Genetics of Gastric Cancer

Matthew S. Strand, MD[a], Albert Craig Lockhart, MD, MHS[b], Ryan C. Fields, MD[a,*]

KEYWORDS

• Gastric adenocarcinoma • Gastric cancer • Hereditary gastric cancer syndromes • Genetics • Targeted therapy • Immunotherapy • Prophylactic gastrectomy

KEY POINTS

- Gastric cancer carries a poor prognosis, is typically diagnosed at a late stage, and has significant geographic differences in incidence and mortality; environmental factors including *Helicobacter pylori* infection, smoking, and diet play a role in many cases.
- Next-generation sequencing has led to molecular classification systems that serve as adjuncts to traditional histologic schemes; these new systems are being used to design new targeted therapies and implement them in clinical trials.
- To date, most trials using targeted therapies against specific mutations have yielded disappointing results, with the notable exception of trastuzumab for HER2+ gastric cancers.
- Immunotherapy has demonstrated some benefit in select cases, with response rates correlating roughly with the mutational burden of the tumor.
- Hereditary syndromes recognized thus far account for about 1% to 3% of gastric cancer cases, but are associated with early onset and aggressive disease, making prophylactic gastrectomy the treatment of choice for many cases.

INTRODUCTION

Gastric cancer represents the third leading cause of cancer mortality worldwide, with an estimated incidence of 951,000 cases, causing 723,000 deaths annually.[1] The American Cancer Society estimates that in the United States in 2016, 26,370 cases of gastric cancer will be diagnosed and 10,730 will die from the disease.[2] More than 70% of new cases arise in the developing world, and despite an overall decline in age-adjusted incidence, the absolute incidence is increasing because of an aging population. Host risk factors in the United States include male gender, age, and nonwhite race.[3] Established environmental risk factors include *Helicobacter pylori* infection, smoking, consumption of foods high in salt or N-nitroso compounds such as processed or smoked meats, and Epstein-Barr virus (EBV) infection.[4] Interestingly,

[a] Department of Surgery, Barnes-Jewish Hospital and Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8109, St Louis, MO 63110, USA; [b] Department of Medicine, Barnes-Jewish Hospital and Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8056, St Louis, MO 63110, USA
* Corresponding author.
E-mail address: fieldsr@wudosis.wustl.edu

Surg Clin N Am 97 (2017) 345–370
http://dx.doi.org/10.1016/j.suc.2016.11.009
surgical.theclinics.com

the incidence of gastric cancer seems to be increasing in younger age groups; however, the cause of this phenomenon is unknown.[5]

This article aims to cover the genetics of gastric cancer as it is currently understood, focusing first on recently developed molecular classification schemes that are useful adjuncts to older histopathological systems. After delving into the molecular subtypes and their defining features, the article discusses additional molecular alterations present across multiple subtypes that are actively being explored for targeted therapy. The results of clinical trials targeting these pathways are presented, followed by a brief review of immunotherapy in gastric cancer. Finally, hereditary gastric cancer and syndromes associated with gastric cancer are summarized.

CLASSIFICATION OF GASTRIC CANCER

The advent of next-generation sequencing and molecular characterization techniques has revolutionized the classification of gastric cancer from a histopathological system to a system based on molecular patterns. The Lauren system, developed in 1965, divides gastric cancer into diffuse and intestinal subtypes,[6] whereas the World Health Organization classification system uses 4 categories: papillary, tubular, mucinous, and poorly cohesive subtypes.[7] Although these older histopathological systems are useful for informing prognosis, they are poor predictors of response to therapy.[8] Modern molecular classification schemes developed within the last few years aim not only to inform prognosis but also to form a framework to predict treatment response, develop targeted therapies, and eventually guide clinical decisions. Two major cancer research groups, The Cancer Genome Atlas Research Group (TCGA) and the Asian Cancer Research Group (ACRG), have developed molecular classification systems based on gene expression profiling.[9,10]

The TCGA system classifies gastric cancer into 4 subtypes: EBV-positive (EBV), microsatellite unstable (MSI), chromosomally unstable (CIN), and genomically stable (GS). These subtypes were derived by subjecting chemotherapy-naive gastric cancers to 6 molecular analyses: whole exome sequencing, somatic copy number analysis, DNA methylation profiling, messenger and microRNA sequencing, and protein analysis. Cluster analysis for each of the 6 modalities was performed, and the results were integrated, yielding 4 distinct gastric cancer subtypes. Hallmarks of each subtype are demonstrated in **Fig. 1**; these molecular features may play a role in defining treatment groups. For example, EBV and MSI gastric cancers have been shown to exhibit significantly higher PD-L1 expression and a greater degree of T-lymphocyte infiltration compared with EBV-negative or GS tumors, suggesting a role for immunotherapy in these subtypes.[11]

EBV-subtype gastric cancers are defined by infection with EBV and comprise approximately 9% of all gastric cancers.[12] More than 75% of the EBV-positive gastric cancers occur in male patients, and most are located in the fundus or body of the stomach. Additional hallmarks of the EBV-subtype include extreme CpG island methylator phenotype, CDKN2A (p16INK4A) promoter hypermethylation, overexpression of PD-L1 and PD-L2, and a PIK3CA mutation rate exceeding 80%. These findings may indicate a role for immunotherapy and PI(3)-kinase inhibition in this subtype.

MSI tumors are characterized by elevated mutation rates, hypermethylation of MLH1 (in contrast to EBV tumors), and frequent mutations in PIK3CA, ERBB2, ERBB3, epidermal growth factor receptor (EGFR), and MHC class 1 genes. Unlike MSI colorectal cancers, gastric MSI tumors lack BRAFV600E mutations. These cancers tend be diagnosed in older patients, with a median age at diagnosis of 72 years. There is also a slight but significant female predominance (56%). In small, preliminary