent results to open surgery for distal gastrectomy, but there remain some technical issues particularly for anastomosis for total gastrectomy [31, 32]. Laparoscopic surgery is becoming one of the recommended options for patients with early gastric cancer; however, it remains to be shown whether laparoscopic surgery can achieve the same results as open surgery in gastric cancers requiring D2 lymphadenectomy. It may be that as techniques predicting lymph node involvement develop, those with negative nodes should be operated laparoscopically, whereas those with predicted positive nodes would require open surgery.

perioperative chemotherapy

Recommendation: Perioperative (pre- and postoperative) chemotherapy with a platinum/fluoropyrimidine combination is recommended for patients with ≥Stage IB resectable gastric cancer [I, A].

The UK MRC MAGIC trial demonstrated an improvement in 5-year survival from 23% to 36% for patients with resectable stage II and III gastric cancers treated with six cycles (three pre- and three postoperative) of perioperative ECF chemotherapy [epirubicin, cisplatin and 5-fluorouracil (5-FU)] compared with surgery alone [33]. A subsequent French trial has reported similar results with the use of a 28-day regimen of perioperative cisplatin and 5-FU [34]. The MAGIC trial recruited predominantly patients with gastric cancers, whereas the French study was composed of a majority of patients with proximal tumours. Therefore, a perioperative treatment approach may be considered evidence-based for both tumour subsites. An EORTC study in which patients were randomised to surgery plus or minus bi-weekly cisplatin (50 mg/m^2) and 5-FU in the de Gramont style also increased R0 resection rates in chemotherapy-treated patients but closed early due to poor accrual and is not powered to show a survival benefit [35]. Perioperative chemotherapy has therefore been widely adopted as a standard of care throughout many parts of Europe [I, A]. Since capecitabine avoids the need for an indwelling central venous access device and is non-inferior to 5-FU in the advanced disease setting [36], capecitabine-containing regimens can also be suggested in the perioperative setting (as ECX: epirubicin, cisplatin, capecitabine, in preference to ECF) [IV, C]. Also, other platinum/fluoropyrimidine doublets or triplets may be considered; in particular, oxaliplatin may replace cisplatin [as EOX (epirubicin, oxaliplatin, capecitabine)]; it is non-inferior to ECX in the metastatic setting [36]).

The effect of dose intensification (e.g. with taxanes) of perioperative chemotherapy in gastric cancer remains unclear. In oesophageal and gastroesophageal junctional AC, intensification of preoperative chemotherapy from two cycles of cisplatin and capecitabine (CX) to four cycles of ECX resulted in improved pathological response rates (secondary end point), but this did not translate into an improvement in overall survival (OS) [37]. However, as this trial did not include gastric cancer patients or a postoperative chemotherapy component, direct cross-trial comparisons are challenging. A study of the German AIO study group investigating a perioperative FLOT regimen (fluorouracil, leucovorin, oxaliplatin, docetaxel) versus ECF/X demonstrated higher rates of pathological response for FLOT (15.6% versus 5.8%); however, correlation with survival outcomes is awaited [38].

Based on these studies, it may be reasonable to use any fluoropyrimidine–platinum doublet or triplet before surgery, although the strongest evidence is for cisplatin/fluorouracil ± epirubicin

combinations. Recommended treatment duration is 2–3 months. There is no current evidence to support the use of perioperative trastuzumab therapy or any other biologically targeted drug, including anti-angiogenic compounds.

adjuvant treatment

Recommendation: For patients with ≥Stage IB gastric cancer who have undergone surgery without administration of preoperative chemotherapy (e.g. due to understaging before the initial decision for upfront surgery), postoperative chemoradiotherapy (CRT) or adjuvant chemotherapy is recommended [I, A]. For patients having undergone preoperative chemotherapy, the addition of postoperative radiotherapy (RT) has no added benefit.

chemoradiotherapy. The North American Intergroup-0116 trial demonstrated that adjuvant therapy with 5-FU/leucovorin (Q28) plus conventionally fractionated RT (45 Gy in 25 fractions) resulted in improved OS years compared with surgery alone, (50% 3-year survival for patients treated with CRT versus 41% for those treated with surgery alone [39]). After 10 years of follow-up, this OS improvement remains significant [I, A] [40]. Therefore, this treatment approach is currently considered as standard therapy in the USA, though it has not gained wide acceptance in Europe due to concerns about potential late toxic effects and the quality of surgery within the trial. Moreover, >50% of patients underwent inadequate (less than D1) lymphadenectomy, suggesting that postoperative CRT may be (mainly) compensating for suboptimal surgery [II, B]. This is supported by retrospective data from the Dutch D1D2 trial, demonstrating that CRT reduces local recurrence rates following D1 resection, but provides no benefit in patients who have undergone D2 resection [41]. However, other randomised and non-randomised data suggest potential benefits from postoperative CRT even after optimal D2 dissection [I, B] [42–45], and this is the subject of ongoing randomised trials.

Regarding patients who have had a microscopically incomplete resection, a retrospective comparison of the Dutch D1D2 trial has suggested significant improvements in OS and local recurrence rates with use of CRT after an R1 resection, a finding that has been confirmed by other retrospective series [IV, B] [41, 46].

In current postoperative 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, 5 fractions/week by intensity-modulated RT techniques [IV, A] [47]. The clinical target volume encompasses the gastric bed (with stomach remnant when present), anastomoses and draining regional lymph nodes [I, B] [44, 45].

adjuvant chemotherapy. The ACTS-GC trial evaluating adjuvant chemotherapy with S-1 following D2 resection in Asian patients demonstrated an OS benefit for patients treated with adjuvant chemotherapy [I, A] [48, 49]. The CLASSIC trial evaluated a capecitabine–oxaliplatin doublet in a similar population and this was associated with significantly improved OS and disease-free survival (DFS) [50, 51] compared with surgery alone.

However, none of sequential S1-paclitaxel, sequential tegafur and uracil (UFT)-paclitaxel or UFT alone resulted in a superior outcome (DFS as the primary end point) when compared with single-agent, adjuvant S1 in a two by two randomised factorial trial [52].

Historically, a greater benefit has been noted with adjuvant chemotherapy in Asian studies, and uptake of adjuvant chemotherapy in Europe for patients with resected gastric cancer remains limited due to a perceived lack of benefit and routine use of perioperative chemotherapy. However, a large individual patient-level meta-analysis of adjuvant chemotherapy in gastric cancer has confirmed a 6% absolute benefit for 5-FU-based chemotherapy, compared with surgery alone [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.76–0.90; $P < 0.001$] in all subgroups tested [I, A] [53]. However, as adjuvant chemotherapy is also less well tolerated than neoadjuvant chemotherapy, a perioperative approach is preferred if possible, so that more patients can benefit from systemic treatment even if the postoperative component of treatment is unable to be delivered.

For adjuvant treatment following preoperative chemotherapy, the preoperatively chosen regimen should be completed after resection for patients who are fit for treatment, independent from pathohistological findings and considerations. The addition of postoperative RT has been shown to not improve survival in patients receiving chemotherapy before and after curative-intent surgery. Recently, the randomised, phase III CRITICS trial concluded that patients undergoing chemotherapy followed by surgery with curative intent had similar OS and progression-free survival (PFS) regardless of whether they received chemotherapy or CRT after surgery [54].

management of advanced/metastatic disease

first-line treatment

Recommendation: Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer [I, A].

Patients with inoperable locally advanced and/or metastatic (stage IV) disease should be considered for systemic treatment (chemotherapy), which has shown improved survival and quality of life compared with best supportive care alone [I, A] [55–57]. However, co-morbidities, organ function and performance status (PS) must always be taken into consideration [II, B].

In general, resection of the primary tumour is not recommended in the palliative setting; however, a small number of patients with initially unresectable locally advanced disease may be deemed operable following a good response to systemic therapy.

Response to systemic treatments should normally be assessed with interval imaging of the chest, abdomen and pelvis, mostly with CT, although alternative imaging techniques may be used if required to monitor known sites of disease (e.g. magnetic resonance imaging for bone lesions).

Doublet combinations of platinum and fluoropyrimidines are generally used, and there remains controversy regarding the utility of triplet regimens. However, a meta-analysis has demonstrated significant benefit from the addition of an anthracycline to a platinum and fluoropyrimidine doublet [58]. For anthracycline-based triplets, the UK REAL-2 trial demonstrated non-inferiority between ECF, ECX, EOF (epirubicin, oxaliplatin, 5-FU) and EOX. The EOX regimen was associated with numerically longer median OS (11.2 versus 9.9 months, HR 0.80, 95% CI 0.66–0.97; $P = 0.02$)

than ECF, without the need for an indwelling catheter and with reduced rates of thromboembolism [59]. Additionally, a combined analysis has demonstrated that capecitabine is associated with improved OS, compared with infused 5-FU within doublet and triplet regimens [I, A] [58].

Triplets containing taxanes are also an evidence-based treatment choice for first-line chemotherapy [60, 61]. In a phase III randomised trial, the addition of docetaxel to 5-FU/cisplatin in a 3-weekly regimen (DCF) was associated with improved OS, but also added significant toxic effects including increased rates of febrile neutropaenia [I, C] [61]. A phase II randomised control trial of a modified 2-weekly DCF regimen compared with original DCF (with growth factor support) halted recruitment in the original DCF arm due to excessive toxicity; however, the study suggested that a substantially modified DCF regimen was tolerable and effective [II, B] [62]. Several other studies have examined the efficacy of docetaxel, fluoropyrimidine and oxaliplatin-containing regimens. The FLOT regimen (fluorouracil, leucovorin, oxaliplatin and docetaxel) resulted in a median PFS of 5.1 months and a median OS of 11 months in a small non-randomised study [63]. An almost identical regimen used in a randomised phase II trial resulted in encouraging median PFS and OS of 7.7 and 14.6 months, respectively [II, B] [64]. As an alternative to platinum-based therapy, irinotecan plus leucovorin and infusional 5-FU (FOLFIRI) has been studied in both phase II trials and one phase III randomised trial in the first-line setting, and may be considered for selected patients [60, 65].

See the metastasectomy section for surgery in stage IV gastric cancer.

elderly patients with gastric cancer

Elderly patients with gastric cancer are under-represented in clinical trials, and there are few randomised data in this setting. Regimens that have been specifically addressed in phase II trials in elderly patients with comparable survival results include capecitabine and oxaliplatin, FOLFOX (leucovorin, 5-FU and oxaliplatin), single-agent capecitabine and S1 (in Asian patients) [III, B] [66–68]. A phase II trial investigated the miniDOX (docetaxel, oxaliplatin and capecitabine) regimen in primarily older patients and also recruited patients with other poor prognostic markers (PS2, weight loss 10%–25%). This regimen was associated with survival comparable to good prognostic groups; however, toxicity was also prominent [69]. In addition, a meta-analysis of three phase III trials comparing patients ≥70 years with younger patients demonstrated no differences in response rates or OS between the two patient groups [II, B] [70]. In the perioperative setting, a German study compared the doublet FLO (infusional 5-FU, leucovorin and oxaliplatin) and the FLOT regimens in 44 elderly gastric cancer patients [71]. Although the FLOT regimen was associated with a trend towards improved PFS, it was also associated with increased toxicity [II, B]. Furthermore, in the MAGIC trial, there was no evidence of heterogeneity of treatment effect for patients over the age of 70 [33]. However, it must be considered that all patients included in these analyses were clinical trial participants, which may not reflect patients treated in a community setting. When making a decision regarding chemotherapy, the functional age of the patient must also be considered, as co-morbidities and PS may have an equal effect on tolerance of chemotherapy as age. Geriatric assessment may be helpful before initiating treatment of older patients.

second- and further-line treatment

Recommendation: Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1 [I, A].

In patients of adequate PS, second-line treatment is associated with proven improvements in OS and quality of life compared with best supportive care, with treatment options including irinotecan, docetaxel or paclitaxel, if not used before [I, A] [72–75]. A randomised phase III trial directly comparing weekly paclitaxel with irinotecan has demonstrated similar efficacy for both regimens [I, A] [76].

The anti-VEGFR-2 monoclonal antibody ramucirumab has shown activity in two randomised phase III trials. As a single agent it is associated with a survival benefit comparable to cytotoxic chemotherapy in the second-line setting [I, A], whereas ramucirumab in addition to paclitaxel is associated with a survival benefit compared with paclitaxel alone [I, A] [77, 78].

Alternatively, in patients with disease progression >3 months following first-line chemotherapy, it may be appropriate to consider a rechallenge with the same drug combination as an additional treatment option [IV, C] [79]. In patients with symptomatic, locally advanced or recurrent disease, hypo-fractionated RT is an effective and well-tolerated treatment modality that may palliate bleeding, obstructive symptoms or pain [III, B] [80].

Treatment options may be used sequentially in second and third line, but there is no clear evidence for a benefit beyond second line treatment.

personalised medicine and targeted therapy

Recommendation: Trastuzumab is recommended in conjunction with platinum and fluoropyrimidine-based chemotherapy for patients with HER2-positive advanced gastric cancer [I, A].

Gastric cancers have been demonstrated to be highly molecularly diverse and may be driven by a number of different genetic and epigenetic abnormalities. Four subtypes of gastric cancer have recently been described in The Cancer Genome Atlas; these are the Epstein Barr Virus, microsatellite instability (MSI) high, genomically stable and chromosomal instability (CIN) subtypes [8]. Each subtype is enriched for selected molecular abnormalities, with some overlap. In particular, the CIN subtype is enriched for copy number changes in key receptor tyrosine kinase oncogenes such as HER2, EGFR, FGFR2 and MET. These findings have potentially important therapeutic implications as oncologists attempt to target the key pathways driving the tumour in each individual patient.

In HER2-positive gastric cancer (10%–15% of cases), the phase III ToGA trial demonstrated clinically and statistically significant improvements in response rate, PFS and OS with the addition of trastuzumab to a cisplatin/fluoropyrimidine doublet (median OS 13.8 versus 11.1 months, HR 0.74, 95% CI 0.60–0.91; $P = 0.0048$) [I, A] [81]. The benefits of trastuzumab were even more marked in the traditionally defined HER2-positive

subgroup with immunohistochemistry (IHC) 2+/FISH+ tumours, or IHC 3+ tumours. In these patients, the median OS was improved from 11.8 to 16.0 months (HR 0.65, 95% CI 0.51–0.83). Following the ToGA trial results, trastuzumab was licensed in Europe for use in HER2-positive disease (IHC3+ or 2+/FISH+) in combination with capecitabine or 5-FU and cisplatin. This regimen now represents the standard of care for these patients [I, A]. However, recent phase III randomised trials targeting the EGFR and MET-HGF axes have not demonstrated improvements in OS for anti-EGFR and anti-MET/HGF therapies [82–85]. In contrast, emerging data from early phase trials suggests that use of immunotherapies such as the PD-1 inhibitors pembrolizumab and nivolumab may result in durable remissions for a proportion of patients with advanced gastric cancer [86, 87]. The interaction between immunotherapy for gastric cancer and other known biomarkers in gastric cancer such as MSI requires further investigation.

A personalised medicine synopsis table is presented in Table 4.

specific situations

metastasectomy

In general, patients with metastatic cancer do not benefit from resection of metastases. Uncontrolled case series have demonstrated prolonged survival for selected patients undergoing liver and lung metastasectomy and surgical removal of Krukenberg tumours [V, C] [88–90]. The randomised REGATTA trial established (in an Asian patient population) that gastrectomy in patients with limited metastatic disease does not improve survival [I, A] [91]. Until further evidence is presented, both gastrectomy and metastasectomy should be considered experimental for patients with gastric cancer.

peritoneal metastases

Several small randomised trials in Asian patients have demonstrated a significant survival benefit for adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in high-risk curatively resected gastric cancer patients; however, these results have not been validated in non-Asian patients [92, 93]. For patients with advanced peritoneal metastases, data from randomised trials in Asia also exist to support the use of cytoreductive surgery plus HIPEC in selected patients [94]. However, randomised data are lacking for non-Asian patients. A large French series demonstrated a median survival of surgery plus HIPEC of 9.2 months, with a 5-year survival rate of 13% for all patients and 23% for those who had complete cytoreductive surgery [IV, C] [95]. Currently, this approach cannot be recommended outside the context of clinical research.

Table 4. Personalised medicine synopsis table for lower oesophageal and gastric cancer

Biomarker	Method	Use	LOE, GOR
HER2	Immunohistochemistry for HER2 protein expression or ISH for HER2 gene amplification	Used to select patients with metastatic disease for treatment with a trastuzumab-containing regimen	I, A

LOE, level of evidence; GOR, grade of recommendation; HER2, human receptor growth factor receptor 2; ISH, in situ hybridisation.

signet cell tumours

Gastric AC associated with signet ring cells is associated with a poor prognosis. Retrospective case series suggest that this gastric cancer subtype may be less sensitive to chemotherapy and CRT [IV] [96, 97]. However, evidence is insufficient to support not adopting standard chemotherapy or surgical approaches for these patients.

follow-up, long-term implications and survivorship

In the setting of operable gastric cancer, the complexity of treatment frequently induces symptoms that adversely affect health-related quality of life. A 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 [III, B] [98, 99].

Follow-up should be tailored to the individual patient and the stage of the disease [V, B] [100]. Dietary support is recommended for patients on either a radical or a palliative pathway with reference to vitamin and mineral deficiencies [V, B] [101, 102].

New strategies for patient follow-up are currently undergoing evaluation, including patient-led self-referral and services led by clinical nurse specialists [103].

In the advanced disease setting, identification of patients for second-line chemotherapy and clinical trials requires regular follow-up to detect symptoms of disease progression before significant clinical deterioration [IV, B].

If relapse/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 chemotherapy or RT [IV, B].

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

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is given in Table 1. Levels of evidence and grades of

Table 5. Summary of recommendations

Incidence and epidemiology

- If a familial cancer syndrome such as HDGC is suspected, referral to a geneticist for assessment is recommended based on international clinical guidelines [V, B]

Diagnosis and pathology

- Diagnosis should be made from a gastroscopic or surgical biopsy reviewed by an experienced pathologist, and histology should be reported according to the WHO criteria [IV, C]

Staging and risk assessment

- Initial staging and risk assessment should include physical examination, blood count and differential, liver and renal function tests, endoscopy and contrast-enhanced CT scan of the thorax, abdomen ± pelvis [V, A]
- Laparoscopy is recommended for patients with resectable gastric cancer [III, B]
- Multidisciplinary treatment planning before any treatment is mandatory [IV, C]
- EUS is helpful in determining the proximal and distal extent of the tumour and provides further assessment of the T and N stage; however, it is less useful in antral tumours [III, B]
- PET-CT imaging may improve staging by detecting involved lymph nodes or metastatic disease. However, PET may not be informative in patients with mucinous or diffuse tumours [III, B]
- Laparoscopy ± peritoneal washings for malignant cells are recommended in all stage IB–III gastric cancers that are considered potentially resectable, to exclude radiologically occult metastatic disease; the benefit may be greater for patients with T3/T4 disease [III, B]

Treatment planning

- Multidisciplinary treatment planning before any treatment decision is mandatory. The core membership of the multidisciplinary team should include surgeons, medical and radiation oncologists, radiologists and pathologists, with other members as available [IV, C]

Management of local/locoregional disease

- Endoscopic resection is appropriate for selected early tumours [III, B]
- For stage IB–III gastric cancer, radical gastrectomy is indicated; perioperative therapy is recommended for these patients [I, A]
- Medically fit patients should undergo D2 resections in high-volume surgical centres [I, B]

Surgery

- Endoscopic resection may be carried out for very early gastric cancers (T1a) if they are clearly confined to the mucosa, well-differentiated, ≤2 cm and non-ulcerated [III, B]
- European Society of Gastrointestinal Endoscopy Guidelines recommend ESD as the treatment of choice for most gastric superficial neoplastic lesions [IV, B]
- For stage IB–III gastric cancer, radical gastrectomy is indicated. Subtotal gastrectomy may be carried out if a macroscopic proximal margin of 5 cm can be achieved between the tumour and the gastroesophageal junction. For diffuse cancers, a margin of 8 cm is advocated. Otherwise, a total gastrectomy is indicated [III, A]. Perioperative therapy is recommended for these patients
- In Asian countries, experience from observational and randomised trials demonstrates that dissection leads to superior outcomes compared with D1 resection [II, B]
- Consensus opinion is that, in Western countries, medically fit patients should undergo D2 dissection that is carried out in specialised, high-volume centres with appropriate surgical expertise and postoperative care [I, B]

Perioperative chemotherapy

- Perioperative (pre- and postoperative) chemotherapy with a platinum and fluoropyrimidine combination is recommended for patients with ≥stage IB resectable gastric cancer [I, A]
- Since capecitabine avoids the need for an indwelling central venous access device, and is non-inferior to 5-FU in the advanced disease setting, capecitabine-containing regimens can also be suggested in the perioperative setting [IV, C]

Adjuvant treatment

- For patients with ≥stage IB gastric cancer who have undergone surgery without administration of preoperative chemotherapy, postoperative CRT or adjuvant chemotherapy is recommended [I, A]
- Adjuvant therapy with 5-FU/leucovorin plus conventionally fractionated RT resulted in improved OS years compared with surgery alone. After 10 years of follow-up, this OS improvement remains significant [I, A]
- Postoperative CRT may (mainly) be compensating for suboptimal surgery [II, B]. However, some data suggest potential benefits from postoperative CRT event after optimal D2 dissection [I, B]
- In patients who have had a microscopically incomplete resection, significant improvements in OS and local recurrence rates with the use of CRT after an R1 resection have been seen [IV, B]
- 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, 5 fractions/week by intensity-modulated RT techniques [IV, A]. The clinical target volume encompasses the gastric bed, anastomoses and draining regional lymph nodes [I, B]

Continued

Table 5. *Continued*

- OS benefit has been demonstrated for patients treated with adjuvant chemotherapy [I, A]
- The benefit of 5-FU-based chemotherapy has been confirmed compared with surgery alone [I, A]

Management of advanced/metastatic disease

First-line treatment
- Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer [I, A]
- Patients with inoperable locally advanced and/or metastatic (stage IV) disease should be considered for systemic treatment (chemotherapy), which has shown improved survival and quality of life compared with best supportive care alone [I, A]. However, comorbidities, organ function and PS must always be taken into consideration [II, B]
- Capecitabine is associated with improved OS compared with infused 5-FU within doublet and triplet regimens [I, A]
- DCF in a 3-weekly regimen was associated with improved OS, but also added significant toxic effects including increased rates of febrile neutropaenia [I, C]

Elderly patients with gastric cancer
- Regimens that have been specifically addressed in phase II trials in elderly patients with comparable survival results include capecitabine and oxaliplatin, FOLFOX, single-agent capecitabine and S1 (in Asian patients) [III, B]
- The FLOT regimen is associated with a trend towards improved PFS but also with increased toxicity [II, B]

Second- and further-line treatment
- Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as a single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1 [I, A]
- Similar efficacy has been demonstrated for weekly paclitaxel and irinotecan [I, A]
- In patients with disease progression >3 months following first-line chemotherapy, it may be appropriate to consider a rechallenge with the same drug combination [IV, C]
- In patients with symptomatic locally advanced or recurrent disease, hypofractionated RT is an effective and well-tolerated treatment modality that may palliate bleeding, obstructive symptoms or pain [III, B]

Personalised medicine and targeted therapy
- Trastuzumab is recommended in conjunction with platinum- and fluoropyrimidine-based chemotherapy for patients with HER2-positive advanced gastric cancer [I, A]

Specific situations

Metastasectomy
- Gastrectomy in patients with limited metastatic disease does not improve survival [I, A]

Peritoneal metastases
- In patients with peritoneal metastases, the use of cytoreductive surgery plus HIPEC has been studied, but this approach cannot yet be recommended outside the context of clinical research.

Follow-up, long-term implications and survivorship
- A 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 [III, B]
- Follow-up should be tailored to the individual patient and the stage of the disease [V, B]
- Dietary support is recommended for patients on either a radical or a palliative pathway, with reference to vitamin and mineral deficiencies [V, B]
- In the advanced disease setting, identification of patients for second-line chemotherapy and clinical trials requires regular follow-up to detect symptoms of disease progression before significant clinical deterioration [IV, B]
- If relapse/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 chemotherapy or RT [IV, B]

HDGC, hereditary diffuse gastric cancer; WHO, World Health Organisation CT, computed tomography; EUS, endoscopic ultrasound; PET-CT, positron emission tomography-computed tomography; ESD, endoscopic submucosal dissection; 5-FU, 5-fluorouracil; CRT, chemoradiotherapy; RT, radiotherapy; OS, overall survival; PS, performance status; DCF, docetaxel, cisplatin, 5-FU; FOLFOX, leucovorin, 5-FU and oxaliplatin; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; PFS, progression-free survival; HER2, human epidermal growth factor receptor 2; HIPEC, hyperthermic intraperitoneal chemotherapy; AC, adenocarcinoma.

recommendation have been applied using the system given in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer-review process.

conflict of interest

ES has reported honoraria from Five Prime Therapeutics for advisory board participation. DC has reported research support from Amgen, AstraZeneca, Bayer, Celgene, Medimmune, Merck

Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [104].

Serono, Merrimack and Sanofi. WA has reported honoraria for presentations at scientific meetings for Taiho, Nestlé and Lilly; honoraria from Nestlé and Lilly for advising on research projects. MV has reported research support from Roche. AC has reported consulting and advisory services for and speaking or writing engagements and public presentations for Merck Serono, Amgen, Servier, Roche, Lilly and Novartis; research support from Roche, Merck Serono, Servier and Takeda. DA has reported honoraria/consultancy for Roche, Merck Serono, Bayer, Lilly and Servier; research support from Roche.

references

1. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87–108.
2. Arnold M, Karim-Kos HE, Coebergh JW et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer 2015; 51: 1164–1187.
3. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol 2006; 20: 633–649.
4. World Cancer Research Fund International/American Institute for Cancer Research. Continuous update project report: diet, nutrition, physical activity and stomach cancer. 2016. wcrf.org/stomach-cancer-2016 (8 August 2016, date last accessed).
5. Zanghieri G, Di Gregorio C, Sacchetti C et al. Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. Cancer 1990; 66: 2047–2051.
6. Palli D, Galli M, Caporaso NE et al. Family history and risk of stomach cancer in Italy. Cancer Epidemiol Biomarkers Prev 1994; 3: 15–18.
7. van der Post RS, Vogelaar IP, Carneiro F et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet 2015; 52: 361–374.
8. Bass AJ, Thorsson V, Shmulevich I et al. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202–209.
9. Ba-Ssalamah A, Prokop M, Uffmann M et al. Dedicated multidetector CT of the stomach: spectrum of diseases. Radiographics 2003; 23: 625–644.
10. Chen CY, Hsu JS, Wu DC et al. Gastric cancer: preoperative local staging with 3D multi–detector row CT—correlation with surgical and histopathologic results. Radiology 2007; 242: 472–482.
11. Kim YN, Choi D, Kim SH et al. Gastric cancer staging at isotropic MDCT including coronal and sagittal MPR images: endoscopically diagnosed early vs. advanced gastric cancer. Abdom Imaging 2009; 34: 26–34.
12. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer. Gastric Cancer 2009; 12: 6–22.
13. Catalano MF, Sivak MV, Jr, Rice T et al. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc 1994; 40: 442–446.
14. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. Gastrointest Endosc 1997; 45: 474–479.
15. Leake PA, Cardoso R, Seevaratnam R et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Gastric Cancer 2012; 15 (Suppl. 1): S27–S37.
16. Leake PA, Cardoso R, Seevaratnam R et al. A systematic review of the accuracy and indications for diagnostic laparoscopy before curative-intent resection of gastric cancer. Gastric Cancer 2012; 15 (Suppl. 1): S38–S47.
17. Sobin LH, Gospodarowicz MK, Wittekind C (eds). TNM Classification of Malignant Tumours, 7th edition. Oxford, UK: Wiley-Blackwell 2009.
18. Edge SB, Byrd DR, Compton CC (eds). AJCC Cancer Staging Manual, 7th edition. New York, NY: Springer 2010.
19. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015; 47: 829–854.
20. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011; 14: 113–123.
21. Bonenkamp JJ, Hermans J, Sasako M et al. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999; 340: 908–914.
22. Cuschieri A, Weeden S, Fielding J et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Br J Cancer 1999; 79: 1522–1530.
23. Degiuli M, Sasako M, Ponti A et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg 2014; 101: 23–31.
24. Songun I, Putter H, Kranenbarg EM et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439–449.
25. Dikken JL, van Sandick JW, Allum WH et al. Differences in outcomes of oesophageal and gastric cancer surgery across Europe. Br J Surg 2013; 100: 83–94.
26. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998; 280: 1747–1751.
27. Birkmeyer JD, Siewers AE, Finlayson EV et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346: 1128–1137.
28. National Oesophago-Gastric Cancer Audit 2015. Healthcare Quality Improvement Partnership Ltd, 2015. http://www.hqip.org.uk/resources/national-oesophago-gastric-cancer-audit-report-2015/ (8 August 2016, date last accessed).
29. Mortensen K, Nilsson M, Slim K et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Br J Surg 2014; 101: 1209–1229.
30. Quan Y, Huang A, Ye M et al. Comparison of laparoscopic versus open gastrectomy for advanced gastric cancer: an updated meta-analysis. Gastric Cancer 2016; 19: 939–950.
31. Lee JH, Nam BH, Ryu KW et al. Comparison of outcomes after laparoscopy-assisted and open total gastrectomy for early gastric cancer. Br J Surg 2015; 102: 1500–1505.

32. Kim W, Kim HH, Han SU et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS–01). Ann Surg 2016; 263: 28–35.
33. Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11–20.
34. Ychou M, Boige V, Pignon JP et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29: 1715–1721.
35. Schuhmacher C, Gretschel S, Lordick F et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010; 28: 5210–5218.
36. Cunningham D, Starling N, Rao S et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358: 36–46.
37. Alderson D, Langley RE, Nankivell MG et al. Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: results from the UK Medical Research Council randomised OE05 trial (ISRCTN 01852072). J Clin Oncol 2015; 33 (Suppl): abstr 4002.
38. Pauligk C, Tannapfel A, Meiler J et al. 36LBA: Pathological response to neoadjuvant 5-FU, oxaliplatin and docetaxel (FLOT) versus epirubicin, cisplatin and 5-FU (ECF) in patients with locally advanced, resectable gastric/esophagogastric junction (EGJ) cancer: data from the phase II part of the FLOT4 phase III study of the AIO. Eur J Cancer 2015; 51(Suppl. S3): 756.
39. 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: 725–730.
40. 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: 2327–2333.
41. Dikken JL, Jansen EP, Cats A et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol 2010; 28: 2430–2436.
42. Kim S, Lim DH, Lee J et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 2005; 63: 1279–1285.
43. 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: 268–273.
44. Zhu WG, Xua DF, Pu J et al. A randomized, controlled, multicenter study comparing intensity-modulated radiotherapy plus concurrent chemotherapy with chemotherapy alone in gastric cancer patients with D2 resection. Radiother Oncol 2012; 104: 361–366.
45. Park SH, Sohn TS, Lee J et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the Adjuvant Chemoradiotherapy in Stomach Tumors trial, including survival and subset analyses. J Clin Oncol 2015; 33: 3130–3136.
46. Stiekema J, Trip AK, Jansen EP et al. The prognostic significance of an R1 resection in gastric cancer patients treated with adjuvant chemoradiotherapy. Ann Surg Oncol 2014; 21: 1107–1114.
47. Trip AK, Nijkamp J, van Tinteren H et al. IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer. Radiother Oncol 2014; 112: 289–294.
48. Sakuramoto S, Sasako M, Yamaguchi T et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357: 1810–1820.
49. Sasako M, Sakuramoto S, Katai H et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011; 29: 4387–4393.
50. Bang YJ, Kim YW, Yang HK et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379: 315–321.
51. Noh SH, Park SR, Yang HK et al. 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: 1389–1396.
52. Tsuburaya A, Yoshida K, Kobayashi M et al. Sequential paclitaxel followed by tegafur and uracil (UFT) or S-1 versus UFT or S-1 monotherapy as adjuvant chemotherapy for T4a/b gastric cancer (SAMIT): a phase 3 factorial randomised controlled trial. Lancet Oncol 2014; 15: 886–893.
53. Paoletti X, Oba K, Burzykowski T et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 2010; 303: 1729–1737.
54. Verheij M, Jansen EPM, Cats A et al. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: first results from the CRITICS study. J Clin Oncol 2016; 34 (Suppl): abstr 4000.
55. Wagner AD, Unverzagt S, Grothe W et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010; 3: CD004064.
56. Glimelius B, Ekström K, Hoffman K et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997; 8: 163–168.
57. Bouché O, Raoul JL, Bonnetain F et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study—FFCD 9803. J Clin Oncol 2004; 22: 4319–4328.
58. Okines AF, Norman AR, McCloud P et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 2009; 20: 1529–1534.
59. Starling N, Rao S, Cunningham D et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 2009; 27: 3786–3793.
60. Dank M, Zaluski J, Barone C et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008; 19: 1450–1457.
61. Van Cutsem E, Moiseyenko VM, Tjulandin S et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24: 4991–4997.
62. Shah MA, Janjigian YY, Stoller R et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. J Clin Oncol 2015; 33: 3874–3879.
63. Al-Batran SE, Hartmann JT, Hofheinz R et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008; 19: 1882–1887.
64. Van Cutsem E, Boni C, Tabernero J et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. Ann Oncol 2015; 26: 149–156.
65. Guimbaud R, Louvet C, Ries P et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: A French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study. J Clin Oncol 2014; 32: 3520–3526.
66. Xiang XJ, Zhang L, Qiu F et al. A phase II study of capecitabine plus oxaliplatin as first-line chemotherapy in elderly patients with advanced gastric cancer. Chemotherapy 2012; 58: 1–7.
67. Lee JL, Kang YK, Kang HJ et al. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 2008; 99: 584–590.
68. Catalano V, Bisonni R, Graziano F et al. A phase II study of modified FOLFOX as first-line chemotherapy for metastatic gastric cancer in elderly patients with associated diseases. Gastric Cancer 2013; 16: 411–419.

69. Rivera F, Massutí B, Salcedo M et al. Phase II trial of miniDOX (reduced dose docetaxel-oxaliplatin-capecitabine) in 'suboptimal' patients with advanced gastric cancer (AGC). TTD 08-02. Cancer Chemother Pharmacol 2015; 75: 319–324.
70. Trumper M, Ross PJ, Cunningham D et al. Efficacy and tolerability of chemotherapy in elderly patients with advanced oesophago-gastric cancer: a pooled analysis of three clinical trials. Eur J Cancer 2006; 42: 827–834.
71. Al-Batran SE, Pauligk C, Homann N et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65 +). Eur J Cancer 2013; 49: 835–842.
72. Thuss-Patience PC, Kretzschmar A, Bichev D et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011; 47: 2306–2314.
73. Ford HE, Marshall A, Bridgewater JA et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014; 15: 78–86.
74. Kang JH, Lee SI, Lim DH et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012; 30: 1513–1518.
75. Roy AC, Park SR, Cunningham D et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Ann Oncol 2013; 24: 1567–1573.
76. Hironaka S, Ueda S, Yasui H et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 2013; 31: 4438–4444.
77. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15: 1224–1235.
78. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383: 31–39.
79. Okines AF, Asghar U, Cunningham D et al. Rechallenge with platinum plus fluoropyrimidine +/- epirubicin in patients with oesophagogastric cancer. Oncology 2010; 79: 150–158.
80. Tey J, Back MF, Shakespeare TP et al. The role of palliative radiation therapy in symptomatic locally advanced gastric cancer. Int J Radiat Oncol Biol Phys 2007; 67: 385–388.
81. Bang YJ, Van Cutsem E, Feyereislova A et al. 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: 687–697.
82. Waddell T, Chau I, Cunningham D et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14: 481–489.
83. Lordick F, Kang YK, Chung HC et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14: 490–499.
84. Cunningham D, Tebbutt NC, Davidenko I et al. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. J Clin Oncol 2015; 33 (Suppl): abstr 4000.
85. Shah MA, Bang YJ, Lordick F et al. METGastric: a phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC). J Clin Oncol 2015; 33 (Suppl): abstr 4012.
86. Le DT, Bendell JC, Calvo E et al. Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): results from the CheckMate-032 study. J Clin Oncol 2016; 34 (Suppl 45): abstr 6.
87. 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: 717–726.
88. Markar SR, Mackenzie H, Mikhail S et al. Surgical resection of hepatic metastases from gastric cancer: outcomes from national series in England. Gastric Cancer 2016. [Epub ahead of print].
89. Shiono S, Sato T, Horio H et al. Outcomes and prognostic factors of survival after pulmonary resection for metastatic gastric cancer. Eur J Cardiothorac Surg 2013; 43: e13–e16.
90. Rosa F, Marrelli D, Morgagni P et al. Krukenberg tumors of gastric origin: the Rationale of surgical resection and perioperative treatments in a multicenter western experience. World J Surg 2016; 40: 921–928.
91. Fujitani K, Yang HK, Mizusawa J et al. 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: 309–318.
92. Fujimoto S, Takahashi M, Mutou T et al. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. Cancer 1999; 85: 529–534.
93. Fujimura T, Yonemura Y, Muraoka K et al. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. World J Surg 1994; 18: 150–155.
94. Yang XJ, Huang CQ, Suo T et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011; 18: 1575–1581.
95. Glehen O, Gilly FN, Arvieux C et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010; 17: 2370–2377.
96. Heger U, Blank S, Wiecha C et al. Is preoperative chemotherapy followed by surgery the appropriate treatment for signet ring cell containing adenocarcinomas of the esophagogastric junction and stomach? Ann Surg Oncol 2014; 21: 1739–1748.
97. Charalampakis N, Nogueras González GM, Elimova E et al. The proportion of signet ring cell component in patients with localized gastric adenocarcinoma correlates with the degree of response to pre-operative chemoradiation. Oncology 2016; 90: 239–247.
98. Allum WH, Blazeby JM, Griffin SM et al. Guidelines for the management of oesophageal and gastric cancer. Gut 2011; 60: 1449–1472.
99. D'Ugo D, Biondi A, Tufo A, Persiani R. Follow-up: the evidence. Dig Surg 2013; 30: 159–168.
100. Baiocchi GL, D'Ugo D, Coit D et al. Follow-up after gastrectomy for cancer: the Charter Scaligero Consensus Conference. Gastric Cancer 2016; 19: 15–20.
101. Hu Y, Kim HI, Hyung WJ et al. Vitamin B(12) deficiency after gastrectomy for gastric cancer: an analysis of clinical patterns and risk factors. Ann Surg 2013; 258: 970–975.
102. Baek KH, Jeon HM, Lee SS et al. Short-term changes in bone and mineral metabolism following gastrectomy in gastric cancer patients. Bone 2008; 42: 61–67.
103. Verschuur EM, Steyerberg EW, Tilanus HW et al. Nurse-led follow-up of patients after oesophageal or gastric cardia cancer surgery: a randomised trial. Br J Cancer 2009; 100: 70–76.
104. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144.