

Gastric cancer: ESMO Clinical Recommendations 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 peak incidence is in the seventh decade, and the male:female ratio exceeds 1.5. There is marked geographic variation. Risks include male gender, cigarette smoking, *Helicobacter pylori* infection, atrophic gastritis, Menetrier's disease and genetic factors such as hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis and Peutz Jeghers syndrome.

diagnosis

Diagnosis should be made from a gastroscopic or surgical biopsy by an experienced pathologist, and histology reported according to the World Health Organization criteria.

staging

Staging consists of physical examination, blood count and differential, liver and renal function tests, endoscopy, CT scan of the abdomen and pelvis, and either chest X-ray or CT of the thorax. Endoscopic ultrasound is helpful in determining the proximal and distal extent of the tumor, although it is less useful in antral tumors. Laparoscopy with or without peritoneal washings for malignant cells should be performed in all those considered to be potentially resectable to exclude metastatic disease.

The stage should be given according to the TNM 2002 system and the AJCC stage grouping (Table 1).

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treatment plan

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

Surgical resection is the only modality that is potentially curative, and is recommended for stages I–IV M0. The extent of optimal regional lymphadenectomy is debated. Several randomized trials have failed to show superiority of extended (D2–3) over limited (D1) lymphadenectomy. However, a minimum of 14, and optimally at least 25 lymph nodes should be recovered.

treatment of localized disease

A UK MRC randomized trial demonstrated that a treatment plan of three cycles of pre- and postoperative epirubicin 50 mg/m², cisplatin 60 mg/m² and continuous i.v. infusion of 5-fluorouracil (5-FU) 200 mg/m²/day (ECF) significantly improved 5-year survival from 23.0% with surgery alone to 36.3%. The main non-hematological toxicities were alopecia, nausea and vomiting. These results are supported by an FFCD trial reported in abstract. This perioperative approach has been adopted as standard of care in most of the UK and parts of Europe.

Table 1. TNM 2002 and AJCC stage grouping

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

A North American intergroup randomized trial demonstrated that five cycles of postoperative chemotherapy with 5-FU/leucovorin before, during and after radiotherapy (45 Gy in 25 fractions over 5 weeks) resulted in an ~15% improvement in 5-year overall survival. 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 toxicity with abdominal chemoradiation, and the type of surgery used. Fifty-four percent of trial participants received less than a D1 dissection, although the trialists found no association between D level and outcome.

Meta-analyses have demonstrated a small survival benefit for adjuvant chemotherapy. 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. Twenty-seven percent did not complete the 12-month course of treatment due to adverse events. Three-year overall survival was 70.1% in the surgery-only group and 81.1% in the group receiving adjuvant therapy. The treatment appeared to prevent mainly nodal and peritoneal relapse. These results will need to be replicated in a Western population before being generalized to this group.

Postoperative chemotherapy alone has not consistently been shown to improve survival even in very high risk patients and it should not be offered to patients outside clinical trials

Treatment of patients with incompletely resected disease remains palliative.

treatment of metastatic disease

Patients with stage IV disease should be considered for palliative chemotherapy. Combination regimens incorporating a platinum, a fluoropyrimidine and an anthracycline are generally used. ECF is among the most active and well tolerated. Docetaxel increases the activity of 5-FU/cisplatin, but is also clearly more toxic. Irinotecan in combination with 5-FU/leucovorin has a similar activity to that of 5-FU/cisplatin and can therefore also be considered in selected patients.

A UK NCRI randomized trial of 1002 patients with advanced esophago-gastric cancer examined the substitution of capecitabine (X) for 5-FU (F), and oxaliplatin (O) for cisplatin (C), in the ECF regimen. With a 2 × 2 design, the trial tested for non-inferiority between ECF, ECX, EOF and EOX. Efficacy and toxicity were comparable between arms, and the primary end-point of non-inferiority was reached. This trial has made ECX or EOX the preferred regimen in many of the centers that were using ECF as a reference regimen, because of the efficacy and relative ease of administration without the need for an indwelling venous access device.

There is no standard second-line chemotherapy regimen and consideration should be given to inclusion in relevant clinical trials. Responses to regimens incorporating taxanes and irinotecan have been seen and are encouraging.

follow-up

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

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.

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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