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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, 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.

diagnosis

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].

staging

Staging consists of physical examination, blood count and differential, liver and renal function tests, endoscopy and CT scan of the abdomen and pelvis and either a CXR or CT of the thorax. Endoscopic ultrasound is helpful in determining the proximal and distal extent of the tumor as well as its T stage, although it is less useful in antral tumors [III, B]. Laparoscopy with or without peritoneal washings for malignant cells should be performed 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 tumors [III, B].

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The stage should be given according to the tumor–node–metastasis (TNM) 2002 system and the American Joint Committee Cancer stage grouping (Table 1) [IV, C].

treatment plan

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

Surgical resection is the only modality that is potentially curative, and is recommended for stages I–IVM0. The extent of optimal regional lymphadenectomy is debated. Several randomized trials have failed to show superiority of extended (D2–3) over limited (D1) lymphadenectomy, most likely due to the increased morbidity associated with the splenectomy and distal pancreatectomy performed in the studies. D2 resection without splenectomy and distal pancreatectomy is recommended [II, B]. A minimum of 14, and optimally at least 25 lymph nodes [III, B] should be recovered even if a formal D2 lymphadenectomy is not performed.

treatment of localized disease

A UK MRC randomized trial demonstrated that a treatment plan of three cycles of pre- and postoperative epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 and continuous i.v. infusion of 5-fluorouracil (5-FU) 200 mg/m^2/day (ECF) significantly improved 5-year survival from 23.0% with surgery alone to 36.3%. Main non-hematological toxicities were alopecia, nausea and vomiting. These results are supported by an FFCD trial reported in abstract [Ib, 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 with 5-FU in advanced disease and because it obviates the need for an indwelling central venous access device, many centres use epirubicin–cisplatin–capecitabine (ECX) in the perioperative setting [IV, C].

A North American Intergroup randomized trial demonstrated that five cycles of post-operative chemotherapy with 5-FU/leucovorin (LV) 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 significant association between D-level and outcome [Ib, A].

Meta-analyses have demonstrated a small survival benefit for adjuvant chemotherapy. [Ia, 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. Twenty-seven percent did not complete the 12-month course of treatment due to adverse advents. 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 [Ib, A]. These results will need to be replicated in a Western population before being generalized to this group.

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 agent and a fluoropyrimidine are generally used [Ia, A]. 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 [Ia, A], and ECF is among the most active and well-tolerated regimens. Docetaxel increases the activity of 5-FU/cisplatin, but is also clearly more toxic. Irinotecan in combination with 5-FU/LV has similar activity to 5-FU/cisplatin and can therefore also be considered in selected patients [Ib, A].

The substitution of capecitabine (X) for 5-FU (F), and oxaliplatin (O) for cisplatin (C), in the ECF regimen was examined in a recent UK NCRI trial. With a 2×2 design, the trial tested for non-inferiority between ECF, ECX, EOF and EOX. Efficacy and toxicity was comparable between arms, and the primary end-point of non-inferiority was reached. The EOX regimen was associated with a longer overall survival (11.2 compared with 9.9 months, hazard ratio 0.80, 95% confidence interval 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 at 7.6% for EOX/EOF versus 15.1% for ECX/ECF, $P = 0.0003$. This trial has made EOX the preferred regimen in many of the centers that were using the ECF regimen, because of the combination of improved efficacy and reduced risk of thromboembolism and relative ease of administration without the need for an indwelling venous access device [IIb]. ECX remains an option. Other studies also show that oxaliplatin can be substituted for cisplatin [Ia] and capecitabine for 5-FU in chemotherapy doublets [Ia], preserving efficacy and offering some toxicity benefits. A recent meta-analysis has shown that capecitabine is actually superior to infused 5-FU for overall survival within doublet and triplet regimes for advanced gastric cancer [Ia, A].

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

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 in phase II trials and are encouraging, but there are currently no data from randomized phase III trials [IIb, B].

In patients that relapse >3 months after first-line chemotherapy, consideration should be given to re-challenging the patient with the same chemotherapy regimen [IV, C].

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, C].

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 clinical practice by the experts and the ESMO faculty.

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