Chapter 1
Introduction

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In 1965, Laurén introduced a classification that would continue to prove its value many decades later. He recognized the existence of two major subtypes of gastric cancer: intestinal and diffuse [1]. This classification reveals profound differences in carcinogenesis, epidemiology, risk factors, molecular characteristics, prognosis, and, possibly, response to treatment. Diffuse-type adenocarcinomas have a number of special features that distinguish them from intestinal-type gastric adenocarcinomas.

Histologically, diffuse carcinomas show a lack of gland formation and less intercellular cohesion, leading to the detection of scattered small clusters of cells infiltrating the stroma, spatially separated from the primary tumor. These cells may or may not contain abundant cytoplasmic mucin producing the classic aspect of signet-ring cell. Laurén's diffuse subtype includes signet-ring cell carcinoma, which was also included in various histologic classifications, such as undifferentiated type by Nakamura in 1968 [2], infiltrative type by Ming in 1977 [3], and high grade by the American Joint Committee on Cancer/Union for International Cancer Control in 2010 [4].

Despite a progressive reduction in gastric cancer incidence and mortality, recent decades have witnessed a steady increase in the incidence of signet-ring cell gastric cancer from 0.3 cases per 100,000 persons in 1973 to 1.8 cases per 100,000 persons in 2000 in the USA [5]. Diffuse subtype is more often diagnosed at younger ages and is more evenly distributed between the sexes [6, 7].

Patients with Laurén's diffuse gastric adenocarcinoma have a worse prognosis. Locoregional disease has shown increased risk of distant recurrence and peritoneal spread [8–11]. Furthermore, gastric cancer patients with advanced disease and diffuse subtype showed reduced overall survival in a recent meta-analysis [11].

In contrast to intestinal-type gastric adenocarcinoma, the diffuse subtype is less linked to environmental factors usually associated with multistep carcinogenesis,

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and precancerous lesions have not been identified. On the other hand, there is a strong association between diffuse gastric adenocarcinoma and hereditary diffuse gastric syndrome due to germline mutations in the cancer-predisposing gene *CDH1* [12]. At the molecular level, hereditary or sporadic diffuse gastric cancer usually shows a lack of E-cadherin expression or other adhesion molecules, although association with *Helicobacter pylori* has also been detected [13]. The frequency of microsatellite instability, CDX2, and HER2 expression is reduced in diffuse gastric cancer in comparison to the intestinal-type subtype [14–16].

These molecular differences may have implications for personalized treatment strategies, although the appropriate design of a tailored approach remains under investigation. The present book will present detailed, current, state-of-the-art knowledge on diffuse gastric cancer, shedding light on its epidemiology, molecular characteristics, diagnosis, and surveillance and discuss appropriate treatment for affected patients. However, the science of many of these aspects is still evolving, and much remains to be discovered that will improve the care of patients suffering from diffuse gastric cancer.

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