Molecular Diagnostics in Esophageal and Gastric Neoplasms: 2018 Update

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KEYWORDS

• Esophagus • Squamous cell carcinoma • Adenocarcinoma • Gastric carcinoma • Molecular genetics • HER-2 • Trastuzumab • Next-generation sequencing

KEY POINTS

- Esophageal cancer (EC) is rapidly increasing in incidence in the United States. Genetic changes associated with the development of EC involve the p16, p53, and APC genes. Human epidermal growth factor 2 (HER-2) overexpression is seen in gastroesophageal junction carcinoma and a subset, gastric carcinoma (GC).
- Trastuzumab is the first Food and Drug Administration–approved target agent for treatment of patients with HER-2 amplified cancers.
- Up to 50% cases of GC are related to *Helicobacter pylori* infection and up to 16% are related to Epstein-Barr virus infection.
- Microsatellite instability (MSI) is observed in up to 39% of GC. American Joint Committee on Cancer *AJCC Cancer Staging Manual* recommends MSI testing on GC.
- Other genetic changes seen in GC include chromosome gains and losses, MSI, changes in expression of vascular endothelial growth factor expression, cyclin E, retinoblastoma, p53, and protection of telomeres 1.

INTRODUCTION

Esophageal carcinoma (EC) is the most rapidly increasing tumor in incidence in the United States. It has an established association with a precursor lesion (Barrett esophagus). Gastric carcinoma (GC) is the second leading cause of cancer death in the world. Most genetic alterations reported in esophageal carcinoma do not show significant differences compared with GC.

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Up to half of the cases of GC are related to *Helicobacter pylori* infection.[1–5] The prognosis for patients with advanced stage GC and EC is poor. Human epidermal growth factor 2 (HER-2) overexpression is seen in gastroesophageal junction (GEJ) carcinoma and a subset of GC. HER-2 overexpressing tumors are eligible for HER-2–targeted therapies, which leads to a better survival in these patients.

EPIDEMIOLOGY

EC is the sixth leading cause of cancer death worldwide.[6] Two subtypes of EC, squamous cell carcinoma and adenocarcinoma (ADC), differ in the incidence and distribution of disease.[6] Squamous cell EC is more prevalent in the Asia-Pacific region, whereas ADC is more common in the Western world. EC is common in men more than 50 years of age, with a strong prevalence in whites.

Squamous cell EC is related to smoking and alcohol, whereas Barrett esophagus, caused by gastroesophageal reflux disease, is the risk factor for ADC.[7] The tumors evolve through a pathway from metaplasia (Barrett esophagus) to dysplasia and finally to cancer.[7]

The incidence of GC is the highest in Eastern Asia, Eastern Europe, and South America.[8] Distal stomach tumors are more common in Asia and tend to have a favorable outcome with surgery[9] compared with gastric cardia tumors, which are more common in US patients.[8]

Diffuse GC has a hereditary form and results from cadherin 1 or E-cadherin (CDH1) deregulation, whereas occurrence of intestinal type is associated with environmental factors, such as obesity, dietary factors, and cigarette smoking as well as with infection by *H pylori.*

CLINICAL FEATURES

EC presents with obstructive symptoms, including dysphagia and odynophagia. Weight loss is also common. Most patients with GC are asymptomatic. Epigastric pain and dyspepsia are the most frequent symptoms. Most tumors are located on the lesser curvature and are 2 cm to 5 cm in size. Multiple tumors are associated with a worse prognosis.[10]

PATHOPHYSIOLOGY AND MOLECULAR GENETICS

The evolution of ADC of the esophagus involves earlier losses of the p16 and p53 genes and later losses of the APC gene.[11] Aneuploidy occurs early and can be found before cancer occurs.

A multistep process has been proposed for GC starting with chronic gastritis to atrophic gastritis, intestinal metaplasia, and dysplasia before resulting in intestinal-type GC.[12] Premalignant counterparts are not seen in diffuse-type cancers.

Helicobacter pylori

H pylori is implicated with atrophic gastritis, intestinal metaplasia, and dysplasia leading to intestinal-type GC.[13,14] A positive association is demonstrated in regions where high-risk CagA (1) *H pylori* strains are endemic.[15] Bacterial virulence factors contributing to GC risk include vacA, babA2, OipA, and CagA.[16] Single-nucleotide polymorphisms in interleukin (IL)-1b and endogenous receptor antagonists (IL-1RN) are associated with increased susceptibility to *H pylori*–induced GC.[17,18]