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

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incidence

Although the incidence of gastric cancer is decreasing, there were still 159 900 new cases in Europe in 2006, and ~118 200 deaths, representing the fifth highest incidence and fourth highest cause of cancer-related death. The overall incidence of gastric cancers is declining; however, there has been a relative increase in the incidence of tumours of the oesophago-gastric junction (OGJ) and gastric cardia. The peak incidence is in the seventh decade, and the disease is approximately twice as common in men as women. There is marked geographic variation, with the highest rates in East Asia, South America and Eastern Europe and the lowest rates in the United States and Western Europe. Risks include male gender, cigarette smoking, *Helicobacter pylori* infection, atrophic gastritis, partial gastrectomy, Menetrier's disease and genetic factors such as hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, hereditary diffuse gastric cancer and Peutz–Jeghers syndrome. Obesity may also be a risk factor for tumours of the OGJ/cardia.

diagnosis

Screening for gastric cancer is routine in Japan and Korea where the incidence is much higher than in Western countries.

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 Organization criteria [IV, C].

Ninety per cent of gastric cancers are adenocarcinomas, which are divided into diffuse (undifferentiated) and intestinal (well-differentiated) types. These recommendations do not apply to rarer gastric malignancies which include gastrointestinal stromal tumours, lymphomas and neuroendocrine tumours.

staging

- Staging consists of physical examination, blood count and differential, liver and renal function tests, endoscopy and CT scan of the thorax, abdomen and pelvis.
- Endoscopic ultrasound (EUS) is helpful in determining the proximal and distal extent of the tumour as well as its T stage, although it is less useful in antral tumours [III, B].
- Laparoscopy with or without peritoneal washings for malignant cells is recommended in all those considered to be potentially resectable to exclude metastatic disease [III, B].
- PET scans, if available, may upstage patients with gastric cancer but can be negative, especially in patients with mucinous and diffuse tumours [III, B].
- The stage should be given according to the TNM 2002 system and the AJCC stage grouping (Tables 1 and 2).

treatment planning

Multidisciplinary treatment planning is mandatory, comprising surgeons, medical and radiation oncologists, gastroenterologists, radiologists and pathologists [IV, C].

treatment of localized disease

surgery

Surgical resection is the only modality that is potentially curative. The extent of resection is determined by the preoperative stage. Early gastric cancer, limited to the mucosa, is increasingly being resected endoscopically. Established criteria for endoscopic mucosal resection (EMR) are mucosal cancers ≤2 cm which are histologically differentiated and not ulcerated [III, B]. These have recently been extended to include larger, ulcerated and undifferentiated tumours but these are being further evaluated because of the potential for nodal disease.

Radical gastrectomy is indicated for stage 1b–III disease. If a macroscopic proximal margin of 5 cm can be achieved

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Table 1. TNM staging of gastric cancer

Primary tumour (T)		Regional lymph nodes (N)		Distant metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph node(s) cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis[a]	M0	No distant metastasis
Tis	Carcinoma *in situ*: intraepithelial tumour without invasion of the lamina propria	N1	Metastasis in 1–6 regional lymph nodes	M1	Distant metastasis
T1	Tumour invades lamina propria or submucosa	N2	Metastasis in 7–15 regional lymph nodes		
T2	Tumour invades muscularis propria or subserosa[a]	N3	Metastasis in >15 regional lymph nodes		
T2a	Tumour invades muscularis propria				
T2b	Tumour invades subserosa				
T3	Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures[b,c]				
T4	Tumour invades adjacent structures[b,c]				

[a]A tumour may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case the tumour is classified as T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum the tumour should be classified as T3.
[b]The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum.
[c]Intramural extension to the duodenum or oesophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

Table 2. AJCC stage grouping

Stage grouping	T-stage	N-stage	M-stage
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2a/b	N0	M0
Stage II	T1	N2	M0
	T2a/b	N1	M0
	T3	N0	M0
Stage IIIA	T2a/b	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1–3	M0
	T1–3	N3	M0
	Any T	Any N	M1

between the tumour and the OGJ, sub-total gastrectomy can be performed. Otherwise a total gastrectomy is indicated [III, A]. The extent of nodal dissection has been extensively debated. The current TNM classification recommendations (sixth edition) include excision of a minimum of 15 lymph nodes to allow reliable staging.

Experience from the Far East has shown in both observational and randomized trials that D2 dissection excising N1 and N2 lymph node tiers is superior to a D1 dissection [II, B]. Two trials have assessed extended lymph node dissection. Wu *et al.* reported superior survival with D2 plus para-aortic node dissection (D3) compared with D1 [II, B]. The larger JCOG 9501 trial reported equivalent survival comparing D2 with D2 and para-aortic node dissection but with greater morbidity with the more extensive procedure. In the West, two randomized controlled trials have shown little initial difference between D1 and D2 lymphadenectomy. Long-term follow-up in the Dutch trial has recently been reported showing better cancer-related survival after D2. Smaller series from specialized centres have shown equivalent results to the Far East. The consensus view therefore in the West is that D2 dissection should be the standard procedure performed in specialized centres with appropriate surgical expertise and postoperative care, for patients considered medically fit enough to tolerate the procedure.

Resection of the spleen and pancreas is only indicated if there is direct invasion. Splenectomy is indicated for tumours of the proximal greater curve and gastric fundus; principally to remove splenic hilar nodes. Resection of adjacent organs is indicated when there is definite or suspected transmural invasion and the patient is fit enough for such radical surgery [II, B].

The place of laparoscopic surgery remains investigational. A small number of randomized controlled trials have confirmed

safety and a faster recovery as well as equivalent nodal harvest in distal gastrectomy. However, a meta-analysis demonstrated longer duration of surgery and reduced nodal harvest with laparoscopic compared with open surgery [I, A]. Careful study and audit are recommended as experience develops.

chemotherapy and chemoradiation

A UK MRC randomized trial demonstrated that a treatment plan of three cycles of preoperative and postoperative epirubicin (E) 50 mg/m^2, cisplatin (C) 60 mg/m^2 and continuous intravenous infusion of 5-fluorouracil (F) 200 mg/m^2/day (ECF) significantly improved 5-year survival from 23.0% with surgery alone to 36.3%. The main non-haematological toxicities were alopecia, nausea and vomiting. These results are supported by an FFCD trial reported in abstract [I, A]. This perioperative approach has been adopted as standard of care in most of the UK and parts of Europe. Because of the non-inferiority of capecitabine (X) with 5-fluorouracil (5-FU) in advanced disease and because it obviates the need for an indwelling central venous access device, many centres use ECX in the perioperative setting [IV, C].

A North American Intergroup randomized trial demonstrated that five cycles of postoperative chemotherapy with 5-flurouracil/leucovorin before, during and after radiotherapy (45 Gy in 25 fractions over 5 weeks) resulted in an ~15% improvement in 5-year overall survival (OS) [I, A]. Although this treatment approach is considered to be standard therapy in the USA, it has not gained wide acceptance in Europe because of concerns about (late) toxicity with abdominal chemoradiation, and the quality of surgery used. Only 10% of trial participants underwent the prescribed D2 dissection whereas the beneficial effect of postoperative chemoradiation appeared greatest in those patients who received a D1 dissection (36% of patients) or less than D1 (54% of patients), although the difference was not statistically significant [II, B]. Although this suggests that postoperative chemoradiation compensates for suboptimal surgery, a large non-randomized observational study suggested a potential clinical benefit from postoperative chemoradiation after optimal D2 dissection [III, B]. In addition, modern high-precision radiation techniques and more intensified chemoradiation regimens are likely to further improve the results of postoperative chemoradiation [IV, D].

Meta-analyses have demonstrated a small survival benefit for adjuvant chemotherapy, with an apparently greater benefit noted in the five studies from Asia [relative risk 0.74, 95% confidence interval (CI) 0.64–0.85] compared with the 14 studies conducted outside Asia (relative risk 0.90, 95% CI 0.85–0.96) recently reported [I, A]. In a Japanese trial of 1059 patients with completely resected stage II/III gastric cancer (Japanese classification) who underwent a D2 or greater dissection, participants were randomized to receive either 12 months of the oral fluoropyrimidine S-1 or observation alone: 27% did not complete the 12 month course of treatment due to adverse advents. Three year OS was 70.1% in the surgery only group and 81.1% [hazard ratio (HR) 0.68, 95% CI 0.52–0.87; $P = 0.003$] in the group receiving adjuvant therapy. The treatment appeared to prevent mainly nodal and peritoneal relapse [I, A]. These results will need to be replicated in a Western population before being generalized to this group.

Although neoadjuvant chemoradiation offers theoretical advantages over postoperative strategies (limited radiation fields, higher chance of radical surgery) it remains experimental and its value has not been confirmed in comparative randomized studies [III, C].

treatment of locally advanced inoperable disease

Patients with inoperable, locally advanced gastric cancer should be treated with palliative chemotherapy and may be reassessed for surgery if a favourable response is achieved [III, B].

Neo-adjuvant chemoradiation with cisplatin and etoposide after induction chemotherapy with cisplatin, 5-FU and leucovorin is feasible for locally advanced carcinomas of the OGJ. However, the study was underpowered due to poor recruitment and no statistically significant survival advantage was demonstrated [III, B].

treatment of metastatic disease

palliative chemotherapy

Patients with stage IV disease should be considered for palliative chemotherapy, which improves survival compared with best supportive care alone [I, A].

Combination regimens incorporating a platinum agent and a fluoropyrimidine are generally used. It remains controversial whether a triplet regimen is needed. However, a meta-analysis demonstrated significant benefit from adding an anthracycline to a platinum and fluoropyrimidine doublet [I, A], and ECF (epirubicin plus cisplatin plus protracted infusion 5-FU) is among the most active and well-tolerated regimens.

Docetaxel increases the activity of 5-FU/cisplatin, but is also more toxic when used in a 3-weekly regimen, with 29% complicated neutropenia reported. A randomized Phase II study demonstrated maintained activity with reduced toxicity when a weekly docetaxel schedule was employed in combination with cisplatin and infused 5-FU or capecitabine.

Irinotecan in combination with 5-FU/LV has similar activity to 5-FU/cisplatin and can therefore also be considered in selected patients [I, A].

The substitution of capecitabine (X) for 5-fluorouracil (F) and oxaliplatin (O) for cisplatin (C), in the ECF regimen was examined in a recent UK NCRI trial, which demonstrated non-inferiority between ECF, ECX, EOF and EOX. The EOX regimen was associated with a longer OS (11.2 versus 9.9 months, HR 0.80, 95% CI 0.66–0.97; $P = 0.02$) than the reference ECF regimen and the rate of thromboembolism was also significantly reduced by the oxaliplatin substitution (7.6% compared with 15.1%, $P = 0.0003$). ECX remains an option that also avoids the need for an indwelling venous access device. Other studies also show that oxaliplatin can be substituted for cisplatin [I, A] and capecitabine for 5-FU in chemotherapy doublets [I, A], preserving efficacy and offering some toxicity benefits. A recent meta-analysis has shown that capecitabine is superior to infused 5-FU for OS within doublet and triplet regimes for advanced gastric cancer [I, A].

targeted agents

A clinically and statistically significant improvement in response rate, median progression-free survival and median OS has been demonstrated from the addition of trastuzumab to cisplatin plus fluoropyrimidine chemotherapy in patients with HER2-positive gastric cancer (median OS 13.8 versus 11.1 months, HR 0.74, 95% CI 0.60–0.91; $P = 0.0048$) [I, B]. Therefore for patients with evidence of HER2 overexpression measured by FISH and/or immunohistochemistry, consideration should be given to treatment with this combination.

The use of cetuximab, panitumumab and bevacizumab in combination with chemotherapy is being explored in clinical trials but remains experimental.

second-line chemotherapy

Irinotecan improves survival compared with best supportive care in patients with advanced gastric and OJG cancers who progress within 6 months after first-line chemotherapy (median 4.0 versus 2.4 months, HR 0.48, 95% CI 0.25–0.92; $P = 0.023$) [II, B]. For patients of adequate performance status on disease progression after first-line chemotherapy, consideration should otherwise be given to inclusion in clinical trials.

Alternatively, in patients who relapse >3 months after first-line chemotherapy, consideration should be given to rechallenging the patient with the same chemotherapy regimen [IV, C].

palliative radiotherapy and surgery

Treatment of patients with incompletely resected disease remains palliative. In patients with symptomatic locally advanced or recurrent disease (hypofractionated) radiotherapy is an effective and well-tolerated modality to palliate bleeding, obstruction or pain [III, B].

Palliative resection is indicated to relieve complications of gastric cancer growth including obstruction, bleeding and perforation but should be considered in the context of multidisciplinary management and tumour natural history for an individual patient.

elderly patients

Patients aged ≥70 years old are under-represented in clinical trials; however, a pooled analysis of three randomized studies has demonstrated no significant differences in the efficacy or tolerability of palliative chemotherapy. Age alone is not a contraindication to palliative chemotherapy; however, co-morbidities, organ function and performance status must be taken into consideration [II, B].

follow-up

There is no evidence that regular intensive follow-up improves patient outcomes. Symptom-driven visits are recommended for most cases [III, B].

If symptoms of relapse occur, patient history, physical examination and directed blood tests should be performed. Radiological investigations should be performed in patients who are candidates for palliative chemo- or radiotherapy [IV, B].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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