



## Gastric cancer

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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.<sup>1</sup> 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.<sup>2</sup> 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%.<sup>3</sup> 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.<sup>4</sup> 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.<sup>4</sup> This slowing of change is probably explained by long-term low and stable prevalence of *Helicobacter pylori* infection in these countries.<sup>4</sup> By contrast, the incidence of gastro-oesophageal-junction adenocarcinomas is increasing sharply.<sup>3</sup> In this Seminar

we provide a comprehensive overview of the aetiology, pathological features, molecular pathogenesis, diagnosis, and treatment of gastric cancer.

### Aetiology

*H pylori* infection is the most important cause of sporadic distal gastric cancer.<sup>6</sup> 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.<sup>7</sup> Some patients with persistent *H pylori* infection develop gastric atrophy followed by intestinal metaplasia, which might evolve into dysplasia and adenocarcinoma.<sup>8–13</sup> Whether or not eradication of *H pylori* in the absence of dysplastic or neoplastic tissues prevents development of gastric cancer is unresolved.<sup>14</sup>

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.<sup>15,16</sup>

Around 10% of gastric cancer cases are aggregated within families.<sup>17</sup> 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.<sup>17</sup> The estimated lifetime risk of developing hereditary diffuse gastric cancer by age 80 years is 67% for men and 83% for women.<sup>18</sup> 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

#### 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.

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.<sup>19</sup> 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.<sup>20,21</sup> Gastric cancers have been found in people with other hereditary cancer syndromes, such as gastric adenocarcinoma and proximal polyposis of the stomach syndrome,<sup>17,22</sup> and in those with mutations in *TP53* (Li-Fraumeni syndrome), *APC* (familial adenomatous polyposis), or *STK11* (Peutz-Jeghers syndrome).<sup>17</sup>

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.<sup>23,24</sup> Obesity has also been associated with an increased risk of gastric cancer (odds ratio 1.22, 95% CI 1.06–1.31),<sup>25</sup> 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.<sup>5</sup>

## 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:<sup>26</sup> 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.<sup>27</sup> 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.<sup>28</sup>

### 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<sup>29</sup> and WHO<sup>30</sup> 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.<sup>31</sup>

### Molecular

The Cancer Genome Atlas research network has published the results of full genomic profiling of 295 primary gastric adenocarcinomas.<sup>32</sup> 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%).<sup>32</sup>

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

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