SEOM clinical guidelines for the diagnosis and treatment of gastric adenocarcinoma

Fernando Rivera · Cristina Grávalos · Rocío García-Carbonero

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Abstract Gastric adenocarcinomas are tumours of decreasing incidence in the Western world, although they are still the fourth leading cause of cancer mortality. The purpose of these clinical guidelines is to provide recommendations for the diagnosis and treatment of this disease based on the best available evidence. Regarding resectable gastric cancer, the various potential therapeutic options are discussed (adjuvant or perioperative chemotherapy, and adjuvant or neoadjuvant chemoradiotherapy). With regard to advanced or metastatic disease, different alternative combinations of conventional cytotoxic agents including a platinum agent (cisplatin or oxaliplatin) and a fluoropyrimidine (5-FU, capecitabine or S1), with or without a third drug (epirubicin or docetaxel), as well as their integration with new biological agents (trastuzumab in HER2+ tumours), are discussed. Finally, an outline is provided of the main lines of research and development of therapies for this disease.

Keywords Gastric adenocarcinoma · Diagnosis · Treatment · Clinical guidelines

Introduction

Gastric cancer (GC) is a major health problem given its high incidence and mortality. It accounts for 10% of all malignant tumours and it is the second leading cause of death from cancer in the world [1]. In Europe, 159,900 new cases were diagnosed and 118,200 patients died of GC in 2006, making it the fourth leading cause of death from cancer. There are large geographical differences in its incidence, which is very high in Asia and South America. In the United States, Western Europe and Australia there has been a marked reduction in distal GC over the last 50 years and, since the 1980s, this evolution has coincided with an increase in the incidence of adenocarcinomas in the lower third of the oesophagus and oesophagogastric junction (EGJ) [2]. Except for Japan, which has screening programmes, the prognosis of patients with GC is still very poor, with 5-year overall survival (OS) rates below 30% in Western countries, including Spain.

GC is more frequent among males and its incidence increases with age (peak presentation is between 65 and 74 years old). Risk factors can be genetic/familial or environmental. The familial cancer syndromes with the greatest incidence of GC include hereditary diffuse gastric cancer (HDGC) syndrome, hereditary nonpolyposis colon cancer (HNPCC), Li-Fraumeni syndrome, familial gastric polyposis, familial adenomatous polyposis and Peutz-Jeghers syndrome. Mutations in the germline of the E-cadherin (CDH1) gene are associated to HDGC but no mutations have yet been identified that increase the risk of intestinal gastric carcinoma.

It is worth noting that EGJ adenocarcinomas [which are subclassified as Siewert type I (predominantly oesophageal), Siewert II (equidistant from oesophagus and stomach) and Siewert III (predominantly gastric)] are included in these GC guidelines but these tumours could be also considered as oesophageal cancers. Environmental factors differ according to tumour location: the main risk factors of adenocarcinomas of the distal oesophagus and
EGJ are reflux oesophagitis, Barrett’s oesophagus, obesity and smoking, while gastric body and distal GCs are associated to *Helicobacter pylori* infections, the intake of food in bad condition or unrefrigerated, excess nitrates and atrophic gastritis. Proximal and distal GCs are different in their epidemiology, biology, histology and clinical expression. Although they are still therapeutically managed as a single entity, there is increasing evidence indicating that in the near future they should be addressed separately. Table 1 summarises the main clinical-pathological differences between the two groups.

These clinical guidelines aim to offer succinct, practical recommendations for diagnosis, treatment and follow-up of GC.

### Diagnosis and staging

#### Diagnosis

For diagnosis, an upper GI endoscopy is essential as well as a biopsy of the suspect lesions. Ninety percent of GCs are adenocarcinomas. The histological study should also include the Lauren classification (intestinal and diffuse). It is also advisable to determine overexpression of HER2, which will be indispensable in cases of advanced disease for which administration of trastuzumab is being considered. Immunohistochemical (IHC) tests should be conducted and validated in accordance with the specific criteria established for GC [3] (which differ from those for breast cancer) and, in the case of IHC 2+, FISH should be conducted [4].

#### Staging

Once diagnosis has been established, and in order to stage the disease and decide on the best therapeutic strategy, the following additional examinations should be carried out [5]:

- Anamnesis, physical examination and blood tests (haemogram, hepatic and renal function tests). This should include an evaluation of the patient’s functional and nutritional status, as well as geriatric assessment in the elderly.
- Computerised axial tomography (CAT) of chest and abdomen: necessary to rule out distant metastasis.
- Upper GI series and endoscopic ultrasound±FNPA of suspect adenopathies: useful to analyse the locoregional extension of the disease (T and N).
- Laparoscopy and positron emission tomography (PET) may be recommendable in potentially resectable patients, although it must be remembered that mucinous and diffuse tumours may be negative on a PET. [III, B]
- Other examinations shall be requested only if clinically indicated.

Staging should be conducted according to the 2010 TNM classification (Table 2). With regard to clinical management, patients are generally classified into four major groups:

a) Early resectable disease (stages 0, I; 10% of patients in our setting); OS at 5 years ~70%.

b) Locally advanced resectable disease (stages II–IIIC, 40% of patients); OS at 5 years ~30%.

c) Locally advanced unresectable disease (20% of patients); OS at 5 years <5%, median OS 12–14 months.

d) Metastatic disease (stage IV, 30% of patients upon diagnosis) or relapse (60% of resected patients); OS at 5 years <5%, median OS ~9–11 months.

### Treatment

The main therapeutic strategies for GC are surgery, systemic therapies and radiotherapy (RT). Active palliation also comprises an important part of treatment and includes placing an endoprosthesis, bypass surgery and support measures. Both diagnosis and treatment of GC require a multidisciplinary approach [6]. A treatment algorithm for gastric cancer is showed in Fig. 1.

Treatment of localised disease

In early resectable disease (stage I), surgery is the treatment of choice. Stages IA do not require any additional treatment whereas in some select stages IB treatment may be considered.

In locally advanced resectable or resected disease (stages II–IIIC) we recommend administering treatment in addition to surgery. For *gastric tumours not involving the EGJ*, there are currently three therapeutic approaches that have proven increased survival: adjuvant chemotherapy (CT), adjuvant chemo-radiotherapy (CT-RT) and perioperative CT. These three options have not been compared head-to-head and, although initially the three could be valid [I, A], perioperative CT is probably the one that offers the greatest potential theoretical advantages and the one most widely

<p>| Table 1 Clinical-pathological differences between cancer of the EGJ/cardias and of the gastric body |</p>
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<tr>
<th>EGJ/cardias</th>
<th>Body</th>
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<td>Incidence</td>
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