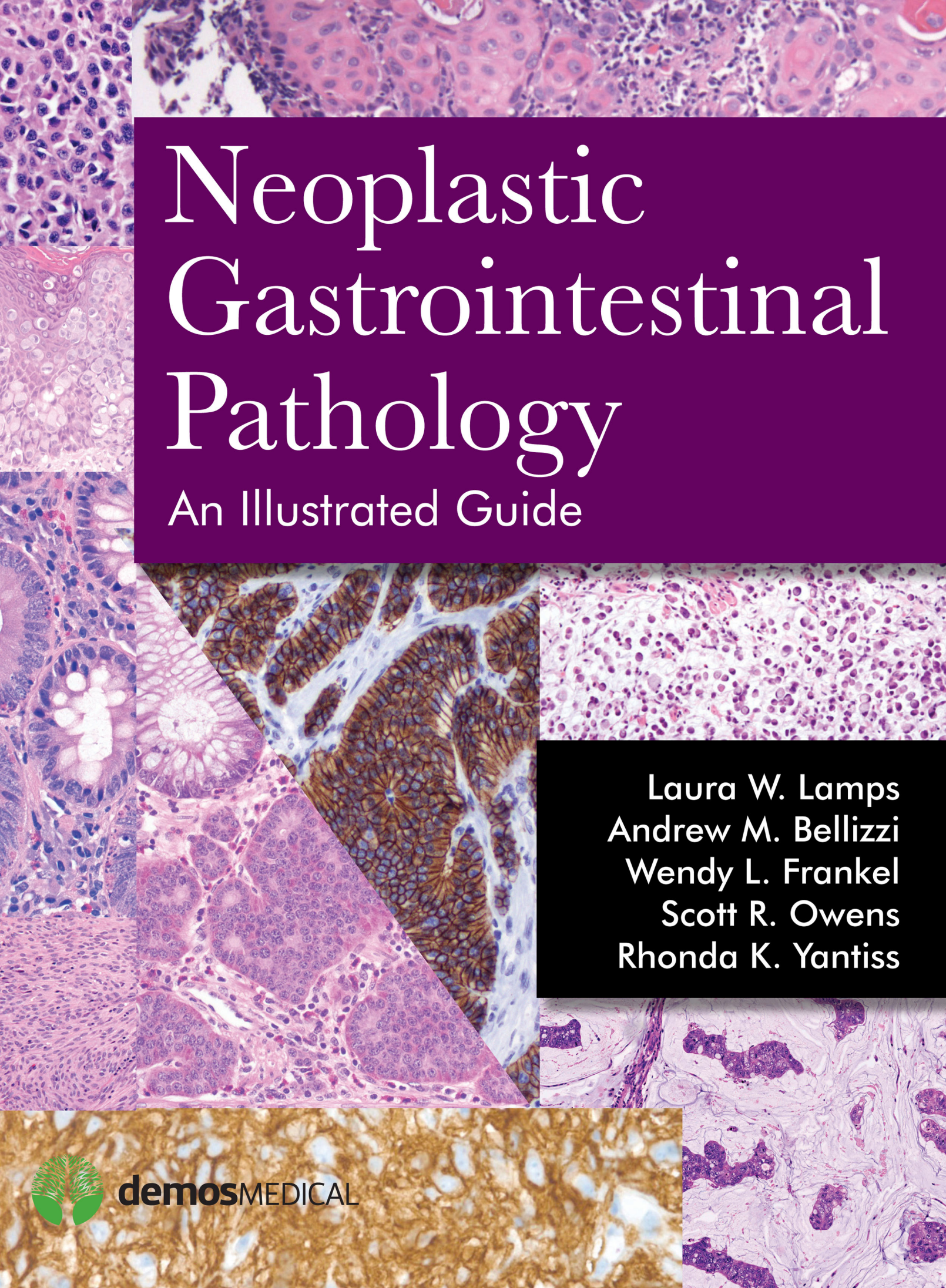

Neoplastic Gastrointestinal Pathology

An Illustrated Guide

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Andrew M. Bellizzi
Wendy L. Frankel
Scott R. Owens
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An Illustrated Guide

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To
Dr. Aubrey J. Hough, Jr.
Chairman, UAMS Dept. of Pathology, 1981–2002
Thank you for giving me the best job ever—LWL

To Sara May and Aidan, for standing by me through thick and thin; to Ed, Wendy, and Jason, for showing me how to be an academic surgical pathologist; to my students, especially Michael, Marty, Bryan, Tom, and Emily, for encouraging me to do great things—AMB

To my husband Brian Rubin for his endless patience—WLF

To Brendan, whose curiosity astounds me and whose precocious wisdom humbles me—SRO

For Madeleine and Zachary, my little loves—RKY

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Preface

"*Omnis cellula e cellula* (All cells come from cells)."
—Rudolph Virchow

Cancer remains one of the leading causes of mortality worldwide, and gastrointestinal malignancies (particularly colorectal, gastric, and esophageal) are responsible for a significant number of cancer deaths around the globe. In addition to the histologic criteria required for the diagnosis of gastrointestinal tumors, knowledge of ever-evolving staging parameters, immunohistochemical markers, and molecular testing for both prognosis and therapeutics is necessary. *Neoplastic Gastrointestinal Pathology: An Illustrated Guide* is intended to serve as an approachable and practical reference for pathologists that includes all of the information needed to evaluate and report these specimens in daily practice.

I am fortunate to have had the opportunity to create this book with a uniquely talented and dedicated group of co-authors; their contributions reflect both their diagnostic abilities and their passion for education. It is my hope that the organization of the book, combined with the extensive number and variety of illustrations, will prove to be a valuable reference companion for all aspects of neoplastic gastrointestinal pathology. We would also like to specifically acknowledge certain colleagues who provided invaluable help and support on this project. Rhonda Yantiss would like to acknowledge Dr. Wade Samowitz for sharing his seemingly endless funds of knowledge and patience. Wendy Frankel would like to thank Shawn Scully in the Department of Pathology at OSU for help with the figures. Personally, I would like to extend a special thanks to all of my residents, fellows, and colleagues who have contributed cases and photographs over the years.

Laura W. Lamps
Andrew M. Bellizzi
Wendy L. Frankel
Scott R. Owens
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Neoplastic Gastrointestinal Pathology: An Illustrated Guide

1

Introduction to Diagnosis and Reporting of Gastrointestinal Tract Neoplasia

ANDREW M. BELLIZZI

INTRODUCTION

This chapter introduces key terminology used throughout this book, including neoplasia, dysplasia, and the benign–malignant dichotomy. General criteria for grading non-neuroendocrine carcinomas, neuroendocrine neoplasms, lymphomas, gastrointestinal stromal tumors (GISTs), and sarcomas are discussed, as are broad issues pertaining to staging. The importance of synoptic reporting of cancer resection specimens is emphasized. Prognostic and predictive markers are distinguished, and several key examples are presented. The concepts of screening and surveillance are reviewed, again with several key examples. The chapter concludes with a general approach to the diagnosis and reporting of biopsy and resection specimens.

KEY TERMINOLOGY

Neoplasia

The term neoplasia is derived from Greek and literally means new growth, creation, or formation. Mid-twentieth century Australian pathologist Rupert Allan Willis's definition of neoplasia is often cited, stating that, "A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change." This definition emphasizes the proliferative and autonomous nature of tumors. Neoplasms need not form "masses of tissue," however. For example, the precursor lesions of inflammation-associated adenocarcinomas are typically flat, and tubular adenomas initially arise in a single crypt.

Clonality and the Benign/Malignant Dichotomy

The idea that all the neoplastic cells in a tumor are the progeny of a single mutated cell is referred to as **clonality**. Although clonality implies neoplasia, it does not equate with malignancy, as benign neoplasms are also clonal. Recent investigations have further emphasized that neoplasms, particularly malignant ones, typically have unstable genomes in addition to being clonal.

Malignancy is characterized by invasive growth and the capacity for metastasis. For epithelial tumors in the tubal gut, the relationship between the anatomic extent of invasion and metastatic risk varies with anatomic site. For example, invasion into the lamina propria in the esophagus, stomach, and small intestine denotes metastatic risk (albeit low). In the colon, invasive neoplasms confined to the mucosa (sometimes termed intramucosal carcinoma) do not metastasize. Conversely, benign tumors typically do not recur after complete excision and do not metastasize.

As suggested by the example of intramucosal carcinoma of the colon above, the benign–malignant dichotomy and the terms associated with this concept are insufficient to describe the spectrum of all tumor behavior. Some neoplasms are locally destructive, yet nonmetastasizing; this phenotype has been described as "intermediate." Examples include verrucous carcinoma of the esophagus or anus and desmoid fibromatosis. For other tumors, the

assessment of risk of metastasis, and thus the assessment of whether or not a tumor can be expected to behave in a benign or a malignant fashion, cannot be predicted on histologic appearance alone and attention to other clinicopathologic parameters is needed. For example, parameters of risk stratification for GIST include anatomic location, tumor size, and mitotic rate, with the risk of metastasis or tumor-related death for various combinations of these three parameters ranging from 0% (essentially benign) to 90% (a high expectation of malignant behavior).

Risk Factors for Neoplasia

There are four basic contexts in which neoplasms arise. Many neoplasms arise in a **background of inflammation**. Carcinomas of the esophagus and stomach are particularly apt to arise in inflammatory backgrounds. Barrett-esophagus-associated adenocarcinomas and chronic-gastritis-associated intestinal-type adenocarcinomas are believed to arise through an inflammation→metaplasia→dysplasia→carcinoma sequence, and gastric adenocarcinomas are etiologically linked to *Helicobacter pylori* gastritis. A large subset (~65%) of gastric neuroendocrine tumors (NETs) arise in a background of autoimmune atrophic gastritis, and extranodal marginal zone lymphomas of the stomach and small intestine (mucosa-associated lymphoid tissue [MALT] lymphomas) are also etiologically linked to *Helicobacter pylori* and *Campylobacter jejuni* infection, respectively. In the small intestine, patients with celiac disease are at increased risk for adenocarcinoma and lymphoma, including enteropathy-associated T-cell lymphoma. Patients with idiopathic inflammatory bowel disease (IBD) are at increased risk for developing colorectal cancer, and this risk is modulated by factors including disease duration, anatomic extent of disease, histologic inflammatory activity, family colon cancer history, and the presence of concomitant primary sclerosing cholangitis. Across the spectrum of inflammation-associated neoplasms, effective treatment of the underlying inflammatory disease is typically associated with improved outcomes and decreased risk of neoplasia. For example, *Helicobacter pylori* eradication has been shown to decrease disease recurrence in early gastric cancer and, in many gastric MALT lymphomas, leads to disease regression. Furthermore, a declining risk of IBD-associated colon cancer in contemporary series has been also attributed, at least in part, to improved medical management of colitis.

Epithelial, lymphoid, and even mesenchymal neoplasms may also arise in association with **oncogenic viruses**. The most common implicated viruses include human papillomavirus (HPV), the major cause of anal intraepithelial neoplasia (AIN) and anal squamous cell carcinoma; Epstein–Barr virus (EBV), which is associated with numerous neoplasms including most cases of gastric carcinoma with lymphoid stroma (also known as lymphoepithelioma-like carcinoma or medullary carcinoma), many types of lymphoma, and smooth muscle tumors in immunosuppressed individuals; and human herpesvirus 8 (HHV8; also known as Kaposi-sarcoma-associated herpesvirus), which drives primary effusion lymphoma, multicentric Castleman disease, and Kaposi sarcoma. Patients with a primary or secondary immunodeficiency, the latter including stem cell or solid organ transplantation, HIV infection, and in some instances, merely advanced age, are at increased risk for this class of tumors. Immunohistochemistry, in situ hybridization, or molecular methods for detection of virus, or surrogate markers (eg, p16 in HPV-driven tumors), may be useful diagnostic adjuncts in this group of tumors.

Neoplasms may also arise in the setting of a **genetic predisposition to cancer**. Hereditary cancer predisposition syndromes are due to highly penetrant germline mutations and share the following features:

1. They are generally autosomal dominant.
2. The tumors occur in relatively young persons (compared to sporadic tumors).
3. The tumors occur at a defined set of anatomic sites.
4. The tumors are often multiple (synchronous or metachronous).

In addition, these tumors, their associated precursors, or other syndromic "marker lesions" often have characteristic clinical and/or histologic features, such as the morphologic features that are seen in Lynch-syndrome-associated colorectal adenocarcinoma.

Most of the tumors that arise in hereditary cancer syndromes are carcinomas, but NETs, GISTs, other mesenchymal tumors, and lymphomas occur in select settings. For example, multiple duodenal gastrinomas and enterochromaffin-like (ECL)-cell gastric NETs may be seen in patients with multiple endocrine neoplasia type I (MEN1), and rarely, patients with neurofibromatosis type I (NF1) manifest periampullary somatostatin-producing NETs. GISTs are seen in patients with NF1, Carney–Stratakis syndrome (due to germline succinate dehydrogenase subunit mutations), and in rare patients with germline mutations in *KIT* or *PDGFRA*. Among other mesenchymal tumors, desmoid fibromatosis is seen in 10% to 30% of patients with familial adenomatous polyposis (FAP), and diffuse-type ganglioneuromatosis is essentially an NF1 or MEN2B-defining lesion. Lymphomas often develop in the very rare patients who inherit two defective copies of a given DNA mismatch repair gene (ie, constitutional Lynch syndrome).

The recognition of a hereditary cancer syndrome may affect the management of a presenting tumor, trigger syndrome-specific surveillance, inform the decision to undergo various prophylactic resections, and, perhaps most importantly, permit the identification of other at-risk family members. The approach to the recognition, diagnosis,

and reporting of HCPSs involving the gastrointestinal (GI) tract will be presented in more detail in Chapter 6.

While hereditary cancer syndromes account for a small percentage of GI malignancies, more commonly, cancers aggregate in families without an obvious Mendelian inheritance pattern. For example, 20% to 30% of colon cancers arise in this setting. These tumors have been referred to as "familial" (rather than hereditary). This phenomenon is believed to reflect shared environment and/or inheritance of (possibly multiple) low-penetrant susceptibility alleles. Patients with a non-Mendelian family history are at increased cancer risk, a fact that is taken into account in screening guidelines.

The majority of neoplasms, including carcinomas, neuroendocrine neoplasms, lymphomas, and mesenchymal tumors appear to arise **sporadically**, that is, outside of any of the predisposing contexts described in the preceding paragraphs.

Dysplasia

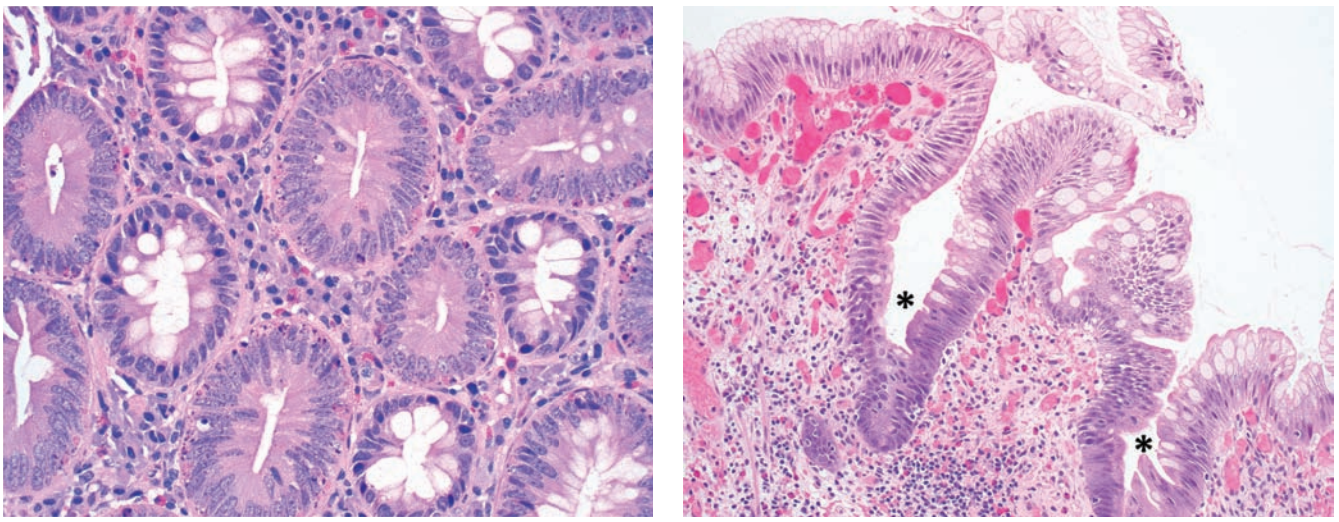
Dysplasia is defined as an unequivocal neoplastic alteration of the epithelium, frequently within the confines of a basement membrane in the tubal gut. Dysplastic epithelium is often a precursor to the development of malignancy. The distinction of reactive atypia from dysplasia, especially in the context of an inflammatory background, is perhaps one of the most difficult exercises in neoplastic GI pathology.

Applying the concept of clonality in the distinction between dysplastic and reactive changes is a useful and powerful concept. The histologic correlate of clonality is the abrupt transition from a non-neoplastic background to dysplasia (Figure 1.1A). Stated another way, dysplasia "stops and starts;" in contrast, reactive atypia usually blends imperceptibly into adjacent areas that are non-neoplastic (Figure 1.1B). Immunohistochemical stains are sometimes useful to highlight an area of abrupt transition when one is concerned about dysplasia/clonality. Examples include p53 in Barrett esophagus (Figures 1.2A–B), chronic gastritis, and IBD; MLH1 in serrated polyps (Figure 1.2C); and SMAD4 in the pancreatobiliary tree (Figure 1.2D). These immunohistochemical applications will be discussed in greater detail in Chapter 13.

Some pathologists use the terms "atypia" and "dysplasia" interchangeably. Epithelial atypia simply refers to cytologic and/or architectural features that deviate from normal. Because dysplasia is, by definition, neoplastic, while the meaning of atypia is less specific, the two terms are not synonymous. Use of the term "atypia" on the diagnostic line, even if qualified as reactive, is therefore discouraged.

Grading of Dysplasia

From an historical standpoint, the Inflammatory Bowel Disease-Dysplasia Morphology Study Group (IBD-DMSG) undertook the key early effort of developing a standardized nomenclature and classification for dysplasia in IBD. "Dysplasia in inflammatory bowel disease: a standardized classification with provisional clinical applications," published by Riddell and colleagues in *Human Pathology*



(A) (B)

FIGURE 1.1 Adenomatous crypts with nuclear elongation and slight stratification as well as striking epithelial apoptosis are sharply demarcated from background, non-neoplastic crypts with small, basally located nuclei and preservation of goblet cells. An abrupt transition is characteristic of a dysplastic process (A). In this biopsy of Barrett mucosa, the greatest degree of atypia is seen in the crypt bases (*), with gradual diminution of nuclear size and progressive accumulation of cytoplasm as cells approach the surface, in keeping with a reactive process (B). Note also the lack of an abrupt transition between the reactive epithelium and the adjacent mucosa.

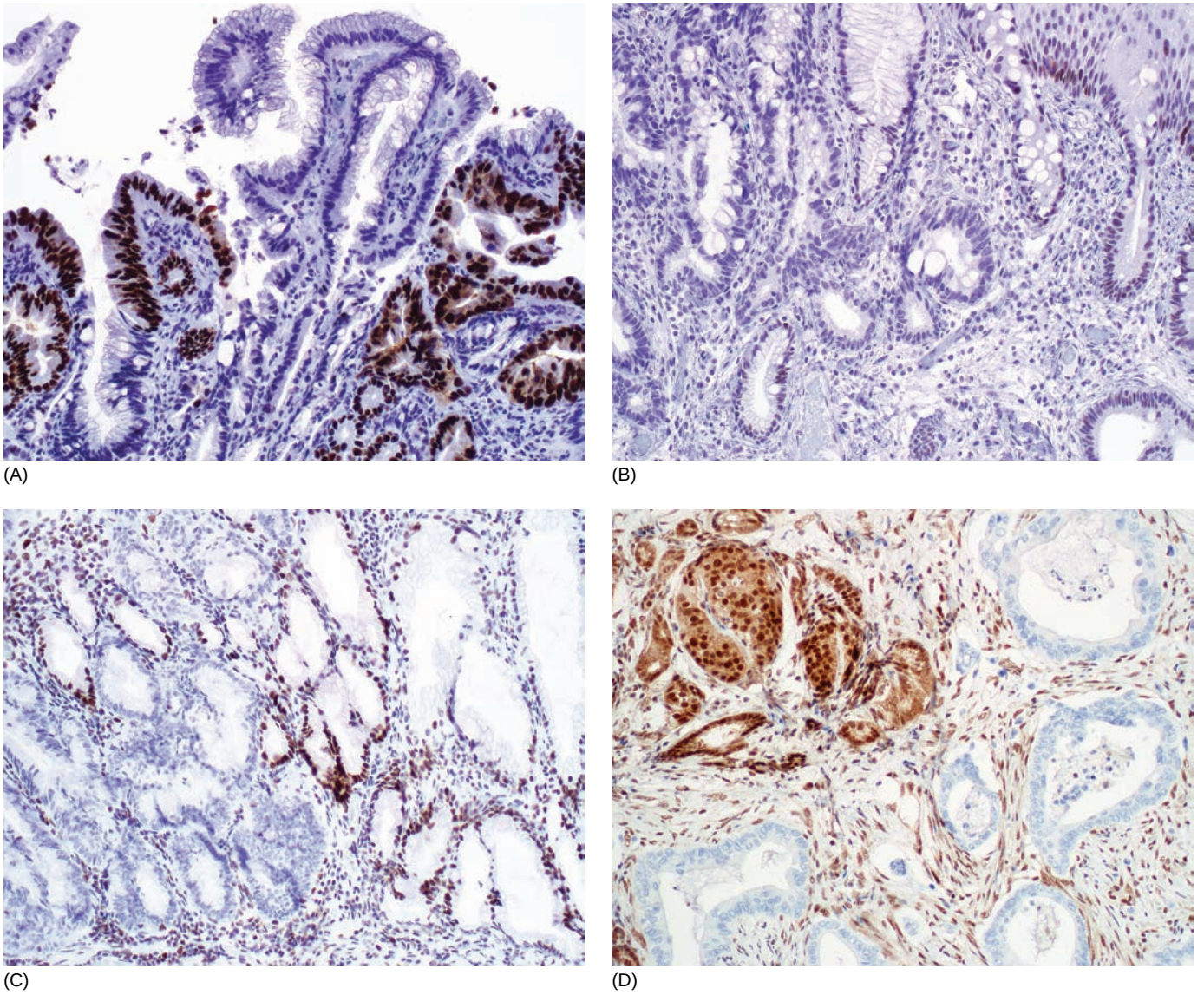


FIGURE 1.2 A p53 immunostain in an esophageal biopsy demonstrates abrupt transitions between foci of diffuse, strong staining in the nuclei of Barrett mucosa with high-grade dysplasia (likely due to *TP53* missense mutation) and focal weak or negative staining in the background Barrett epithelium without dysplasia (A). A p53 immunostain demonstrates the abrupt transition between foci of completely absent staining in dysplastic Barrett epithelium (likely due to *TP53* deletion or truncating mutation) and moderately intense (wild-type pattern) staining in non-dysplastic Barrett mucosa and adjacent squamous epithelium (B). Clonal loss of MLH1 expression corresponding to the acquisition of cytologic dysplasia in a background of sessile serrated polyp (C). Clonal loss of SMAD4 expression in a pancreatic ductal adenocarcinoma, compared to intact expression in stroma and adjacent non-neoplastic islets and ductules (D).

in 1983, remains a seminal reference work in GI pathology. This classification forms the foundation of dysplasia assessment in Western GI pathology, and has been adopted for columnar lesions throughout the tubal gut.

Whereas previously dysplasia was graded as mild, moderate, or severe, the IBD-DMSG introduced the categories "negative for dysplasia," "indefinite for dysplasia," and "positive for dysplasia." The "positive for dysplasia" group is subdivided into "low-grade dysplasia (LGD)" and "high-grade dysplasia (HGD)". Due to their work and the recognition of the limits of interobserver reproducibility, the "mild, moderate, severe" classification scheme has been largely discarded and is no longer appropriate for grading dysplasia in the tubal gut. Grading of dysplasia will be discussed in more detail in the organ-specific chapters that follow.

By including "indefinite for dysplasia," the group formally recognized diagnostic uncertainty in the form of lesions that could not be readily classified as negative or positive. In clinical practice, when a lesion is worrisome

TABLE 1.1 Key Features of the Inflammatory Bowel Disease-Dysplasia Morphology Study Group Classification of Dysplasia

Defined dysplasia as "unequivocally neoplastic epithelium"
As a consequence, the term "atypia" could no longer be used synonymously with dysplasia
Established the category of indefinite for dysplasia
Established the categories of low-grade dysplasia and high-grade dysplasia and made provisional clinical recommendations based on these diagnoses
Recommended seeking a second opinion in diagnostically challenging cases
Contained an interobserver variability study
Provided an atlas of 84 images
Stated that low-grade dysplasia could directly give rise to adenocarcinoma

for dysplasia but is very focal, there is significant background inflammation, or the transition between the lesion and adjacent non-neoplastic mucosa is not well-visualized, the term "indefinite for dysplasia" is appropriate.

Another key goal of the group was to create a classification scheme that was clinically actionable. The group made provisional clinical recommendations based on their classification that, for dysplasia in IBD, have largely stood the test of time. Recommendations included short interval follow-up for diagnoses of LGD or indefinite for dysplasia, and consideration of colectomy for HGD. The results of the interobserver variability component of the group's work highlighted the importance of seeking a second opinion in diagnostically challenging cases, which is emphasized today in multidisciplinary medical position statements/practice guidelines regarding the management of Barrett esophagus and IBD. The contributions of the IBD-DMSG are summarized in Table 1.1.

Dysplasia detected at an index examination (or within 1 year) is referred to as "prevalent," while that detected in the context of surveillance is "incident." The natural history of prevalent dysplasia appears more aggressive than incident dysplasia.

Alternative Classifications

Western pathologists generally use a modified IBD-DMSG definition of dysplasia that defines it as a "*pre-invasive* unequivocal neoplastic epithelial proliferation." When used as such, dysplasia is a carcinoma precursor. The third edition of the *WHO Classification of Tumours of the Digestive System* (*WHO GI Blue Book*) introduced the generally synonymous term "intraepithelial neoplasia," and an alternative international consensus classification known as the Vienna system refers to "non-invasive neoplasia." For practical purposes, this textbook will refer to "dysplasia" throughout, except in the anus, where intraepithelial neoplasia (anal intraepithelial neoplasia [AIN]) has gained more widespread usage.

Carcinoma In Situ and Intramucosal Carcinoma

Historically, carcinoma in situ (CIS) generally refers to a tumor that is "cytologically malignant" but has yet to breach the basement membrane. As such, it has no metastatic potential, and is essentially equivalent to dysplasia. Theoretically, CIS is considered "more advanced" than HGD, but the distinction between these entities is not reproducible. Some authors have also used CIS to refer to tumors without metastatic potential, regardless of whether or not they are confined to the basement membrane (this broader definition encompasses colonic tumors that have invaded into but not beyond the mucosa). Again, given the lack of reproducibility in distinguishing HGD and CIS, compounded by the ambiguity of meaning, use of the term "carcinoma in situ" in reporting specimens from the tubal gut is strongly discouraged.

In intramucosal carcinoma (IMC), tumor cells have breached the basement membrane to invade into, but not beyond, the mucosa. This includes tumors that have invaded into the lamina propria and those that have invaded into, but not through, the muscularis mucosae. In the esophagus and stomach, IMC is associated with a small but definite risk of lymph node metastasis (4% or less) and is staged as T1a (as are small intestinal adenocarcinomas). In contrast, in the colon, IMC is not associated with lymph node metastasis and, thus, is staged as Tis (as are appendiceal tumors). Because the distinction of IMC from HGD in the colon is not as biologically meaningful as it is in the upper GI tract, some pathologists avoid this term and do not diagnose IMC in the colon.

Similar to the grading of dysplasia, the diagnosis of IMC is subject to significant interobserver variability. Cases in which single cells or small groups of cells are present in the lamina propria are readily recognized as IMC (Figure 1.3A), as are those characterized by large expanses of anastomosing glands (Figure 1.3B) or sheets of cells. Since IMC is defined by tumor cells having breached the basement membrane, and pathologists do not directly visualize that breach, the degree of architectural perturbation that is required to distinguish a small focus of IMC from HGD is not well defined (Figure 1.4). Two groups have published criteria for a category intermediate between HGD and IMC, referred to as "high-grade dysplasia with marked glandular architectural distortion, cannot exclude intramucosal carcinoma" and "high-grade dysplasia with features 'suspicious' for invasive carcinoma." These concepts will be discussed further in Chapter 7.

As with the distinction of dysplasia from reactive changes, the concept of clonality is again applicable to grading dysplasia and distinguishing HGD from early carcinoma; the notion of "neoplastic progression" is additionally useful. As one considers the diagnosis of HGD, it is useful if one can identify a specific area that is cytologically and/or architecturally distinct from the background LGD (ie, a