Pathology of Gastric Cancer and Its Precursor Lesions

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KEYWORDS

• Chronic gastritis • *Helicobacter pylori* • Atrophic gastritis • Intestinal metaplasia
• Spasmolytic polypeptide–expressing metaplasia • Intestinal-type adenocarcinoma
• Diffuse (signet ring) type adenocarcinoma • Proximal gastric cancer

KEY POINTS

- The intestinal and diffuse types of gastric adenocarcinoma have unique and overlapping epidemiologic, pathogenetic, molecular, and histologic features.
- The development of the intestinal type of gastric adenocarcinoma is a multistep process starting with chronic gastritis triggered by *Helicobacter pylori* and progressing through atrophy, intestinal metaplasia, and dysplasia to carcinoma (Correa model).
- In addition to intestinal metaplasia a distinct type of metaplasia, spasmolytic polypeptide–expressing metaplasia, has been recognized and has a strong association with the intestinal type of gastric adenocarcinoma.
- Loss of E-cadherin expression caused by *CDH1* gene alteration is the primary carcinogenic event in the Carneiro model of the hereditary diffuse gastric cancer.
- Proximal gastric adenocarcinoma results from either gastroesophageal reflux or *Helicobacter pylori* gastritis, each with distinct morphologic, immunohistochemical, and molecular features.

INTRODUCTION

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer-related death worldwide.[1] Although the incidence of gastric cancer in North America is lower than other parts of the world, survival remains poor. It has been recognized that gastric carcinogenesis is a multistep process.[2] Precancerous conditions, including chronic *Helicobacter pylori*–associated gastritis, epithelial atrophy, intestinal and spasmolytic polypeptide–expressing metaplasia (SPEM), and precancerous lesions (dysplasia or intraepithelial neoplasia) precede the development of the intestinal type of gastric adenocarcinoma. Recent genetic advances have shed light on the molecular pathogenesis of hereditary diffuse gastric cancer (HDGC). A

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better understanding and definition of gastric cancer and the molecular events preceding its development is critical in the prevention, diagnosis, and targeted therapy for this malignancy.

CLASSIFICATION OF GASTRIC CANCER

Gastric cancer is not a single disease, but a heterogeneous group of tumors with different morphologies, molecular backgrounds, and histogenesis. Most (95%) gastric malignancies originate from glandular epithelium and are designated as adenocarcinoma. Several systems have been proposed to aid in the classification of gastric adenocarcinoma based on macroscopic features (Borrmann)[3] or exclusively on the histologic tumor growth pattern (Ming, Carniero, Goseki).[4–6] The two most commonly used histologic classifications are the Lauren and World Health Organization (WHO) systems (**Table 1**).[7,8] More recently, molecular classifications based on gene expression profiles and proteomics have been proposed; however, these have not been routinely used.[9–11]

Lauren Classification: Intestinal and Diffuse Types of Gastric Cancer

A seminal classification system of gastric adenocarcinomas was introduced by Lauren[7] in the mid-1960s. The Lauren scheme separates gastric adenocarcinomas into two primary types: intestinal and diffuse. Tumors exhibiting features of both the intestinal and diffuse types are designated as mixed-type adenocarcinoma. **Table 2** summarizes the clinicopathologic features of the intestinal and diffuse types of gastric adenocarcinoma. In the past, intestinal-type tumors were considered more common, accounting for more than 50% of gastric adenocarcinomas; however, more recently the incidences of intestinal and diffuse cancers have been shown to be equal in the Western world.[12] The intestinal type is characterized by the formation of glands exhibiting various degrees of differentiation and extracellular mucin production (**Fig. 1**A). In contrast, the diffuse type of gastric adenocarcinoma is composed of poorly cohesive cells with no gland formation (see **Fig. 1**B). This type of tumor often contains cells with abundant intracytoplasmic mucin, known as “signet ring cells.”

The Lauren classification is used by pathologists in routine practice, and by epidemiologists and clinicians for evaluating the natural history of gastric adenocarcinoma, especially with regard to incidence trends, and etiologic precursors,[13] although all

Table 1
Lauren and World Health Organization classification systems of gastric cancer

Lauren	World Health Organization 2010
Intestinal type	Papillary adenocarcinoma Tubular adenocarcinoma Mucinous adenocarcinoma
Diffuse type	Poorly cohesive carcinoma (including signet ring cell carcinoma and other variants)
Mixed type (equal intestinal and diffuse)	Mixed type, mixture of glandular (tubular/papillary) and poorly cohesive/signet ring
Indeterminate	Undifferentiated carcinoma
	Adenosquamous carcinoma Carcinoma with lymphoid stroma (medullary carcinoma) Hepatoid adenocarcinoma Squamous cell carcinoma