Neoplastic Gastrointestinal Pathology
An Illustrated Guide

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Neoplastic Gastrointestinal Pathology
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.

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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 peripancreatic 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 ganglio-neuromatosis 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 cytopathologic 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*.

![Figure 1.1](image1.jpg) **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.
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

**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).
intraepithelial neoplasia (anal intraepithelial neoplasia refer to “dysplasia” throughout, except in the anus, where neoplasia.” For practical purposes, this textbook will

1 Introduction to Diagnosis and Reporting of Gastrointestinal Tract Neoplasia

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

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clonal area that has progressed) (Figure 1.5). This assumes, of course, confidence in the underlying diagnosis of dysplasia, and one may not always have the luxury of a background of LGD (although it is nearly always present in an adenomatous colon polyp with HGD). A similar approach may be used when one is considering a diagnosis of IMC in a background of HGD in the setting of Barrett esophagus.

**FIGURE 1.3** Intramucosal carcinoma is readily diagnosed when single cells or small groups of cells (arrows) are visualized in the lamina propria (A) or in the setting of an expansive anastomosing gland pattern (the so-called never-ending gland pattern) (B). These examples are from Barrett esophagus-associated neoplasms.

**FIGURE 1.4** This focus of dysplastic Barrett epithelium shows at least high-grade dysplasia, and some would consider the degree of gland branching and budding (*) compatible with intramucosal carcinoma. The dilated glands with intraluminal debris also suggest a more advanced lesion.

**FIGURE 1.5** The right half of this mucosal biopsy specimen shows low-grade dysplasia. The discrete foci of more complex, cribriformed architecture (*) on the left are characteristic of a higher-grade lesion.

Discrepancies Between Western and Eastern Neoplasia Assessment

The histologic features of LGD and HGD presented here and in subsequent chapters, and the concept that invasion defines carcinoma, represent distinctly Western viewpoints. It has long been recognized that many lesions classified as LGD or HGD by Western pathologists are diagnosed as early carcinomas by Japanese pathologists.
While Western pathologists seek “objective” evidence of invasion to secure a diagnosis of carcinoma, Japanese pathologists place greater weight on nuclear and architectural features, and, actually arrive at a diagnosis of carcinoma independent of the presence of invasion. These very different approaches to diagnosis profoundly affect the comparability of the incidence and survival rates for early carcinoma in Western and Japanese series (this applies mainly to gastric cancer, since Barrett-associated neoplasia is rare in Japan and colonic IMC lacks the capacity to metastasize). This textbook will reflect the Western viewpoint throughout because it is the one we have learned, the one we apply in our practices, and the one upon which Western clinical guidelines are based.

Submucosally Invasive Carcinoma

Once tumors invade beyond the muscularis mucosae, they initially encounter the submucosa, and are thus submucosally invasive. As the submucosa is frequently not well-represented in endoscopic mucosal biopsy material, this diagnosis can be challenging. In cases where the boundary between the mucosa and submucosa is not readily apparent, there are two histologic clues that suggest a diagnosis of submucosal invasion. First, the presence of desmoplastic (ie, cellular, fibroblastic, often blue-tinged) stroma strongly correlates with the presence of submucosal invasion (Figures 1.6A–B). Second, one can search for the close approximation of neoplastic epithelium to thick-walled, muscular submucosal blood vessels. These vessels are readily apparent in endoscopic mucosal resections (Figure 1.7A) and can usually be identified in well-oriented polypectomy specimens of larger, pedunculated lesions (Figure 1.7B). A desmin immunostain can also help define the boundaries of the muscularis mucosae (as well as the muscularis propria), which is especially useful in cases where the microanatomy is obscured by fibrosis or inflammation (Figure 1.8A–B). This is less helpful in cases that are tangentially embedded.

GRADING AND STAGING OF GASTROINTESTINAL MALIGNANCIES

Tumor Grading

Tumor grading has traditionally represented an assessment of how well (or poorly) a given tumor resembles the normal tissue type it recapitulates (ie, differentiation). This assessment is inherently qualitative. For some tumor types, grading has incorporated more objective, reproducible features (eg, mitotic rate). Grade is prognostically significant and in many instances influences clinical management. For example, in pT3 N0 colon cancer, patients with poorly differentiated/high-grade tumors may be offered adjuvant chemotherapy, and patients with resected high-risk GISTs generally receive adjuvant tyrosine kinase inhibitor therapy. In addition, chemotherapy regimens are entirely different for low-grade versus high-grade lymphomas and well-differentiated NETs versus neuroendocrine carcinomas (NECs). Table 1.2 compares the grading of the major categories of tumor in the tubal gut.

For non-neuroendocrine carcinomas of the tubal gut, mainly adenocarcinomas and squamous cell carcinomas, there is no uniformly agreed upon, extensively clinically validated grading system as there is in breast (Nottingham...
grade), kidney (Fuhrman grade), or prostate (Gleason grade). For adenocarcinomas of the colon and rectum, the WHO suggests that tumors may be graded based on the extent of gland formation, although this only applies to “adenocarcinoma, NOS” (ie, adenocarcinoma with no special morphologic features). Throughout the tubal gut, grading may be two-, three-, or four-tiered, with two-tiered grading (high-grade versus low-grade) increasingly advocated based on greater reproducibility and clinical utility. Tumor grading will be discussed in greater detail in the organ-specific chapters.

The grading system for neuroendocrine neoplasms is entirely different from that used for non-neuroendocrine tumors. In the World Health Organization (WHO) 2010 Classification, gastroenteropancreatic neuroendocrine epithelial neoplasms are graded based on mitotic rate and Ki-67 proliferation index. In this system, morphologically well-differentiated neuroendocrine neoplasms are referred

**FIGURE 1.7** Barrett esophagus-associated adenocarcinoma (A) and adenocarcinoma arising in an adenomatous polyp (B) each infiltrate up to and around thick-walled muscular blood vessels, suggesting a diagnosis of submucosal invasion. Stromal desmoplasia is also seen in (B).

**FIGURE 1.8** While this Barrett esophagus-associated adenocarcinoma was suspicious for invasion into the superficial submucosa (A), a desmin immunostain clarified that, at its deepest point, the tumor is confined by strands of muscularis mucosae (B).
to as “neuroendocrine tumors (NETs),” while poorly differentiated examples (small cell and large cell) are termed “neuroendocrine carcinomas (NECs).” NETs with a low mitotic rate (less than 2 per 10 high-power fields [HPFs]) and proliferation index (2% or less) are considered G1, while those with a mitotic rate between 2 and 20 per 10 HPF and/or a proliferation index of 3% to 20% are G2. NECs (G3 in this classification) demonstrate more than 20 mitotic figures per 10 HPF and/or a proliferation index greater than 20%. This classification supplants the WHO 2000 Classification, in which well-differentiated tumors were “graded” based on the absence (well-differentiated endocrine tumor) or presence (well-differentiated endocrine carcinoma) of metastases and/or gross local invasion, with the former category further stratified based on the following parameters: size, angioinvasion, perineural invasion (PNI), mitotic count, and Ki-67 proliferation index. Of note, the current mitotic threshold for G3/NEC (greater than 20 per 10 HPF) is greater than in the 2000 system (greater than 10 per 10 HPF). Rarely, morphologically well-differentiated tumors demonstrate a mitotic rate and/or proliferation index in the G3 range; these behave somewhat better than typical, poorly differentiated G3 tumors.

Tumor type largely defines the grade (low vs. high grade) in lymphoma. Follicular lymphoma (FL) can be further graded based on the number of centroblasts in neoplastic follicles per HPF, based on an assessment of at least 10 HPFs. In the 2008 WHO Classification of Tumours...
of Haematopoietic and Lymphoid Tissues, the separation of grade 1 from grade 2 FL is discouraged, as this is not a clinically meaningful distinction. The presence of diffuse architecture distinguishes diffuse large B-cell lymphoma (DLBCL) from FL, grade 3. Grading of GI lymphomas will be further discussed in Chapter 4.

GISTs are graded based on mitotic rate. Low-grade/G1 tumors demonstrate 5 or fewer mitotic figures per 5 mm², while high-grade/G2 tumors contain 5 or more mitotic figures per 5 mm². Grade, tumor size, and anatomic location are combined to determine the overall “risk assessment” in GIST (none, very low risk, low risk, intermediate risk, high risk, overtly malignant/metastatic), which correlates with the likelihood of metastasis or tumor-related death. Of special note, mitotic rates in GIST were historically described in relation to 50 HPFs. It was recently discovered that the microscopes used to count mitotic figures in the initial clinical studies that form the evidence basis of the risk assessment had much smaller field areas than most modern microscopes. For many modern microscopes, 5 mm² is equal to approximately 20 high-power (40×) fields. Grading of mesenchymal tumors will be discussed in more detail in Chapter 5.

For sarcomas, the American Joint Committee on Cancer (AJCC), the College of American Pathologists (CAP), and the WHO each advocate use of the Fédération Nationale de Centre de Lutte Contre le Cancer (FNCLCC) grading system. Tumors are assessed for differentiation, mitotic rate, and tumor necrosis. Each of these three parameters is given a score, and the overall grade is assigned based on the sum of the scores. FNCLCC grade correlates with metastatic risk and overall survival, while adequacy of excision is a better predictor of local recurrence.

Tumor Staging

Historically, tumor stage has represented the anatomic extent of disease. It is typically expressed in the form of the tumor, node, metastasis (TNM) classification. Aside from tumor type, stage is the single most important determinant of an individual patient’s therapy and prognosis. Accurate staging is also critical to the conduct of clinical trials and facilitates the comparison of cancer outcomes on large scales (eg, regionally, nationally, and internationally). The TNM Committee of the Union for International Cancer Control (UICC) and the AJCC work together to define T, N, and M stage categories and stage groups (also known as anatomic stage/prognostic groups) for each anatomic site. For a given site, any combination of T, N, and M can be expressed as an overall stage group (I through IV), with combinations of similar prognostic assigned to the same stage group (eg, T4a N1 M0 and T1 N2b M0 colon cancers are each considered stage IIIB disease).

The UICC/AJCC Classification is periodically revised (most recently at 6–8-year intervals), increasingly based on large, population-based clinical datasets. The AJCC first published a staging manual in 1977; the AJCC Cancer Staging Manual is now in its seventh edition (AJCC 7). This classification went into effect on January 1, 2010. It includes, for the first time, TNM staging for GISTs and NETs. Appendiceal carcinomas, classified with colorectal tumors in the sixth edition, are now separately classified. For every site in the tubal gut (except the anal canal), various T, N, and M categories were redefined or subclassified and various stage groupings were reassigned. For pathologists, the most significant change to their routine practices was perhaps the creation of the N1c category in colon cancer, defined as the presence of “tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis” (discussed further in Chapter 11).

In the past, stage groupings at a given site in the tubal gut were determined exclusively by TNM. In AJCC 7 this is no longer the case. The so-called nonanatomic factors, including tumor type, location within an organ, grade, and mitotic rate, affect staging at some sites (summarized in Table 1.3). Additional nonanatomic factors, including molecular-based ones, will have increasing influence on stage groupings going forward. For the foreseeable future, however, anatomic factors will continue to form the core of tumor staging, as they permit comparisons of stage data over time and because they are applicable to the majority of patients worldwide who may not have access to advanced medical technologies.

Clinical Versus Pathologic Staging

Clinical staging is performed at disease presentation, before definitive treatment, and takes into account data obtained by any combination of history and physical examination, diagnostic imaging, endoscopy, biopsy (of the primary tumor and/or a regional lymph node), and surgical exploration without resection. If a biopsy is performed, the pathologist’s role in clinical staging is to confirm the presence of tumor, rather than to define its anatomic extent, the latter of which is based on nonpathologic information (eg, imaging results). Clinical staging provides an estimate of prognosis and, most importantly, determines the initial treatment course.

The pathologic stage is based mainly on histologic examination of a surgically resected specimen. This provides more precise prognostic information and informs the need for additional treatment (eg, adjuvant chemotherapy or radiation). The value of synoptic reporting as a tool to ensure completeness of reporting of pathologic stage and other clinically significant parameters will be discussed in the section on synoptic reporting.
Staging After Neoadjuvant Therapy

Neoadjuvant therapy refers to the use of chemotherapy and radiation, either singly or in combination, prior to surgical resection. Adjuvant therapy refers to chemotherapy and/or radiation administered after the definitive surgical procedure. In the adjuvant setting, radiation is generally applied to improve local control, while chemotherapy is used to achieve a systemic effect. Chemotherapy may also sensitize the tumor to the effects of radiation. In the neoadjuvant setting, combined chemoradiotherapy aims to downstage tumors and treats occult metastatic disease. In some patients it converts locally advanced, unresectable tumors to resectable ones, and it may improve the resectability of “borderline-resectable” tumors. In patients who are marginal surgical candidates (eg, due to comorbid conditions), a period of neoadjuvant therapy may provide the opportunity for metastasis to declare itself, sparing these patients surgery from which they would not derive benefit.

Neoadjuvant chemoradiotherapy is the standard of care for clinical stage T3/4 rectal cancer, in which it has been proven in clinical trials to significantly decrease the risk of local recurrence (compared to adjuvant therapy). It is also generally applied in patients with clinical nodal disease. Neoadjuvant chemoradiotherapy is also the evolving standard of care for patients with clinical stage T2 or greater esophageal/gastroesophageal junction/proximal gastric cancers. Its application in distal gastric cancers is more variable. In addition, neoadjuvant imatinib therapy may be used in locally advanced and/or high-risk GISTs.

Pathologic staging after neoadjuvant therapy is designated by the prefix “y” (ie, ypTNM). The use of this symbol is a vital component of accurate staging. For example, the prognosis of a patient with pT2 N0 disease may be very different than that of a patient with ypT2 N0 disease, who may have had clinically positive lymph nodes at presentation. Furthermore, for the purpose of research, these stages are not comparable. The ypTNM stage is based on the extent of viable tumor. Evidence of regressed tumor in the form of fibrosis, calcifications, and acellular mucin pools does not affect stage. Significant tumor regression in the face of neoadjuvant therapy may be associated with improved prognosis. Assessment of treatment effect after neoadjuvant therapy is a CAP required data element for carcinomas of the esophagus, stomach, pancreas, colorectum, and anal canal; assessment in GIST is optional, with a recommendation to report the percentage of viable tumor. There are several published regression grading systems, including three-, four-, and five-tiered examples. The CAP Cancer Protocols include a four-tiered example (see Table 1.4). This is discussed in more detail in Chapter 11.

### TABLE 1.3 “Nonanatomic Factors” Influencing AJCC/UICC Tubal Gut Stage Groupings

<table>
<thead>
<tr>
<th>Anatomic Site (or Tumor Type)</th>
<th>Factor</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>Tumor type</td>
<td>Separate stage groupings for squamous cell carcinoma (SCC) and adenocarcinoma (AdCa)</td>
</tr>
<tr>
<td></td>
<td>Tumor location (ie, upper, middle, lower)</td>
<td>Applies to SCC</td>
</tr>
<tr>
<td></td>
<td>Grade (ie, 1, 2, 3)</td>
<td>Applies to SCC and AdCa</td>
</tr>
<tr>
<td>Appendix</td>
<td>Grade (ie, 1, 2, 3)</td>
<td>Low-grade appendiceal mucinous neoplasm with extra-appendiceal spread is considered G1; separate stage groupings for G1 vs. G2/3 tumors with intraperitoneal metastasis beyond the right lower quadrant</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor (GIST)</td>
<td>Mitotic rate (ie, ≤5 per 5 mm² vs. &gt;5 per 5 mm²)</td>
<td>Separate stage groupings for gastric/omental GISTs vs. nongastric/nonomental GISTs based on increased aggressiveness of the latter</td>
</tr>
<tr>
<td></td>
<td>Tumor location (ie, stomach/omentum vs. small intestine/esophagus/colorectum/mesentery/peritoneum)</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine tumor (NET)</td>
<td>Tumor location</td>
<td>Separate stage groupings for appendiceal NETs vs. all other tubal gut NETs</td>
</tr>
<tr>
<td>Stomach, small intestine, colon, and rectum</td>
<td>None</td>
<td>Stage groupings based purely on TNM</td>
</tr>
</tbody>
</table>

### TABLE 1.4 Tumor Regression Grading in Neoadjuvant Treated Tumors (Four-Tiered)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histologic Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (complete response)</td>
<td>No residual viable tumor</td>
</tr>
<tr>
<td>1 (moderate response)</td>
<td>Single cells or small groups of tumor cells</td>
</tr>
<tr>
<td>2 (minimal response)</td>
<td>Residual tumor outgrown by fibrosis</td>
</tr>
<tr>
<td>3 (poor response)</td>
<td>Little or no tumor kill; extensive residual tumor</td>
</tr>
</tbody>
</table>
SYNOPTIC VERSUS NARRATIVE REPORTING

For cancer resections, synoptic reporting (also known as checklist-based, template-driven, and pro forma reporting) has largely supplanted traditional narrative (ie, free-text) reporting. Multiple published studies have shown that synoptic reporting improves the completeness (and thus the prognostic and therapeutic relevance) of cancer reporting. A 1991 CAP Q-Probes Quality Improvement Study, based on data from 15,940 reports of resected primary colorectal cancers from 532 laboratories, related the completeness of reporting for 11 gross and microscopic parameters to: (a) use of a cancer checklist; (b) use of a microscopic description; (c) teaching institution status; (d) whether the institution had a pathology residency; and (e) bed size. The use of a cancer checklist was the single most important predictor of completeness of reporting, statistically significant for 8 of 11 parameters. Interestingly, at that time, only 12.5% of the 532 laboratories surveyed employed synoptic reporting.

More contemporary data demonstrating the significance of the adoption of synoptic reporting in an individual laboratory are presented in Table 1.5. Messenger and colleagues found synoptic reporting to significantly increase the completeness of reporting for 7 of 10 data elements in a series of 498 rectal cancer resections. Several of these increases are quite dramatic and affect parameters that are highly clinically actionable, such as lymphovascular invasion, perineural invasion, and tumor deposits. They also showed that while narrative reports from GI pathologists were more complete for the data elements lymphovascular invasion and extramural venous invasion, after the adoption of synoptic reporting, reports from non-GI and GI pathologists were equally complete. Furthermore, detection rates for lymphovascular invasion, perineural invasion, and extramural venous invasion dramatically increased (tripled to quadrupled) with the advent of synoptic reporting, presumably because pathologists prompted by checklist items performed more diligent searches for these features.

Synoptic reporting also increases the clarity of reporting, and thus the effectiveness of communication, between the pathologist and the treating clinicians. Sheldon Markel and Samuel Hirsch, credited with coining the term “synoptic reporting,” expressed frustration over the disconnect between their perception of carefully crafted “conventional paragraphic” reports and occasional dissatisfaction with these reports by their clinicians, stating, “To our chagrin, surgeons and other clinicians frequently questioned why certain information, which was actually in the body or our reports, was not.” Synoptic reports also facilitate data mining and reporting to cancer registries.

Not surprisingly, the quality of oncology reporting is of interest to laboratory accrediting bodies. The CAP Laboratory Accreditation Program Anatomic Pathology Checklist includes the Phase II requirement that “All data elements required in applicable CAP Cancer Protocols are included in the surgical pathology report.” (Phase II deficiencies on inspection require a written response and documentation demonstrating compliance.) Furthermore, the required data elements must relate to the current edition of the protocols, with an 8-month grace period. The American College of Surgeons Commission on Cancer (CoC), which accredits cancer programs, similarly mandates the inclusion of CAP Cancer Protocol required data elements in surgical pathology reports. While neither the CAP nor the CoC dictates the specific use of the CAP Cancer Protocols, but rather that reports contain the required data elements from those protocols, AJCC 7 specifically recommends the use of CAP Cancer Protocols for pathology reporting.

The CAP Cancer Protocols were originally developed in 1989 and are frequently updated by the CAP Cancer Committee and CAP Cancer Protocol Review Panels. At the time of writing this chapter, all the protocols relevant to the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Narrative (n = 183), % Complete</th>
<th>Synoptic (n = 315), % Complete</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>99</td>
<td>99</td>
<td>NS</td>
</tr>
<tr>
<td>TNM stage</td>
<td>24</td>
<td>96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor type</td>
<td>99</td>
<td>99</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>92</td>
<td>98</td>
<td>0.004</td>
</tr>
<tr>
<td>Circumferential/radial margin (CRM) status</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Distance to CRM</td>
<td>86</td>
<td>97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>39</td>
<td>98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extramural venous invasion</td>
<td>41</td>
<td>97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>14</td>
<td>94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regional deposits</td>
<td>13</td>
<td>83</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Prognostic and Predictive Markers

#### Prognostic Markers

A prognostic marker provides information that allows one to make a probabilistic statement about a patient’s anticipated disease course. Although we typically think of these in the setting of overt malignancies (eg, tumor grade, microscopic tumor extension, presence or absence of lymphovascular invasion), the presence of Barrett esophagus, the extent of a patient’s chronic colitis, the absence or presence and grade of flat dysplasia, and the number and size of neoplastic colon polyps can all be considered prognostic markers. Many prognostic markers are directly clinically actionable (eg, influence decision to place a patient into surveillance and determine surveillance intensity; inform decision to give adjuvant chemotherapy), emphasizing the importance of accuracy of assessment and completeness of reporting. This textbook will specifically highlight issues related to the pathologic assessment of the most clinically significant prognostic markers.

#### Predictive Markers

Predictive markers provide information about whether a given patient will (or will not) respond to a specific therapy. Estrogen receptor and HER2 status in breast cancer represent the most well-known examples. At present, there are four main clinical applications of predictive markers in the GI tract:

1. HER2 testing to select patients for anti-HER2 therapy in advanced esophageal, gastroesophageal, and gastric adenocarcinoma;
2. KRAS mutation testing (and in some instances, assessment of related molecular markers) to determine the appropriateness of anti-EGFR (epidermal growth factor receptor) therapy in metastatic colorectal cancer;
3. DNA mismatch repair function testing (ie, mismatch repair protein immunohistochemistry and/or MSI testing) in colorectal cancer to inform the decision regarding adjuvant chemotherapy in stage II disease;
4. KIT and PDGFRα mutation analysis in GIST to predict response to specific tyrosine kinase inhibitors.

Predictive marker assays are generally held to a “higher standard,” in terms of clinical validation and reporting than are purely diagnostic markers. These four sets of markers will be discussed further in the relevant organ-specific chapters, as well as Chapters 13 and 14.

### Screening and Surveillance

#### Screening

Screening refers to an effort to identify early, treatable disease in asymptomatic individuals. In the setting of neoplasia, the goal is to identify lesions at risk for neoplastic progression or early, treatable cancers. Screening may be undertaken in “average-risk” individuals or targeted to specific at-risk groups, based on factors such as the disease burden in the population and a precursor lesion’s risk for neoplastic progression. These data, along with the availability of good screening tests and the cost of a screening program to the population, are considered in the construction of clinical guidelines.

As an example, the lifetime risk of developing colon cancer is 5% to 6%, with more than 90% of new diagnoses and cancer deaths occurring in patients over age 50. Cancer arises in neoplastic polyps, with a fairly long interval between a polyp becoming macroscopically evident and

---

**TABLE 1.6** College of American Pathologists Required Data Elements for Carcinomas and Neuroendocrine Tumors of the Tubal Gut, Regardless of Anatomic Site

<table>
<thead>
<tr>
<th>Specimen (ie, organs received)</th>
<th>Procedure</th>
<th>Tumor site</th>
<th>Tumor size</th>
<th>Histologic type</th>
<th>Histologic grade</th>
<th>Microscopic tumor extension</th>
<th>Margin status</th>
<th>Distance to closest margin, if uninvolved</th>
<th>Treatment effect*</th>
<th>Lymphovascular invasion**</th>
<th>Number of regional lymph nodes examined and involved***</th>
<th>Pathologic staging (pTNM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*not mentioned in appendix checklist</td>
<td>**not required for anal canal</td>
<td>***applies to resections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The tubal gut had been updated within the prior 4 months. The protocols contain both “required” and “not required” data elements, the latter denoted by a “+.” The required data elements are considered essential for cancer care and have a strong evidence base. A summary of required data elements common to all the checklists germane to this textbook is presented in Table 1.6. At each anatomic site, there may be additionally required data elements (eg, perineural invasion in colon cancer, mitotic rate per 10 HPF in NETs, risk assessment in GIST), which will be further discussed in subsequent chapters. Nonrequired elements have less data to support them or are less routinely used in patient care (eg, histologic features suggestive of microsatellite instability [MSI] in colon cancer, tumor necrosis in NET, treatment effect in GIST).

Further information about synoptic reporting is available in the following document:


Finally, the CAP Cancer Protocols are accessible online in PDF and Word format at the CAP website through the “Reference Resources and Publications” tab.
progression to cancer. Several reasonably sensitive tests exist to identify polyps or early cancers (eg, flexible sigmoidoscopy, colonoscopy, and/or fecal occult blood test), and polypectomy or treatment of early cancers has been proven to lead to decreased mortality from colon cancer. In this setting, the United States Preventative Services Task Force, the American Cancer Society (ACS), the American College of Radiology (ACR), and the United States Multi-Society Task Force (USMSTF; a collaboration between the American College of Gastroenterology, the American Society for Gastrointestinal Endoscopy [ASGE], and the American Gastroenterological Association [AGA]) each recommend colorectal cancer screening in average-risk individuals beginning at age 50. Screening recommendations are modifiable based on the presence of additional risk factors. In patients with colon cancer or adenomatous polyps diagnosed in a first-degree relative 60 years or older or with colorectal cancer diagnosed in two second-degree relatives, an ACS/USMSTF/ACR guideline recommends that screening commence at age 40.

In contrast, the lifetime risk of developing esophageal adenocarcinoma is only 0.5%. Cancer arises in Barrett esophagus, which is found in 1% to 2% of the general population and up to 10% of patients with chronic gastroesophageal reflux disease (GERD) (by comparison, 30% of average-risk patients 50 years or older will have polyps at an index colonoscopy). The risk of progression from Barrett esophagus to adenocarcinoma is reportedly 0.25% or less per year. Barrett esophagus is not as amenable to eradication as are neoplastic colon polyps, and endoscopic ablative techniques are associated with a significant risk of stricture. Up to half of the patients presenting with esophageal adenocarcinoma do not report a history of GERD symptoms. Fifty to sixty percent of patients present with locally advanced or metastatic disease, and even in patients with localized disease, the 5-year survival is less than 40% (though substantially better in patients with T1 and especially T1a disease). Thus, in the general population, the costs associated with screening for esophageal adenocarcinoma clearly outweigh the benefits. In a 2011 medical position statement, the AGA recommended screening for Barrett esophagus specifically in patients with multiple risk factors associated with esophageal adenocarcinoma (age 50 years and above, male, Caucasian, chronic GERD, hiatal hernia, elevated body mass index, and intra-abdominal distribution of body fat), in whom the benefits of screening would appear to outweigh the costs. Table 1.7 summarizes GI conditions in which screening may be considered, the means of screening, the lesion the screening test aims to detect, and relevant expert guidelines.

### Surveillance

Surveillance refers to testing in patients with “at-risk” lesions with the goal of identifying more advanced lesions or

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**TABLE 1.7 Screening for Neoplasia in the Tubal Gut**

<table>
<thead>
<tr>
<th>Underlying Condition</th>
<th>Procedure</th>
<th>Target Lesion</th>
<th>Comment(s)</th>
<th>Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>Upper endoscopy</td>
<td>Barrett esophagus, prevalent dysplasia</td>
<td>In patients with multiple risk factors for esophageal adenocarcinoma (ie, age ≥ 50, male, White, chronic GERD, hiatal hernia, elevated body mass index, and intra-abdominal distribution of body fat), Screening not recommended in general population with GERD</td>
<td>AGA 2011</td>
</tr>
<tr>
<td>Pernicious anemia (autoimmune atrophic gastritis)</td>
<td>Intestinal metaplasia, prevalent dysplasia, neuroendocrine proliferations</td>
<td>Insufficient data to support routine surveillance after single endoscopy</td>
<td>ASGE 2006</td>
<td></td>
</tr>
<tr>
<td>Long-standing idiopathic inflammatory bowel disease</td>
<td>Colonoscopy</td>
<td>Colitis, prevalent dysplasia</td>
<td>To determine if disease extent warrants surveillance</td>
<td>AGA 2010</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 50 years in patients with average colon cancer risk</td>
<td>Multiple options including flexible sigmoidoscopy, colonoscopy, double contrast barium enema, computed tomography colonoscopy, fecal occult blood test, fecal immunochemical test, or stool DNA test</td>
<td>Adenoma and sessile serrated poly, early colon cancer</td>
<td>Positive screening tests are followed up with colonoscopy</td>
<td>ACS/USMSTF/ACR 2008</td>
</tr>
<tr>
<td>Age 40 years in patients with a family history of colon cancer/ polyps (defined here as colon cancer or adenomas in a first-degree relative ≥ age 60 or two second-degree relatives with colon cancer)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*references available in the Screening and Surveillance section of the references
early, treatable cancers. It is the presence of a baseline “at-risk” lesion that distinguishes surveillance from screening. The “at-risk” lesion may represent an inflammatory condition, neoplasm, known germline mutation, or even a family history highly suspicious for a family cancer syndrome. Patients with a positive screening test are typically entered into surveillance. (A positive fecal occult blood test is an exception; it is followed up with colonoscopy, and patients may be entered into surveillance based on the results of this second test.) For example, if a patient with chronic GERD and the multiple risk factors for esophageal adenocarcinoma discussed previously undergoes screening endoscopy, the detection of Barrett esophagus (the “at-risk” lesion) would dictate patient placement into endoscopic surveillance. Patients in whom the “at-risk” lesion is genetic are generally placed directly into surveillance, without first undergoing screening. For example, in a patient with a known germline mutation in a DNA mismatch repair gene (ie, Lynch syndrome), surveillance colonoscopy, at an interval of 1 to 2 years, should commence at age 20 to 25, or 10 years earlier than the youngest colon cancer in the immediate family. Another characteristic of surveillance is that the intensity (ie, the surveillance interval and, in some instances, the number of biopsies) is adjusted based on biopsy results. For example, for the patient with chronic GERD and Barrett esophagus discussed previously, the finding of no dysplasia on biopsy might dictate a surveillance interval of 3 to 5 years with four-quadrant biopsies taken every 2 cm of metaplasia (as recommended in a recent AGA guideline), while follow-up in 6 to 12 months with biopsies every 1 cm would be recommended, given a biopsy finding of LGD.

Major indications for GI surveillance are listed in Table 1.8. The ones most frequently encountered include Barrett esophagus, extensive IBD, and precancerous colon polyps.

GENERAL APPROACH TO THE BIOPSY SPECIMEN

When faced with a biopsy specimen, the pathologist should seek the answers to a series of questions. Patient age, gender, and the clinical indication for the biopsy inform the further evaluation of the specimen.

First, is the tissue normal or abnormal? If the tissue is apparently normal, does that make clinical sense, and if not, would step sections be helpful? Step sections should be considered in many situations, particularly if the endoscopist saw a lesion or abnormality, yet the initial biopsy sections are normal.

If the tissue is abnormal, is the lesion inflammatory or neoplastic? The answer to this question is not always obvious. As discussed previously, neoplasms are clonal. As a consequence of this, pre-invasive epithelial neoplasms (dysplasias) are characterized by abrupt transitions from the non-neoplastic background. Epithelial lesions worrisome for dysplasia but for which the diagnosis cannot be made with certainty may be interpreted as “indefinite for dysplasia.” The distinction of lymphoma from a reactive inflammatory process may require the demonstration of immunoglobulin heavy chain or T-cell receptor gene rearrangements or evidence of an aberrant immunophenotype.

If neoplastic, what is the tumor type? Primary considerations include epithelial (generally columnar or squamous), neuroendocrine, hematolymphoid, mesenchymal, melanocytic, mesothelial, and germ cell.

If the histogenesis is uncertain, could immunohistochemistry be helpful? For especially poorly differentiated tumors, broad spectrum keratins, LCA/CD45, and S100 are a useful start. Even if the broad tumor type is fairly certain (eg, lymphoma), immunohistochemistry may be useful to secure a more specific diagnosis (eg, demonstration of CD20 and cyclin D1 expression to support a diagnosis of mantle cell lymphoma).

If epithelial, is the lesion pre-invasive or invasive? Pre-invasive neoplasms are confined to the basement membrane. Single cells or small groups of cells, a never-ending gland pattern, and sheets of cells suggest invasion.

If pre-invasive, what is the grade of dysplasia? Two-tiered grading is recommended (low-grade or high-grade).

If invasive, what is the microscopic tumor extension? For columnar lesions, stromal desmoplasia and the juxtaposition of glands and thick-walled muscular blood vessels suggest a tumor is at least submucosally invasive.

Are there any other potentially clinically actionable histologic parameters that should be sought out? Tumor type and microscopic tumor extension are the key parameters. Additional features are important in select settings. For example, in polypectomy specimens of pedunculated adenomas in which an associated adenocarcinoma invades the stalk submucosa, tumor grade, LVI status, and margin status determine the adequacy of polypectomy versus the need for segmental colectomy.

Could the reporting of any additional histologic information be helpful to the clinician or to a pathologist interpreting a subsequent resection specimen from this patient? This is especially applicable to resections seen as intraoperative consultations. For example, a diagnosis of “invasive adenocarcinoma,” though perhaps sufficient to drive neoadjuvant chemoradiotherapy and resection in esophageal carcinoma, is not as useful as one of “invasive adenocarcinoma, poorly differentiated, intestinal-type/tubular (or diffuse-type/poorly cohesive or mixed),” as signet ring cells, especially in small numbers, are notoriously difficult to interpret at a frozen section.

Finally, are any additional studies indicated on the biopsy material? For example, HER2 testing should be considered for esophageal/gastroesophageal/gastric adenocarcinomas; Ki-67 immunohistochemistry is necessary
### TABLE 1.8  Surveillance for Neoplasms in the Tubal Gut

<table>
<thead>
<tr>
<th>Condition</th>
<th>Qualifier</th>
<th>Surveillance Method</th>
<th>Surveillance Interval</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Barrett esophagus</strong></td>
<td>No dysplasia</td>
<td>Upper endoscopy with random four-quadrant biopsies every 2 cm of Barrett length**</td>
<td>3–5 years</td>
<td>AGA 2011</td>
</tr>
<tr>
<td></td>
<td>Indefinite for dysplasia</td>
<td>Not defined</td>
<td>Not defined</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-grade dysplasia</td>
<td>Four-quadrant biopsies every 1 cm**</td>
<td>6–12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-grade dysplasia</td>
<td>Four-quadrant biopsies every 1 cm**</td>
<td>3 months (strongly consider endoscopic eradication)</td>
<td></td>
</tr>
<tr>
<td><strong>History of caustic ingestion</strong></td>
<td></td>
<td></td>
<td></td>
<td>ASGE 2006</td>
</tr>
<tr>
<td><strong>Extensive inflammatory bowel disease (ie, left-sided, subtotal, or pan-ulcerative colitis; or Crohn’s colitis involving at least one third of the colon)</strong></td>
<td>No dysplasia</td>
<td>Colonoscopy with four-quadrant biopsy specimens approximately every 10 cm of colitic segment; 33 and 64 biopsy specimens detect dysplasia with 90% and 95% confidence, respectively; consider increased sampling (eg, every 5 cm) in rectosigmoid</td>
<td>1–3 years****</td>
<td>AGA 2010</td>
</tr>
<tr>
<td></td>
<td>Indefinite for dysplasia</td>
<td></td>
<td>3–12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polypoid low-grade dysplasia, adenoma-like</td>
<td></td>
<td>If entirely removed and no other flat dysplasia, regular or increased surveillance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unifocal flat low-grade dysplasia</td>
<td></td>
<td>3–6 months (consider colectomy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multifocal flat low-grade dysplasia</td>
<td></td>
<td>3–6 months (consider colectomy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polypoid dysplasia, non-adenoma-like</td>
<td>Indication for colectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flat high-grade dysplasia</td>
<td>Indication for colectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colon polyps at prior examination, otherwise average risk</strong></td>
<td>Findings at baseline colonoscopy:</td>
<td></td>
<td></td>
<td>USMSTF 2012</td>
</tr>
<tr>
<td></td>
<td>No polyps</td>
<td></td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Small (ie, &lt;1 cm) rectosigmoid hyperplastic polyps</td>
<td></td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–2 small tubular adenomas</td>
<td></td>
<td>5–10 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–10 tubular adenomas OR any adenoma ≥ 1 cm OR any adenoma with villous features OR any adenoma with high-grade dysplasia</td>
<td>Colonoscopy with polypectomy</td>
<td>3 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 adenomas</td>
<td></td>
<td>&lt;3 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sessile serrated polyp(s) &lt;1 cm without cytologic dysplasia</td>
<td></td>
<td>5 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sessile serrated polyp(s) ≥1 cm OR with cytologic dysplasia OR Traditional serrated adenoma</td>
<td></td>
<td>3 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serrated polyposis syndrome</td>
<td></td>
<td>1 year</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
to accurately grade NETs; and mismatch repair protein immunohistochemistry should be considered for colorectal adenocarcinomas.

**GENERAL APPROACH TO THE RESECTION SPECIMEN**

Analogous to the approach to biopsy specimens described previously, evaluation should begin with patient age, gender, and the clinical indication for the procedure. Often, however, pathologists evaluating a resection specimen have access to the results of a diagnostic biopsy and all of the information that is included in that evaluation, which may make the evaluation of the resection specimen easier.

Given an established diagnosis, the first step in interpreting a resection specimen is to confirm that diagnosis. If available, review of prior diagnostic material is sometimes helpful. Once the diagnosis is confirmed, a systematic assessment of key histologic parameters, as represented by the required data elements of the appropriate synoptic reporting form, should be undertaken. As with biopsy specimens, additional immunohistochemical or molecular studies may be appropriate. For example, repeat HER2 testing may be considered on gastroesophageal adenocarcinomas as overexpression may be heterogeneous and, thus, not identified on a biopsy specimen. If a Ki-67 immunostain has been performed on the biopsy of a NET, repeat testing may again be useful, as the proliferation index may also be heterogeneous. MSI testing may be useful to confirm normal mismatch repair protein immunohistochemistry results, as up to 5% of Lynch syndrome mutations abrogate protein function (resulting in MSI), while maintaining antigenicity (resulting in falsely normal immunohistochemistry results).

**SELECTED REFERENCES**

**Key Terminology**


**Grading and Staging of Gastrointestinal Malignancies**


Prognostic and Predictive Markers


Screening and Surveillance


