Gastric cancer

Eric Van Cutsem, Xavier Sagaert, Baki Topal, Karin Haustermans, Hans Prenen

Lancet 2016; 388: 2654–64
Published Online May 5, 2016
http://dx.doi.org/10.1016/S0140-6736(16)30354-3

Department of Gastroenterology/Digestive Oncology (Prof E Van Cutsem MD, H Prenen MD), **Department of Pathology** (X Sagaert MD), **Department of Abdominal Surgery** (Prof B Topal MD), **and Department of Radiation Oncology** (Prof K Haustermans MD), **University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium**

Correspondence to: Prof Eric Van Cutsem, Department of Gastroenterology/Digestive Oncology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium
Eric.VanCutsem@uzleuven.be

Gastric cancer is one of the leading causes of cancer-related death worldwide. Many patients have inoperable disease at diagnosis or have recurrent disease after resection with curative intent. Gastric cancer is separated anatomically into true gastric adenocarcinomas and gastro-oesophageal-junction adenocarcinomas, and histologically into diffuse and intestinal types. Gastric cancer should be treated by teams of experts from different disciplines. Surgery is the only curative treatment. For locally advanced disease, adjuvant or neoadjuvant therapy is usually implemented in combination with surgery. In metastatic disease, outcomes are poor, with median survival being around 1 year. Targeted therapies, such as trastuzumab, an antibody against HER2 (also known as ERBB2), and the VEGFR-2 antibody ramucirumab, have been introduced. In this Seminar, we present an update of the causes, classification, diagnosis, and treatment of gastric cancer.

Introduction

Gastric cancer is an important health problem, being the fourth most common cancer and the second leading cause of cancer death worldwide. More than 950 000 new diagnoses are made every year. An estimated 720 000 patients died from gastric cancer in 2012.[1] Gastric cancer is separated anatomically into true gastric adenocarcinomas (non-cardia gastric cancers), of which there were 691 000 new cases in 2012, and gastro-oesophageal-junction adenocarcinomas (cardia gastric cancers), of which there were 260 000 new cases in that year.[2] Despite a decline in incidence and mortality and despite important advances in the understanding of the epidemiology, pathology, molecular mechanisms, and therapeutic options and strategies, the burden remains high.

Gastric cancer is a main contributor to the global burden of disability-adjusted life-years from cancer in men and accounts for 20% of the total worldwide, following lung and liver cancers, which, respectively, account for 23% and 28%.[3] The burden of gastric cancer remains very high in Asia, Latin America, and central and eastern Europe, whereas in North America and most western European countries, it is no longer a common cancer.[4] Nevertheless, the decline in the incidence of gastric cancer has gradually lessened in some countries, particularly the USA. In other countries, such as France, mortality is predicted not to decrease further in the middle-aged population.[4] This slowing of change is probably explained by long-term low and stable prevalence of *Helicobacter pylori* infection in these countries.[4] By contrast, the incidence of gastro-oesophageal-junction adenocarcinomas is increasing sharply.[5] In this Seminar we provide a comprehensive overview of the aetiology, pathological features, molecular pathogenesis, diagnosis, and treatment of gastric cancer.

Search strategy and selection criteria

We searched PubMed for articles published in English up to April 30, 2015. We used the search terms "gastric cancer", "etiology", "pathology", "molecular pathogenesis", "genetics", "pathophysiology", "diagnosis", "chemotherapy", "radiation", "surgery", and "targeted agent". No other parameters were applied.

Aetiology

H pylori infection is the most important cause of sporadic distal gastric cancer.[6] During the chronic inflammation induced by *H pylori* infection and the subsequent carcinogenesis, various factors, including bacterial, host, and environmental factors, interact to facilitate damage repair. Altered cell proliferation, apoptosis, and some epigenetic modifications to the tumour suppressor genes might occur, which could eventually lead to inflammation-associated oncogenesis.[7] Some patients with persistent *H pylori* infection develop gastric atrophy followed by intestinal metaplasia, which might evolve into dysplasia and adenocarcinoma.[8–13] Whether or not eradication of *H pylori* in the absence of dysplastic or neoplastic tissues prevents development of gastric cancer is unresolved.[14]

Another pathogen associated with gastric cancer is the Epstein-Barr virus. This pathogen is found in the malignant cells, but not the normal epithelial cells, of 80% of gastric carcinomas with lymphoid stroma. Its role in carcinogenesis, however, remains unclear.[15,16]

Around 10% of gastric cancer cases are aggregated within families.[17] Truly hereditary cases are thought to account for 1–3% of all gastric cancer. They consist of three main syndromes: hereditary diffuse gastric cancer, gastric adenocarcinoma and proximal polyposis of the stomach, and familial intestinal gastric cancer. In countries and regions where the incidence of gastric cancer is low, most familial cases are probably due to heritable pathogenic mutations that increase risk from birth. A genetic basis—causative mutations in *CDH1*—has been found in only around 40% of families affected by hereditary diffuse gastric cancer. Mutations in *CTNNA1* have also been identified as a genetic cause of hereditary diffuse gastric cancer.[17] The estimated lifetime risk of developing hereditary diffuse gastric cancer by age 80 years is 67% for men and 83% for women.[18] The lifetime risk of developing breast cancer (mainly the lobular type) is increased in women with hereditary diffuse gastric cancer, up to 20–40% from 10–12%. Total

gastrectomy is recommended in at-risk family members older than 20 years who have a *CDH1* mutation, or in individuals with a positive biopsy, regardless of age.[19] In those younger than 20 years with *CDH1* mutations and those older than 20 years who have elected to delay surgery or for whom prophylactic gastrectomy is unacceptable, endoscopic surveillance is recommended.[20,21] Gastric cancers have been found in people with other hereditary cancer syndromes, such as gastric adenocarcinoma and proximal polyposis of the stomach syndrome,[17,22] and in those with mutations in *TP53* (Li-Fraumeni syndrome), *APC* (familial adenomatous polyposis), or *STK11* (Peutz-Jeghers syndrome).[17]

Environmental factors have important causal roles in gastric cancer. Low consumption of fruits and vegetables and high intake of salts, nitrates, and pickled foods, as well as smoking, have been associated with increased risk of gastric cancer.[23,24] Obesity has also been associated with an increased risk of gastric cancer (odds ratio 1·22, 95% CI 1·06–1·31),[25] and gastro-oesophageal reflux disease and obesity have been clearly related to gastro-oesophageal-junction adenocarcinoma and contribute to the increasing incidence of gastro-oesophageal-junction cancers.[5]

Classification

Anatomical

Tumour classification on the basis of anatomical location is important because true gastric (non-cardia) and gastro-oesophageal-junction cancers (cardia) differ in terms of incidence, geographical distribution, causes, clinical disease course, and treatment. Gastro-oesophageal-junction cancers are widely categorised according to the Siewert classification:[26] in true carcinomas of the cardia (Siewert type II) the tumour epicentre is located 1–2 cm below the gastro-oesophageal junction; in distal oesophageal adenocarcinomas (Siewert type I) and subcardial gastric cancers (Siewert type III) the epicentres are located at least 1 cm above or at least 2 cm below the gastro-oesophageal junction, respectively. Whether Siewert type II and type III tumours differ biologically is unclear.[27] The Siewert classification, however, has been criticised because it includes no specific criteria for identifying gastro-oesophageal-junction adenocarcinomas. To aid correct tumour classification, the TNM classification has introduced simplified categories: if the epicentre of the tumour is in the distal oesophagus, the gastro-oesophageal junction, or within the proximal 5 cm of the stomach, with the tumour mass extending into the gastro-oesophageal junction or distal oesophagus, it is classified as an oesophageal carcinoma; if the epicentre is within 5 cm of the gastro-oesophageal junction but the tumour does not extend into the gastro-oesophageal junction or oesophagus, or if the epicentre is more than 5 cm distal to the gastro-oesophageal junction, the tumour is classified as a gastric carcinoma.[28]

Histological

Most gastric cancers are gastric adenocarcinomas, but are highly heterogeneous with respect to architecture and growth, cell differentiation, histogenesis, and molecular pathogenesis. This variety partly explains the diversity of histopathological classification schemes. The most commonly used are the Lauren[29] and WHO[30] schemes. According to the Lauren classification, gastric carcinomas are separated into two main histological types, diffuse and intestinal, in addition to the mixed and indeterminate types. Diffuse carcinomas are poorly differentiated and are composed of solitary or poorly cohesive tumour cells in the absence of gland formation. By contrast, intestinal carcinomas are mostly well to moderately differentiated and form glandular structures reminiscent of colorectal adenocarcinomas, which explains the subtype name.

Although the Lauren scheme is simple and robust, the WHO classification, which includes five main histopathological cancer entities, has the advantage that it is in accordance with histological classifications of cancers in other parts of the gut and improves classification harmonisation. The WHO categories are based on the predominant histological patterns of the carcinoma (tubular, papillary, mucinous, poorly cohesive, and rare variants). The prominent feature often coexists with less dominant histological elements. The WHO tubular and papillary carcinomas roughly correspond to the intestinal type described by Lauren, and poorly cohesive carcinomas (encompassing cases constituted partly or totally by signet ring cells) correspond to the Lauren diffuse type.[31]

Molecular

The Cancer Genome Atlas research network has published the results of full genomic profiling of 295 primary gastric adenocarcinomas.[32] Through complex statistical analyses, four tumour subgroups were identified: positive for Epstein-Barr virus (9%), microsatellite unstable tumours (22%), genomically stable tumours (20%), and chromosomally unstable tumours (50%). Correlation with histological characteristics revealed enrichment of the diffuse subtype in the genomically stable group (73%). Frequency of chromosomally unstable tumours was increased in gastro-oesophageal-junction adenocarcinomas, and most tumours positive for Epstein-Barr virus were located in the fundus or body of the stomach. Finally, tumours positive for this virus were mostly found in men (81%), but predominance of microsatellite unstable tumours slightly favoured women (56%).[32]

Classification of gastric carcinomas based on molecular subtypes might be used in the near future to determine prognosis and to customise treatment (figure 1). The molecular features of chromosomally unstable and microsatellite unstable tumours are the best understood of the subgroups. Chromosomal

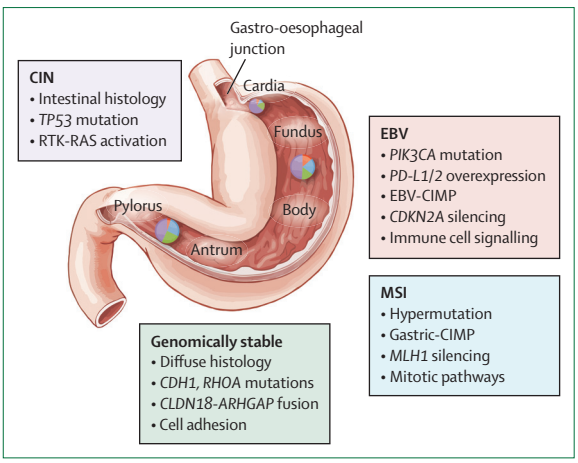

Figure 1: **Molecular characterisation of subtypes of gastric carcinomas**
CIN=chromosomally unstable tumours. EBV=Epstein-Barr virus-infected tumours. CIMP=CpG island methylation phenotype. MSI=microsatellite unstable tumours. Reproduced from reference 32 by permission of Nature Publishing Group.

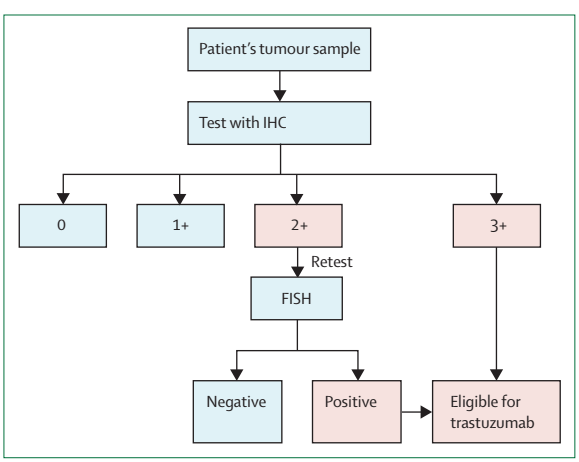

Figure 2: **Testing algorithm for *HER2* status in gastric and gastro-oesophageal-junction adenocarcinomas**
IHC=immunohistochemistry. FISH=fluorescence in-situ hybridisation.

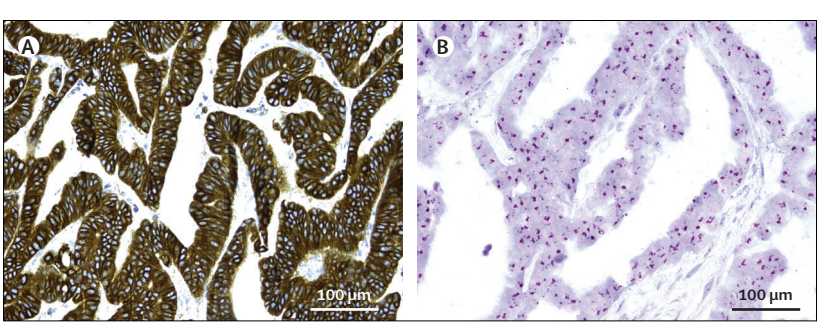

Figure 3: **Histological appearance of *HER2*-positive tumour**
(A) Immunohistochemistry intensity score 3+. (B) Amplification of the *HER2* gene shown by a red *HER2* probe in a chromogenic in-situ hybridisation test.

instability is characterised by DNA aneuploidy, structural changes of chromosomes (eg, translocations), and mutations in various proto-oncogenes and tumour-suppressor genes,[32,33] and is associated with response to cisplatin-based chemotherapy and poor survival.[34] Microsatellite instability is characterised by genomic instability due to a deficient DNA mismatch repair system.[32] In microsatellite unstable sporadic gastric cancer, the mismatch repair defect is most frequently caused by an epigenetic event, which is hypermethylation in the *MLH1* promoter region.[35] In rare cases, a germline mutation in a mismatch repair gene is inherited and causes Lynch syndrome or hereditary non-polyposis colorectal cancer syndrome, which most often leads to colorectal and endometrial cancer, but gastric cancers also arise in up to 10% of families.[36] Microsatellite unstable gastric cancers caused by hypermethylation or mutations are generally intestinal type tumours (Lauren classification) with antral location, less frequent lymph-node metastasis, non-responsiveness to fluorouracil, and a better prognosis than those not located antrally.[37–39]

Molecular classification based on *HER2* (also known as *ERBB2*) status was introduced for gastric cancers because of therapeutic implications. HER2, which is a member of the human epidermal growth factor receptor (EGFR) family of proteins, is a transmembrane tyrosine-kinase receptor that regulates cell proliferation, differentiation, and survival.[40] 12–20% of gastric adenocarcinomas are *HER2* positive (by gene amplification, protein overexpression, or both).[41] Some studies have reported that *HER2*-positive status in gastric cancer is associated with worsening of prognosis, increased aggressiveness of disease, and shortened survival,[42–46] but others have reported no prognostic value for *HER2* status.[47] The ToGA trial[48] showed that trastuzumab, a humanised monoclonal antibody against HER2, when combined with chemotherapy, was associated with extended overall survival and progression-free survival in people with *HER2*-positive advanced gastric cancers. *HER2* testing, therefore, was adopted as a routine test in advanced disease (figure 2). Gastric carcinomas are defined as *HER2* positive if the immunohistochemical intensity score is 3+ or 2+ with positive fluorescence in-situ hybridisation ([FISH] figure 3). Only five clustered positive cancer cells in a tissue biopsy sample or at least 10% of neoplastic cells positive in a surgical resection specimen are needed to achieve these scores provided that the immunostaining reveals intense complete basolateral or lateral membranous positivity. Further classifications based on molecular alterations are being developed.[49–52]

Symptoms and diagnosis

Most patients with early-stage gastric cancer are asymptomatic and, therefore, diagnosis is frequently made when disease is at an advanced stage. The most common symptoms at diagnosis are anorexia, dyspepsia, weight loss, and abdominal pain. Patients with tumours at the gastro-oesophageal junction or proximal stomach might also present with dysphagia.

The diagnosis of gastric cancer relies on endoscopy and biopsy. Endoscopic ultrasonography and CT of the chest and abdomen are currently the primary means of staging for locally advanced gastric cancer. Laparoscopy is used to exclude small-volume peritoneal metastatic disease. A meta-analysis showed that the sensitivity and specificity of endoscopic ultrasonography could discriminate between T1–T2 (superficial) and T3–T4 (advanced) gastric carcinomas, with sensitivity of 0·86 (95% CI 0·81–0·90).[53] The sensitivity values for diagnosis of superficial tumours (T1a *vs* T1b) and lymph node status (positive *vs* negative) were 0·87 (0·81–0·92) and 0·83 (0·79–0·87), respectively.[53]

PET-CT and MRI are not routinely used for staging in gastric cancer, although growing evidence suggests that PET-CT could improve staging through increased detection of involved lymph nodes and metastatic disease. These tests, however, are not always informative, especially in patients with mucinous tumours, as they might understage the disease.[54,55] A role for MRI also seems to be emerging, especially for the detection of peritoneal metastases. Intraperitoneal metastases are common in people with gastric or gastro-oesophageal-junction carcinomas, and are difficult to diagnose with conventional imaging methods.

Laparoscopic staging, with or without peritoneal lavage for malignant cells, remains controversial, but expert groups recommend this approach in patients with potentially curable gastric or gastro-oesophageal-junction carcinomas.[55,56] Peritoneal lavage showing positive cytology, in the absence of macroscopic peritoneal metastases, is associated with poor survival and is defined as metastatic disease.[57] Serosal infiltration is a strong indicator of peritoneal carcinomatosis, which develops in up to 60% of patients with gastric cancer.[58]

The TNM classification should be recorded and the corresponding stage determined according to the seventh edition of the guidelines and staging manual.[59,60] Careful tumour staging by an experienced team is crucial to ensure that appropriate treatment and interventions are selected.

Surgical treatment

Adequate surgical resection is the only curative therapeutic option for gastric cancer.[61,62] Endoscopic resection might be suitable as an alternative to surgery for small well differentiated early-stage tumours (T1a),[55,63] Advances in technology and minimally invasive strategies have created new opportunities for surgery in gastric cancer. Minimally invasive procedures are associated with reduced surgical trauma and immunosuppression compared with conventional open surgery and, therefore, might improve quality of care as long as the principles of surgical oncology are respected.

The extent of surgery is determined by tumour stage, diameter, location, and histological type. Adequate surgery in the stomach is defined as complete resection of the primary cancer with tumour-free surgical margins of at least 4 cm and adequate lymphadenectomy. In practice, these requirements correspond to total gastrectomy for gastric cancers with signet-ring cells (linitis plastica), and those located in the upper third of the stomach or with atrophic gastritis. Cancer in the lower two-thirds of the stomach can often be treated with subtotal gastrectomy. Surgery in Japan and east Asia has traditionally been more extensive and aggressive than that in other developed countries. Although there is no worldwide consensus on the degree of lymphadenectomy, D2 lymphadenectomy (perigastric [D1] plus coeliac artery and its branches) is generally recommended if the associated postoperative morbidity and mortality rates are acceptably low—for instance, in high-volume hospitals with experienced surgeons.[64] This approach has contributed to improved cure rates in various registries and studies, from 30% to up to 55% in the past decade. Other reasons are stage migration because of improved methods for staging, increased use of adjuvant and neoadjuvant therapies, and centralisation of surgery, which has led to improvements in postoperative mortality.[65] At least 16 lymph nodes should be removed to enable adequate tumour staging and ensure optimum surgical resection.

Transabdominal total gastrectomy is the standard surgical approach to treat patients with Siewert type II or III cancer of the gastro-oesophageal junction. The procedure is extended with a transhiatal resection of the distal oesophagus and lymphadenectomy of the lower mediastinum and the abdominal D2 nodal compartment. A thoracoabdominal approach in these patients can increase the risk of morbidity without improving survival and, therefore, is not usually recommended to treat cardia (type II) or subcardia (type III) gastric cancers.[66]

Early gastric cancer is limited to the mucosa or submucosa (pathologically staged as T1 or lower), regardless of nodal status. Even in early gastric cancer, use of a multidisciplinary approach to determine the best therapeutic strategy (ie, endoscopic or surgical resection) is mandatory because lymph-node metastases occur in up to 20% of patients and correlate well with tumour penetration of the stomach wall and large tumour diameter.[67,68] Endoscopic versus surgical management of early gastric cancer has not been studied in randomised clinical trials, but surgical resection is viewed as the gold standard and is associated with 5-year recurrence-free survival of up to 98%.[69] For patients with early disease and suspected or histologically proven lymph-node metastasis, endoscopic resection should not be attempted. For mucosal gastric carcinoma (T1a), endoscopic resection is deemed sufficient in all European guidelines because the incidence of lymph-node metastatic disease is very low.[63,68] If the histopathological findings confirm a submucosal carcinoma (T1b) after endoscopic resection, surgical resection that includes systematic lymphadenectomy has to be done, because lymph-node involvement is seen in up to 20% of these patients. Endoscopic resection of early gastric cancer

should be done as a complete en-bloc resection to allow full histological assessment of the lateral and basal margins.[63] Patients who have endoscopic resection should be monitored frequently by endoscopic surveillance.

Most patients with locally advanced gastric cancer, which invades the muscularis propria and beyond (pathologically staged as T2 or higher), present with metastases in lymph nodes, distant organs, or both. Locally advanced gastric cancer might need en-bloc resection of involved structures. Prophylactic splenectomy is discouraged because it increases the risk of operative morbidity and mortality without any survival benefit, but might be necessary if the spleen or its hilar lymph nodes are affected.[70] Only patients without metastatic disease are potential candidates for surgical management with curative intent, although selected patients with peritoneal carcinomatosis or positive peritoneal cytology might benefit from aggressive surgery in expert centres.[71] Several randomised clinical trials and cohort studies have addressed the use of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for prevention and treatment of peritoneal carcinomatosis from gastric cancer. A systematic review and meta-analysis of 20 prospective randomised clinical trials involving 2145 patients suggested that cytoreductive surgery with hyperthermic intraperitoneal chemotherapy was associated with improved overall survival at 1, 2, and 3 years, but not at 5 years.[71] Most of the trials, however, did not fulfil high-quality standards. With modern combination systemic chemotherapy regimens and biological agents, well designed randomised clinical trials with robust methods are needed to confirm the potential benefits of this approach.

Over the past decade, minimally invasive surgery by laparoscopy has gained widespread acceptance in surgical oncology. The procedure seems to be feasible and safe and can represent an alternative to treat early and advanced gastric cancers in expert centres. A meta-analysis and systematic review[72] of studies with 3411 patients showed that laparoscopic distal gastrectomy compared with open surgery was associated with similar lymph-node dissection and long-term survival and with reduced intraoperative blood loss, postoperative complications, analgesic consumption, and length of hospital stay. Another meta-analysis[73] of data from 1819 patients in ten eligible studies showed similar overall and disease-free survival for laparoscopic and open gastrectomy in expert centres. Laparoscopic gastrectomy was also associated with similar lymph-node dissection and reduced intraoperative blood loss, postoperative complications, and length of hospital stay. However, because of potential study biases and notable heterogeneity between studies assessing short-term and long-term outcome measures in gastric cancer, data from well designed randomised clinical trials with robust methods should be awaited before laparoscopic gastrectomy is implemented in daily clinical practice.

Management of locally advanced disease

Adjuvant and neoadjuvant therapies are generally accepted to improve disease-free survival and overall survival in patients who have undergone adequate complete surgical resection (R0) of locally advanced gastric cancer by eradicating microscopic disease locoregionally and at a distance from the primary tumour. 5-year overall survival is increased by 10–15% with the addition of these treatments, but there is no global consensus about the optimum strategy. Perioperative chemotherapy additional to R0 is the most popular strategy in Europe, whereas in the USA it is postoperative chemoradiotherapy, and in Asia it is postoperative chemotherapy.[61,62] Adjuvant and neoadjuvant therapies are generally recommended for patients with T3, T4, or node-positive tumours.

Two European studies have shown improved outcomes with perioperative chemotherapy, including fluoropyrimidine-based and platinum-based chemotherapy, and with postoperative chemotherapy. In the MAGIC trial,[74] treatment with three cycles of the epirubicin, cisplatin, and fluorouracil regimen before and after surgery was compared with surgery alone in patients with resectable stage II and III gastric cancers. In the chemotherapy group, 5-year overall survival was 36%, compared with 23% in the surgery alone group. A French study[75] of perioperative fluorouracil and cisplatin showed similar results. Fluorouracil is frequently replaced by capecitabine on the basis of findings from several studies, as discussed later in this Seminar. Subgroup analyses suggested the largest benefits are achieved in patients with gastro-oesophageal-junction tumours. Potential advantages of preoperative chemotherapy include the possibility of reducing tumour size and burden, controlling microscopic disease, and increasing the likelihood of achieving an R0 resection.

The US 0116 trial[76] randomised patients with T3, node-positive, or both, gastric cancers to undergo surgery alone or with postoperative chemoradiation (bolus fluorouracil and leucovorin before, during, and after radiotherapy of up to 45 Gy in 1·8 Gy fractions). The potential advantage of the postoperative treatment is that patients are surgically and pathologically staged before it is started. The goal of postoperative radiation is to eradicate microscopic disease remaining in the surgical bed. By adding chemotherapy, malignant cells in the irradiated volume are radiosensitised and microscopic deposits outside are treated. Adjuvant chemoradiotherapy was associated with substantial reductions in overall and locoregional relapse. Subset analyses showed robust treatment benefits in all subgroups except patients with diffuse histology,[77] although this finding has been criticised, mainly because surgery was suboptimum (54% of patients underwent less than D1 dissection).

The ARTIST trial[78] in South Korea was done to assess the efficacy of postoperative chemotherapy with capecitabine and cisplatin, with or without radiation to

45 Gy, in patients who underwent D2 lymph-node dissection. Overall, the addition of radiotherapy to chemotherapy did not significantly extend disease-free survival or overall survival, but in patients with pathologically proven lymph-node metastasis, disease-free survival was longer in those who received chemoradiation than in those who received chemotherapy alone (estimated 3-year disease-free survival 77·5% *vs* 72·3%, p=0·0365). The ARTIST-II trial is underway and is randomising patients with lymph-node-positive gastric cancer to receive postoperative chemotherapy or chemoradiation (NCT01761461). In the CRITICS study, being done in Europe, all patients with stage Ib–IVa non-metastatic gastric cancer are being assigned to receive preoperative chemotherapy followed by at least a D1 resection, then random assignment to postoperative chemotherapy or chemoradiotherapy (NCT00407186).

Asian studies have shown traditionally larger benefits from an adjuvant chemotherapy than have those in developed countries. The Japanese ACTS-GC trial[79] showed a survival benefit with the oral fluoropyrimidine derivative S-1 after D2 resection, and the Korean CLASSIC trial[80] showed improved overall survival and disease-free survival with postoperative combined capecitabine and oxaliplatin. Moreover, although most other randomised studies showed no significant benefit in overall survival with adjuvant chemotherapy, a large meta-analysis confirmed a 6% absolute survival benefit with fluorouracil-based postoperative chemotherapy compared with surgery alone in all subgroups assessed.[81]

Preoperative chemoradiotherapy is frequently used in patients with oesophageal and gastro-oesophageal-junction tumours, although results from randomised trials of preoperative chemoradiotherapy in gastric cancer are not yet available. Preoperative chemoradiation has clear potential advantages. Delineation of the target for radiation is easier when the tumour is still in place, and generally leads to smaller irradiated volumes and thus less acute and fewer late toxic effects than postoperative chemoradiation. Moreover, preoperative treatment leads to downstaging and downsizing, which increase the possibility of achieving an R0 resection. In theory, the tumour bed is better vascularised before than after surgery, which increases drug exposure and radiosensitivity. The Australian and European TOP GEAR phase 2/3 trial is being done to compare perioperative chemotherapy with preoperative chemoradiotherapy followed by postoperative chemotherapy (NCT01924819).

Management of metastatic disease

The outlook for patients with metastatic gastric cancer is very poor, with median survival ranging from 4 months when treated only with best supportive care to around 12 months when treated with combination cytotoxic chemotherapy.[82–84] Studies have also shown improved quality of life. Patients with good performance status scores and with organ function should be offered the option to receive systemic chemotherapy for palliation and to improve survival.

Several cytotoxic agents are active against gastric cancer: fluoropyrimidines (fluorouracil, capecitabine, and S-1), platinums (cisplatin and oxaliplatin), taxanes (paclitaxel, docetaxel), the anthracycline epirubicin, and the topoisomerase inhibitor irinotecan. When used alone these agents elicit poor responses, with the greatest being with fluoropyrimidines (20–40% in older studies),[82–85] taxanes (20%),[86,87] and irinotecan (20%).[88] Only a few randomised trials have compared these drugs alone (mostly fluorouracil) with combination regimens. Separately the studies showed no or small differences in survival,[82,89–93] but a Cochrane meta-analysis[82] indicated a significant survival benefit in favour of combination chemotherapy (median survival 8·3 *vs* 6·7 months).

Table 1 summarises a selection of landmark trials for combination chemotherapy in metastatic gastric cancer. In the early 1980s combined fluorouracil, doxorubicin, and mitomycin was a standard regimen.[94] In 1991, a randomised phase 3 study[95] showed improved survival

	Treatment regimen	Number of patients	Proportion with response to treatment	Overall survival (months)
MacDonald et al, 1980[94]	Fluorouracil, doxorubicin, and mitomycin	62	42%	5·5
Wils et al, 1991[95]	Fluorouracil, adriamycin, and mitomycin *vs* fluorouracil, adriamycin, and methotrexate	79 *vs* 81	9% *vs* 41%	6·7 *vs* 9·7
Webb et al, 1997[96]	Epirubicin, cisplatin, and fluorouracil *vs* fluorouracil, adriamycin, and methotrexate	111 *vs* 108	45% *vs* 21%	8·9 *vs* 5·7
Van Cutsem et al, 2006[97]	Cisplatin and fluorouracil *vs* docetaxel, cisplatin, and fluorouracil	133 *vs* 137	24% *vs* 24%	8·2 *vs* 9·6
Cunningham et al, 2008[98]	Epirubicin, cisplatin, and fluorouracil *vs* epirubicin, cisplatin, and capecitabine *vs* epirubicin, oxaliplatin, and fluorouracil *vs* epirubicin, oxaliplatin, and capecitabine	263 *vs* 250 *vs* 245 *vs* 244	41% *vs* 46% *vs* 42% *vs* 48%	9·9 *vs* 9·9 *vs* 9·3 *vs* 11·2
Al-Batran et al, 2008[99]	Fluorouracil, leucovorin, and cisplatin *vs* fluorouracil, leucovorin, and oxaliplatin	108 *vs* 112	25% *vs* 35%	8·8 *vs* 10·7
Ajani et al, 2010[100]	Cisplatin and fluorouracil *vs* cisplatin and S-1	526 *vs* 527	32% *vs* 29%	7·9 *vs* 8·6

Table 1: **Landmark phase 3 trials of first-line cytotoxic chemotherapy regimens for advanced or metastatic gastric cancer**

with combined fluorouracil, doxorubicin, and methotrexate compared with fluorouracil, doxorubicin, and mitomycin (10·5 *vs* 7·3 months). This regimen became a reference regimen until further increased overall survival was shown with the epirubicin, cisplatin, and fluorouracil regimen (8·9 *vs* 5·7 months).[96] Epirubicin-containing regimens are still used in some countries as reference regimens, although the importance of adding epirubicin has become controversial. The Cochrane meta-analysis[82] suggests a role for epirubicin, whereas the meta-analysis of the GASTRIC group,[101] which was based on data from individual patients, showed no role for epirubicin in combination with a fluoropyrimidine and a platinum.

Improved overall survival was reported for the combination of docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil alone (table 1).[97] Although the frequency of toxic effects was higher with the triplet regimen, this schedule offered a non-surgical first-line treatment option for patients with good performance status scores and with organ function. Various modified docetaxel, cisplatin, and fluorouracil regimens have also been proposed for metastatic and recurrent gastric cancers.[102] The randomised phase 3 REAL2 trial[98] used a two-by-two design to investigate an epirubicin-based regimen in which capecitabine was substituted for fluorouracil and oxaliplatin was substituted for cisplatin, and revealed no differences from epirubicin, cisplatin, and fluorouracil in overall survival, progression-free survival, or response between the four regimens. Another phase 3 trial confirmed that cisplatin can be substituted by oxaliplatin with comparing fluorouracil, leucovorin, and oxaliplatin with fluorouracil, leucovorin, and cisplatin.[99] Therefore, oxaliplatin and capecitabine are suitable alternatives to cisplatin and fluorouracil.

S-1 is an oral combination fluoropyrimidine that is most widely used in Asia. It includes tegafur, (a prodrug of fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase), and oteracil (an inhibitor of phosphorylation of intestinal fluorouracil). The double inhibition leads to increased concentrations of cytostatic drugs in serum and tumour tissues.[103] The SPIRITS trial[90] assessed S-1 alone and in combination with cisplatin, and showed extended overall survival with the combination regimen (13 *vs* 11 months). Subsequently, a large study across various countries was done in which more than 1000 patients were randomly assigned to receive cisplatin plus fluorouracil or S-1.[100] Overall survival did not differ between groups, and the combination with S-1 had a more favourable side-effect profile, although this improvement might have been related to lower cisplatin dose intensity in the S-1 group than in the fluorouracil group (93·3% *vs* 98·0%).

Irinotecan is active against metastatic gastric cancer, but is not approved for use in gastric cancer because it is not superior to fluorouracil and cisplatin.[104] Several trials have assessed irinotecan combined with docetaxel, cisplatin, fluoropyrimidines, or combinations of these drugs,[93,105–107] but no superiority has been shown in phase 3 trials for any irinotecan-based schedule over a cisplatin-based triple regimen.

Chemotherapy as part of second-line treatment can improve overall survival, although not substantially. Several small non-randomised and a few randomised studies[108–110] have shown activity against gastric cancer with docetaxel, paclitaxel, or irinotecan in second-line therapy. In a large Asian phase 3 trial,[109] patients previously treated with fluoropyrimidines and a platinum were randomly assigned to receive either best supportive care or chemotherapy (docetaxel or irinotecan). Second-line chemotherapy was associated with a median improvement of 1·5 months in overall survival (5·3 *vs* 3·8 months). In an English trial,[110] a similar benefit was seen for overall survival as well as a clinical benefit.

The overall survival in trials from east Asia is usually slightly longer than that in developed countries. This difference might be because patients in east Asia are treated with later lines of chemotherapy more frequently, possibly because of lower tumour burden owing to earlier diagnosis. Evidence that molecular characteristics also contribute to this difference is increasing, but has been not been shown definitively and is a topic of continuing research.

The most frequently used standard first-line chemotherapy regimen in metastatic gastric cancer is a combination of a fluoropyrimidine with a platinum, although triple regimens including docetaxel might be useful in otherwise healthy patients with a high tumour burden. Median survival does usually not exceed 1 year.[97,98] In patients with good performance status and organ function, second-line treatment with agents that were not used in first-line treatments (ie, taxanes or irinotecan) can lead to slight survival benefits.[109,110]

Targeted therapies have been introduced for clinical use in patients with advanced gastric cancer. Up to 20% of gastric tumours overexpress the HER2 receptor,[41,48,111] mostly because of *HER2* amplification. The pivotal ToGA trial[48] was the first randomised, prospective, multicentre phase 3 trial to study the efficacy of first-line trastuzumab (a monoclonal antibody against HER2) in patients with HER2-positive advanced gastric or gastro-oesophageal-junction cancer. Patients were randomly assigned to receive standard chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy plus trastuzumab. Of 3665 patients originally screened for *HER2*, 810 (22%) had *HER2*-positive tumours (immunohistochemistry intensity score of 3+ or 2+ and HER2:CEP17 ratio ≥2 on FISH). 584 were enrolled and received study treatment at least once. Median overall survival was 13·8 months in the trastuzumab group, compared with 11·1 months in the chemotherapy group. The longest survival (median 16·0 months) was seen in patients with high HER2 protein overexpression and *HER2* amplification. On the basis of this study,

	Treatment	Number of patients (randomisation ratio)	Endpoint	Survival (months)	Hazard ratio (95% CI)	p value
REGARD[117]	BSC *vs* BSC plus ramucirumab	335 (2:1)	Overall survival	3·8 *vs* 5·2	0·776 (0·603–0·998)	0·0047
RAINBOW[118]	Paclitaxel *vs* paclitaxel plus ramucirumab	665 (1:1)	Overall survival	7·4 *vs* 9·6	0·807 (0·678–0·962)	0·0169

BSC=best supportive care.

***Table 2*: Phase 3 studies of ramucirumab as second-line treatment for advanced gastric cancer**

trastuzumab in combination with cisplatin and a fluoropyrimidine has been approved for first-line treatment of advanced *HER2*-positive gastric and gastro-oesophageal-junction adenocarcinomas. There are currently no data on the second-line use of trastuzumab.

Randomised trials have included assessments of antibodies against EGFR in combination with chemotherapy, but results have generally shown no benefits. For instance, the EXPAND trial of cetuximab[112] and the REAL3 trial of panitumumab[113] showed no benefits in patients with metastatic gastric cancer. Lapatinib, a tyrosine-kinase inhibitor targeting EGFR and HER2, plus paclitaxel showed activity in the second-line treatment of patients with HER2-positive advanced gastric cancer (positive on FISH and with an immunohistochemical intensity score of 3+), but did not significantly improve overall survival when assessed by intention to treat.[114]

New and promising agents targeting the HER2 receptor are under investigation. Pertuzumab and TDM-1 are being studied in phase 3 studies in, respectively, first-line and second-line treatment of *HER2*-positive gastric adenocarcinoma. Antiangiogenic agents have also been investigated as treatments for advanced gastric cancer. Bevacizumab, an antibody against vascular endothelial growth factor (VEGF), did not improve overall survival when used in combination with capecitabine and cisplatin compared with placebo in the AVAGAST trial,[115] but a benefit was seen in progression-free survival in the entire population and in overall survival among patients from non-Asian countries.[115] VEGF-1 concentrations in plasma and tumour neuropilin-1 concentrations are potential biomarkers for predicting clinical outcomes in patients with advanced gastric cancer treated with bevacizumab.[116]

Despite the failure of bevacizumab in first-line trials, targeting VEGFR-2 with the antibody ramucirumab, proved useful in second-line treatment of advanced gastric cancer. In the phase 3 REGARD trial,[117] patients with metastatic gastric cancer progressive after first-line chemotherapy that included a fluoropyrimidine and a platinum were randomly assigned to receive ramucirumab or placebo plus best supportive care. Overall survival was significantly extended in the ramucirumab group, with a similar survival benefit to that seen with conventional second-line chemotherapy (table 2). The RAINBOW trial[118] assessed ramucirumab in combination with paclitaxel versus paclitaxel alone for second-line treatment of advanced gastric cancer, and showed a significantly improved median survival with the combined regimen (table 2). With a favourable side-effect profile compared with cytotoxic chemotherapy, treatment with ramucirumab has become a useful option in second-line treatment or a reference option in combination with paclitaxel in patients with good performance status scores and organ function.

Several other biological targeted agents are being or have been investigated. Everolimus showed no survival benefit compared with placebo in second-line or third-line treatment, despite interesting activity in early clinical trials.[119] The hepatocyte growth factor HGF and its receptor, the transmembrane tyrosine kinase cMET, and the fibroblast growth factor receptor are among the candidate targets for new agents in advanced gastric cancer.[49,65] Additionally, in view of the new data from the Cancer Genome Atlas research network, CD274 (programmed cell death 1 ligand 1) and PDCD1LG2 (programmed cell death 1 ligand 2) may serve as emerging targets for treatment,[32] and initial promising results have been reported with pembrolizumab.[120]

Conclusions

Progress has been made in understanding the pathogenesis and the molecular biology of gastric cancer and in optimising the available treatment options and modalities. However, in the future, the focus should be on further unravelling the taxonomy of gastric cancer, fine-tuning treatment strategies, and developing new drugs for patients with advanced gastric cancer.

Contributors

EVC conceived the Seminar. EVC and HP did the literature searches. All authors contributed to the writing, review, and approval of the paper.

Declaration of interests

We declare no competing interests.

References

1 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; **49:** 1374–403.

2 Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 2015; **64:** 1881–88.

3 Soerjomataram I, Lortet-Tieulent J, Parkin D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012; **380:** 1840–50.

4 Ferro A, Peleteiro B, Malvezzi M, et al. Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. *Eur J Cancer 2014*; **50:** 1330–44.

5 Pohl H, Sirovich B, Welch H. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev* 2010; **19:** 1468–70.

6 Bornschein J, Selgrad M, Warnecke M, Kuester D, Wex T, Malfertheiner P. *H. pylori* infection is a key risk factor for proximal gastric cancer. *Dig Dis Sci.* 2010; **55:** 3124-31.

7 Wang F, Meng W, Wang B, et al. *Helicobacter pylori*-induced gastric inflammation and gastric cancer. *Cancer Lett 2014*; **345:** 196–202.

8 Correa P. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48:** 3554–60.

9 Leung WK, Lin SR, Ching JY, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. *Gut* 2004; **53:** 1244–49.

10 Ley C, Mohar A, Guarner J, et al. *Helicobacter pylori* eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev* 2004; **13:** 4–10.

11 Mera R, Fontham E, Bravo L, et al. Long term follow up of patients treated for Helicobacter pylori infection. *Gut* 2005; **54:** 1536–40.

12 You W, Brown L, Zhang L, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst* 2006; **98:** 974–83.

13 Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372:** 392–97.

14 Ito M, Takata S, Tatsugami M, et al. Clinical prevention of gastric cancer by *Helicobacter pylori* eradication therapy: a systematic review. *J Gastroenterol* 2009; **44:** 365–71.

15 Wu M, Shun C, WU C, et al. Epstein-Barr virus-associated gastric carcinomas: relation to H. pylori infection and genetic alterations. *Gastroenterology* 2000; **118:** 1031–38.

16 Wang H, Wu M, Shun C, et al. Lymphoepithelioma-like carcinoma of the stomach: a subset of gastric carcinoma with distinct clinicopathological features and high prevalence of Epstein-Barr virus infection. *Hepatogastroenterology* 1999; **46:** 1214–19.

17 Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. *Lancet Oncol* 2015; **16:** e60–70.

18 Pharoah T, Guilford P, Caldas C, et al. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology* 2001; **121:** 1348–53.

19 Blair V, Martin I, Shaw D, et al. Hereditary. Hereditary diffuse gastric cancer: diagnosis and management. *Clin Gastroenterol Hepatol* 2006; **4:** 262–75.

20 Kaurah P, MaxMillan A, Boyd N, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA* 2007; **297:** 2360–72.

21 Shaw D, Blair V, Framp A, et al. Chromoendoscopic surveillance in hereditary diffuse gastric cancer: an alternative to prophylactic gastrectomy? *Gut* 2005 **54:** 461–68.

22 Worthley D, Phillips K, Wayte N, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome. *Gut* 2012; **61:** 774–79.

23 Lunet N, Valbuena C, Vieira A, et al. Fruit and vegetable consumption and gastric cancer by location and histological type: case-control and meta-analysis. *Eur J Cancer Prev* 2007; **16:** 312–27.

24 Ladeiras-Lopes R, Pereira A, Nogueira A, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control* 2008; **19:** 689–701.

25 Yang P, Zhou Y, Chen B, et al. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer* 2009; **45:** 2867–73

26 Siewert J, Stein H. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1998; **85:** 1457–59.

27 Demicco EG, Farris AB 3rd, Baba Y, et al. The dichotomy in carcinogenesis of the distal esophagus and esophagogastric junction: intestinal-type vs cardiac-type mucosa-associated adenocarcinoma. *Mod Pathol* 2011; **24:** 1177–90.

28 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging manual, 7th edn. New York, NY: Springer, 2010.

29 Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64:** 31–49.

30 Lauwers G, Carneiro F, Graham D. Gastric carcinoma. In: Bosman FT, Carneiro F, Hruban RH, Thiese ND, eds. WHO classification of tumours of the digestive system, 4th edn. Lyon: IARC, 2010: 44–58.

31 Carneiro F. Classification of gastric carcinomas. *Curr Diagn Pathol* 1997; **4:** 51–59.

32 Bass A, Thorsson V, Shmulevich I, et al. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513:** 202–09.

33 Lengauer C, Kinzler K, Vogelstein B. Genetic instabilities in human cancers. *Nature* 1998; **396:** 643–49.

34 Ott K, Vogelsang H, Mueller J, et al. Chromosomal instability rather than p53 mutation is associated with response to neoadjuvant cisplatin-based chemotherapy in gastric carcinoma. *Clin Cancer Res* 2003; **9:** 2307–15.

35 Fleisher AS, Esteller M, Wang S, et al. Hypermethylation of the hMLH1 gene promoter in human gastric cancers with microsatellite instability. *Cancer Res* 1999; **59:** 1090–95.

36 Gylling A, Abdel-Rahman W, Juhola M, et al. Is gastric cancer part of the tumour spectrum of hereditary non-polyposis colorectal cancer? A molecular genetic study. *Gut* 2007; **56:** 926–33.

37 Beghelli S, de Manzoni G, Barbi S, et al. Microsatellite instability in gastric cancer is associated with better prognosis in only stage II cancers. *Surgery* 2006; **139:** 347–56.

38 Wu M, Lee C, Shun C, et al. Distinct clinicopathologic and genetic profiles in sporadic gastric cancer with different mutator phenotypes. *Genes Chromosomes Cancer* 2000; **27:** 403–11.

39 Grundei T, Vogelsang H, Ott K, et al. Loss of heterozygosity and microsatellite instability as predictive markers for neoadjuvant treatment in gastric carcinoma. *Clin Cancer Res* 2000; **6:** 4782–88.

40 Akiyama T, Sudo C, Ogawara H, et al. The product of the human *c-erbB-2* gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. *Science* 1986; **232:** 1644–46.

41 Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer* 2015; **18:** 476–84

42 Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008 **19:** 1523–29.

43 Rüschoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. *Virchows Arch* 2010; **45:** 299–307.

44 Park D, Yun J, Park J, et al. HER-2/neu amplification is an independent prognostic factor in gastric cancer. *Dig Dis Sci* 2006; **51:** 1371–79.

45 Tanner M, Hollmén M, Junttila T, et al. Amplification of HER-2 in gastric carcinoma: association with topoisomerase IIα gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. *Ann Oncol* 2005; **16:** 273–78.

46 Begnami M·Fukuda E, Fregnani J, et al. Prognostic implications of altered human epidermal growth factor receptors (HERs) in gastric carcinomas: HER2 and HER3 are predictors of poor outcome. *J Clin Oncol* 2011; **29:** 3030–36.

47 Yoon H, Shi Q, Sukov W, et al. Association of HER2/ErbB2 expression and gene amplification with pathologic features and prognosis in esophageal adenocarcinomas. *Clin Cancer Res* 2012; **18:** 546–54.

48 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:** 687–97.

49 Tan IB, Ivanova T, Lim KH, et al. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology* 2011; **141:** 476–85.

50 Deng N, Goh LK, Wang H, et al. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. *Gut* 2012 **61:** 673–84.

51 Zouridis H, Deng N, Ivanova T, et al. Methylation subtypes and large-scale epigenetic alterations in gastric cancer. *Sci Transl Med* 2012; **4:** 156ra140.

52 Lei Z, Tan I, Das K, et al. Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil. *Gastroenterology* 2013; **145:** 554–65.

53 Mocellin S, Pasquali S. Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. *Cochrane Database Syst Rev* 2015; **2:** CD009944.

54 Altini C, Niccoli Asabella A, Di Palo A et al. FDG PET/CT role in staging of gastric carcinomas: comparison with conventional contrast enhancement computed tomography. *Medicine* 2015; **94:** e864.

55 Waddell T, Verheij M, Allum W, et al. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013 **24** (suppl 6): vi57–63.

56 Van Cutsem E, Van de Velde C, Roth A, et al. Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and Treatment of Cancer (EORTC)-gastrointestinal cancer group. *Eur J Cancer* 2008; **44:** 182–94,

57 Mezhir J, Shah M, Jacks L, et al. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. *Indian J Surg Oncol* 2011; **2:** 16–23.

58 Nakamura K, Ueyama T, Yao T, et al. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 1992; **70:** 1030–37.

59 Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours, 7th edn. Oxford: Wiley-Blackwell, 2009.

60 Edge S, Compton C. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17:** 1471–74.

61 Van Cutsem E, Dicato M, Geva R et al. The diagnosis and management of gastric cancer: expert discussion and recommendations from the 12th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2010. *Ann Oncol* 2011; **22** (suppl 5): v1–9.

62 Lutz M, Zalcberg J, Ducreux M, et al. Highlights of the EORTC St. Gallen international expert consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer—differential treatment strategies for subtypes of early gastroesophageal cancer. *Eur J Cancer* 2012; **48:** 2941–53

63 Moehler M, Baltin C, Ebert M, et al. International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus. *Gastric Cancer* 2015; **18:** 550–63.

64 Songun I, Putter H, Kranenbarg E, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11:** 439–49.

65 Lordick F, Allum W, Carneiro F, et al. Unmet needs and challenges in gastric cancer: the way forward. *Cancer Treat Rev* 2014; **40:** 692–700.

66 Sasako M, Sano T, Yamamoto S, et al, for the Japan Clinical Oncology Group (JCOG9502). Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol* 2006; **7:** 644–51.

67 An J, Baik Y, Choi M, et al. Predictive factors for lymph node metastasis in early gastric cancer with submucosal invasion: analysis of a single institutional experience. *Ann Surg* 2007; **246:** 749–53.

68 Dinis-Ribeiro M, Areia M, de Vries A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). *Endoscopy* 2012; **44:** 74–94.

69 Youn H, An J, Choi M, et al. Recurrence after curative resection of early gastric cancer. *Ann Surg Oncol* 2010; **17:** 448–54.

70 Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501. *J Clin Oncol* 2004; **22:** 2767–73.

71 Coccolini F, Cotte E, Glehen O, et al. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. *Eur J Surg Oncol* 2014; **40:** 12–26.

72 Zeng Y, Yang Z, Peng J, et al. Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer: evidence from randomized and nonrandomized clinical trials. *Ann Surg* 2012; **256:** 39–52.

73 Choi Y, Bae J, An J, et al. Laparoscopic gastrectomy for advanced gastric cancer: are the long-term results comparable with conventional open gastrectomy? A systematic review and meta-analysis. *J Surg Oncol* 2013; **108:** 550–56.

74 Cunningham D, Allum W, Stenning S, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355:** 11–20.

75 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:** 1715–21

76 Macdonald J, Smalley S, 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:** 725–30.

77 Smalley S, Benedetti J, Haller D, 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:** 2327–33.

78 Lee J, Lim do H, 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:** 268–73.

79 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:** 4387–93.

80 Bang Y, Kim Y, Yang H, et al, for the CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379:** 315–21.

81 Paoletti X, Oba K, Burzykowski T, et al, for the GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010; **303:** 1729–37.

82 Wagner A, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010; **3:** CD004064.

83 Murad A, Santiago F, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993; **72:** 37–41.

84 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:** 163–68.

85 Hong Y, Song S, Lee S, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol* 2004; **15:** 1344–47.

86 Mavroudis D, Kourousis C, Androulakis N, et al. Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor (G-CSF): a phase II trial. *Am J Clin Oncol* 2000; **23:** 341–44.

87 Sulkes A, Smyth J, Sessa C, et al, for the EORTC Early Clinical Trials Group. Docetaxel (Taxotere) in advanced gastric cancer: results of a phase II clinical trial. *Br J Cancer* 1994; **70:** 380–83.

88 Köhne C, Catane R, Klein B, et al. Irinotecan is active in chemonaive patients with metastatic gastric cancer: a phase II multicentric trial. *Br J Cancer* 2003; **89:** 997–1001.

89 Cullinan S, Moertel C, Wieand H, et al, for the North Central Cancer Treatment Group. Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer. *J Clin Oncol* 1994; **12:** 412–16.

90 Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9:** 215–221.

91 Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003; **21:** 54–59.

92 Lutz M, Wilke H, Wagener D, et al. Weekly infusional high-dose fluorouracil (HD-FU), HD-FU plus folinic acid (HD-FU/FA), or HD-FU/FA plus biweekly cisplatin in advanced gastric cancer: randomized phase II weekly infusional high-dose fluorouracil (HD-FU), HD-FU plus folinic acid (HD-FU/FA), or HD-FU/FA plus biweekly cisplatin in advanced gastric cancer: randomized phase II trial 40953 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group and the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2007; **25:** 2850–55.

93 Boku N, Yamamoto S, Fukuda H, et al, for the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol* 2009; **10:** 1063–69.

94 MacDonald JS, Schein PS, Woolley PV, et al. 5-fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980; **93:** 533–36.

95 Wils J, Klein H, Wagener D, et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin—a step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991; **9:** 827–31.

96 Webb A, Cunningham D, Scarffe J, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 2007; **15:** 261–67.

97 Van Cutsem E, Moiseyenko V, 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:** 4991–97.

98 Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358:** 36–46.

99 Al-Batran S, Hartmann J, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26:** 1435–42.

100 Ajani J, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010; **28:** 1547–53.

101 Oba K, Paoletti X, Bang YJ, et al, for the GASTRIC Group. Role of chemotherapy for advanced/recurrent gastric cancer: an individual-patient-data meta-analysis. *Eur J Cancer* 2013; **49:** 1565–77.

102 Van Cutsem E, Boni, C, Tabernero, J, et al. Randomized phase II study (GATE study) of docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer. *Ann Oncol* 2015; **26:** 149–56.

103 Chu Q, Hammond L, Schwartz G, et al. Phase I and pharmacokinetic study of the oral fluoropyrimidine S-1 on a once-daily-for-28-day schedule in patients with advanced malignancies. *Clin Cancer Res* 2004; **10:** 4913–21.

104 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:** 1450–57.

105 Enzinger P, Ryan D, Clark J, et al. Weekly docetaxel, cisplatin, and irinotecan (TPC): results of a multicenter phase II trial in patients with metastatic esophagogastric cancer. *Ann Oncol* 2009; **20:** 475–80.

106 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 Study—FFCD 9803. *J Clin Oncol 2004*; **22:** 4319–28.

107 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:** 3520–26

108 Thuss-Patience P, 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:** 2306–14.

109 Kang J, Lee SI, Lim Do H, 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:** 1513–18.

110 Ford H, Marshall A, Bridgewater J, et al, for the COUGAR-02 Investigators. 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.

111 Jørgensen J. Targeted HER2 treatment in advanced gastric cancer. *Oncology* 2010; **78:** 26–33.

112 Lordick F, Kang Y, Chung H, et al, for the Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators. 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:** 490–99.

113 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:** 481–89.

114 Satoh T, Xu RH, Chung HC et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN-A randomized, phase iii study. *J Clin Oncol* 2014; **32:** 2039–49.

115 Ohtsu A, Shah M, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29:** 3968–76

116 Van Cutsem E, de Haas S, Kang Y, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012; **30:** 2119–27.

117 Fuchs C, Tomasek J, Yong C, et al, for the REGARD Trial Investigators. 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.

118 Wilke H, Muro K, Van Cutsem E, et al, for the RAINBOW Study Group. 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:** 1224–35.

119 Ohtsu A, Ajani J, Bai Y, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31:** 3935–43.

120 Muro K, Bang Y, Shankaran V, et al. A phase 1B study of pembrolizumab (PEMBRO; MK-3475) in patients with advanced gastric cancer. *Ann Oncol* 2014; **25** (suppl 4)**:** LBA15.