Note: This article was posted on the Archives Web site as an Early Online Release. Early Online Release articles have been peer reviewed, copyedited, and reviewed by the authors. Additional changes or corrections may appear in these articles when they appear in a future print issue of the Archives. Early Online Release articles are citable by using the Digital Object Identifier (DOI), a unique number given to every article. The DOI will typically appear at the end of the abstract.

The DOI for this manuscript is doi: 10.5858/arpa.2020-0047-RA

The final published version of this manuscript will replace the Early Online Release version at the above DOI once it is available.
Recent Advances in Digestive Tract Tumors

Updates From the 5th Edition of the World Health Organization “Blue Book”

Raul S. Gonzalez, MD; Anwar Raza, MD; Robert Propst, DO; Oyedele Adeyi, MD; Justin Bateman, MD; Sabrina C. Sopha, MD; Janet Shaw, MD; Aaron Auerbach, MD, PhD

In mid-2019, the World Health Organization (WHO) released the 5th edition of its WHO Classification of Tumours: Digestive System Tumours, 5th edition, was published in 2019 and shows several impactful changes as compared with the 4th edition published in 2010. Changes include a revised nomenclature of serrated lesions and revamping the classification of neuroendocrine neoplasms. Appendiceal goblet cell adenocarcinoma is heavily revised, and intrahepatic cholangiocarcinoma is split into 2 subtypes. New subtypes of colorectal carcinoma and hepatocellular carcinoma are described. Precursor lesions are emphasized with their own entries, and both dysplastic and invasive lesions are generally recommended to be graded using a 2-tier system. Hematolymphoid tumors, mesenchymal tumors, and genetic tumor syndromes each have their own sections in the 5th edition. New hematolymphoid lesions include monomorphic epitheliotropic intestinal T-cell lymphoma; duodenal-type follicular lymphoid lesions include a revised nomenclature of serrated lesions and revamping the classification of neuroendocrine neoplasms. Appendiceal goblet cell adenocarcinoma is heavily revised, and intrahepatic cholangiocarcinoma is split into 2 subtypes. New subtypes of colorectal carcinoma and hepatocellular carcinoma are described. Precursor lesions are emphasized with their own entries, and both dysplastic and invasive lesions are generally recommended to be graded using a 2-tier system. Hematolymphoid tumors, mesenchymal tumors, and genetic tumor syndromes each have their own sections in the 5th edition. New hematolymphoid lesions include monomorphic epitheliotropic intestinal T-cell lymphoma; duodenal-type follicular lymphoma; intestinal T-cell lymphoma, not otherwise specified; and indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. This paper will provide an in-depth look at the changes in the 5th edition as compared with the 4th edition.

Objective.—To provide a comprehensive, in-depth update on the World Health Organization classification of digestive tumors, including changes to nomenclature, updated diagnostic criteria, and newly described entities.

Data Sources.—The 5th edition of the World Health Organization Classification of Tumours: Digestive System Tumours, as well as the 4th edition.

Conclusions.—The World Health Organization has made many key changes in its newest update on tumors of the digestive system. Pathologists should be aware of these changes and incorporate them into their practice as able or necessary.

(Arch Pathol Lab Med. doi: 10.5858/arpa.2020-0047-R)

GENERAL UPDATES

As with previous updates, the classification of digestive neuroendocrine neoplasms has been revised based on current understanding of these lesions. The vast majority represent either well-differentiated neuroendocrine tumors (NETs) or poorly differentiated neuroendocrine carcinomas (NECs), a distinction made primarily on histology. Grading still relies on mitotic rate and Ki67 index. Neuroendocrine tumors can be grade 1, 2, or 3, and a Ki67 of less than 3% now qualifies1,3 as grade 1 (formerly 0%–2% in the printed 2010 edition2) (Figure 1, A and B). Grade 3 NETs have been best studied in the pancreas, as discussed below. Mitotic rate is now counted per 2 mm², not per 10 high-power fields. As NECs are essentially always high-grade, they do not require being assigned a numerical grade. The term mixed adenoneuroendocrine carcinoma has been subsumed into the conceptual term of mixed neuroendocrine-nonneuroendocrine neoplasm, which is more inclusive; the actual diagnosis should indicate the components of the individual lesion.4 Each component should still represent at least 30% of the neoplasm, though an exception can be made for a minor component of small cell NEC.

A 2-tier grading scheme (low-grade and high-grade) is now recommended throughout the text for most carcinomas, replacing the previous 3- or 4-tier schemes (well differentiated, moderately differentiated, poorly differentiated, undifferentiated). Additionally, the concept of poorly
Figure 1. A, Well-differentiated neuroendocrine tumors consist of nests of cells with salt-and-pepper nuclei and amphophilic cytoplasm. B, This case shows a Ki67 index above 20%, classifying it as World Health Organization grade 3, which is now acceptable for neuroendocrine tumors (hematoxylin-eosin, original magnification ×200 [A]; Ki67 immunohistochemical stain, original magnification ×400 [B]).

Figure 2. Undifferentiated carcinoma of the esophagus is a distinct entity with no morphologic or immunohistochemical evidence of glandular, squamous, or neuroendocrine differentiation (hematoxylin-eosin, original magnification ×400).

Figure 3. Oxyntic gland adenoma is a rare gastric neoplasm composed of rounded and angular oxyntic glands with little atypia. It exists along a spectrum with gastric adenocarcinoma of fundic gland type, with the distinction sometimes unclear (hematoxylin-eosin, original magnification ×200).
cohese carcinoma, used for gastric cancer in the 4th edition, has been introduced into other chapters (including colon and pancreas) for the 5th edition. Signet ring cell carcinoma is generally considered a subtype of this entity.

From an organizational perspective, benign and precursor mass lesions generally have their own separate listings now, allowing for expanded information on each. Hematolymphoid lesions, mesenchymal lesions, and syndromes have been separated into their own respective chapters, rather than being included in organ-specific chapters. Similarly, there is now a separate chapter on “other tumors” that covers mucosal melanoma, germ cell tumors, and metastatic lesions.

**ESOPHAGUS AND GASTROESOPHAGEAL JUNCTION**

Several esophageal and gastroesophageal junction (GEJ) tumor entities in the 4th edition have now been moved or given their own sections in the 5th edition. For example, esophageal adenocarcinoma and GEJ adenocarcinoma are now combined into the same chapter because of their similar histologic characteristics, risk factors, and genetic abnormalities. Undifferentiated carcinoma of the esophagus (Figure 2) is now considered a separate entity in the 5th edition, instead of being a subtype of squamous cell carcinoma (SCC) as it was in the previous edition, as it lacks any evident differentiation (squamous, glandular, or neuroendocrine). This rare, understudied malignancy has a poor prognosis. Esophageal squamous cell papilloma, a benign and usually incidental lesion not always caused by infectious organisms, was not discussed in the 4th edition and now has its own listing.

A greater emphasis is now placed on the role of gastroesophageal reflux disease in the inflammation-metaplasia-dysplasia adenocarcinoma model of esophageal adenocarcinoma development, as the majority of cases occur in the setting of reflux. Additional risk factors, including obesity and male sex, are listed in a box (box 2.02). For Barrett esophagus, a 2-tier grading system of low-grade and high-grade dysplasia is recommended. The 2 most common types of dysplasia are intestinal type and foveolar/gastric type, which differ primarily based on morphology (the former resembling colonic adenomas and the latter displaying intracytoplasmic mucus). Particularly in high-risk populations, cytology-based diagnosis by brush sampling is increasingly being used in surveillance of Barrett esophagus (detecting goblet cells and dysplasia).

It is also important to note the change in the definition of GEJ adenocarcinoma from the previous edition. Gastroesophageal junction adenocarcinoma is defined as adenocarcinoma with an epicenter located less than 2 cm from the GEJ, with extension of the tumor into the esophagus. Adenocarcinomas with an epicenter located more than 2 cm distally from the GEJ are now considered gastric adenocarcinomas, even when the tumor involves the GEJ. A table (table 2.02) showing the Mandard and Becker systems, which assess esophageal adenocarcinoma following neoadjuvant therapy, has been added to the new edition.

The ERBB2 (HER2) status of esophageal adenocarcinoma has been found to be predictive of response to targeted anti-HER2 therapy in the treatment of gastroesophageal adenocarcinoma. Expression should be graded on a 0 to 3+ scale based on the strength of HER2 immunohistochemistry (IHC), which often demonstrates basolateral or lateral membranous staining, rather than complete circumferential membranous staining.

A 2-tier system of classifying squamous dysplasia as either low-grade or high-grade is now recommended over the previous 3-tier system, with the main cutoff being whether more than half of the epithelium is affected. Similarly, a 2-tier grading system may be more clinically relevant when grading esophageal SCC than a 3-tier system, mostly because of interobserver variability between grades 1 and 2. The role of human papillomavirus in the development of SCC remains unclear for most subtypes of esophageal SCC, although some cases of verrucous SCC have shown an association with some human papillomavirus strains. TP53 mutations are now known to be instrumental in the development of a majority of esophageal dysplasia and SCC, along with other genes regulating the cell cycle (such as NOTCH1, NOTCH3, and EGFR).

**STOMACH**

Epithelial tumors of the stomach have been expanded in the 5th edition, and separate sections for fundic gland polyps (FGPs) and hyperplastic polyps are now included. Many of the genetic and epigenetic abnormalities associated with precancerous lesions have been found to be associated with FGPs and hyperplastic polyps. For example, FGPs have been shown to have mutations in the APC/β-catenin pathway. However, sporadic FGPs have also been shown to harbor mutations in CTNNB1 while at the same time showing wild-type APC. Some FGPs also show epigenetic alterations such as CpG island methylation. Similarly, research into malignant transformations of hyperplastic polyps has revealed TP53 mutations or overexpression of p53.

Gastric adenomas have been added as individual entities in the 5th edition and are subtyped into intestinal-type gastric adenomas, foveolar-type adenomas, pyloric gland adenomas, and oxyntic gland adenomas (Figure 3). In addition to morphologic differences, these subtypes show distinct molecular and genetic changes. Intestinal-type gastric adenomas show mutations in APC, KRAS, ERBB2, and ARID2 and can also show microsatellite instability (MSI) in rare cases. Foveolar-type adenomas are typically syndromic adenomas (such as in patients with familial adenomatous polyposis), but sporadic cases can harbor APC and KRAS mutations. Pyloric gland adenomas tend to coexist with background atrophy, metaplastic changes, and/or Helicobacter pylori infection. Pyloric gland adenomas can also harbor GNAS, APC, and/or KRAS mutations. The risk factors and pathogenesis of oxyntic gland adenomas are still being elucidated, as this subtype is quite rare. All gastric adenomas are now graded on a 2-tier system of low-grade versus high-grade dysplasia.

---

Figure 4. Gastroblastoma is a rare biphasic neoplasm usually arising in male patients in their third decade. It comprises both an epithelial component (bottom left) and a spindled component (upper right) (hematoxylin-eosin, original magnification ×100). Courtesy of Rondell P. Graham, MBBS.

Figure 5. Intra-ampullary papillary-tubular neoplasms arise within the ampulla and can progress to invasive adenocarcinoma (hematoxylin-eosin, original magnification ×40).
The 5th edition\(^1\) has clarified that most sporadic gastric adenocarcinomas are inflammation driven, specifically because of chronic infection by *H pylori*. Other studies have shown environmental risk factors, including radiation, tobacco use, and working with rubber manufacturing agents, as contributors to the development of gastric cancer.\(^17\) To this end, pathways describing the atrophic gastritis–metaplasia–dysplasia–adenocarcinoma progression have been elucidated further and described in the 5th edition.\(^1\) As these pathways begin with chronic gastritis, the Operative Link on Gastritis Assessment staging system for gastritis has been added, which helps to identify the risk of progression to cancer from gastritis.\(^18\) Such histologic grading of gastritis into low- versus high-risk types facilitates patient-tailored surveillance programs. Metaplasia is the next step in this sequence and is differentiated into pseudopyloric and intestinal types (with goblet cells and columnar mucin-rich cells). Intestinal metaplasia may be of small intestinal (complete) or colonic (incomplete) type. The incomplete/colonic type metaplasia appears most prone to neoplastic transformation. Finally, gastric dysplasia (or gastric intraepithelial neoplasia) has been placed in a separate section, as opposed to being included within the gastric carcinoma section. It is now defined by molecular findings including chromosomal instability, MSL, and CpG island methylation in addition to histologic findings.\(^19\) TP53 loss is now seen as a major factor in the development of gastric cancer from dysplasia, and APC mutations are found in a large portion of low-grade and high-grade dysplasia.\(^1,19\) A 2-tier grading system of low-grade versus high-grade dysplasia has been shown to be strongly related to prognosis.\(^20,20\)

Multiple classifications of gastric cancer have been proposed in the 5th edition.\(^1\) Genetic classifications include The Cancer Genome Atlas Research Network, which divides gastric cancer into 4 molecular subtypes (Epstein-Barr virus [EBV]–positive, MSI, genomically stable, and chromosomally unstable), and the Asian Cancer Research Group, which also divides gastric cancer into 4 subtypes (MSI, microsatellite stable with epithelial-mesenchymal transition gene signature, microsatellite stable and TP53 active, and microsatellite stable and TP53 inactive).\(^21–23\) Genetic classifications also include consideration of neuroendocrine markers, goblet cell adenocarcinoma is now not considered a neuroendocrine entity. Genetic mutations specified.\(^29\) Finally, pyloric gland adenoma is recognized as a rare subtype of small bowel adenoma with frequent GNAS mutation; it is typically located in the proximal duodenum and appears morphologically similar to pyloric gland adenomas elsewhere in the digestive tract.\(^30\)

### SMALL BOWEL AND AMPULLA

The main change to these chapters is organizational, as they have been combined into one for the 5th edition.\(^1\) Still, the chapter distinguishes between ampullary and non-ampullary adenomas and carcinomas. A new box (box 4.02) details numerous mutations described in nonampullary small bowel adenocarcinomas, most notably in *TP53, CTNNB1, SMAD4, and KRAS*. Serrated forms of dysplasia, although uncommon in the small intestine, have been added in the classification box at the beginning of the chapter.

There are new officially adopted terms and categorizations, as follows. Intra-ampullary papillary-tubular neoplasm is added as a subtype of ampullary adenoma characterized by location within the intra-ampullary channel (Figure 5).\(^28\) Anatomic localization of ampullary adenocarcinomas is discussed, based on an existing 4-tier categorization grouping them into periampullary, intra-ampullary, ampullary ductal, and ampulla not otherwise specified.\(^29\) Finally, pyloric gland adenoma is recognized as a rare subtype of small bowel adenoma with frequent GNAS mutation; it is typically located in the proximal duodenum and appears morphologically similar to pyloric gland adenomas elsewhere in the digestive tract.\(^30\)

### APPENDIX

Several additions and changes have been made to the appendix chapter, based primarily on improved molecular data and increased recognition of rare tumor types. Perhaps the biggest change is the renaming of goblet cell carcinoid to goblet cell adenocarcinoma (Figure 6), with a new grading system, based on the findings of Yozu et al,\(^31\) summarized in a table (table 5.03). Lesions previously termed “adenocarcinoma ex goblet cell carcinoid” now instead represent high-grade goblet cell adenocarcinoma. Despite expression of neuroendocrine markers, goblet cell adenocarcinoma is not considered a neuroendocrine entity. Genetic mutations reported in goblet cell adenocarcinoma include genes in the Wnt signaling pathway\(^32,33\) and genes involved in chromatin remodeling.\(^35\)

Sessile serrated adenoma/polyp is renamed to sessile serrated lesion (SSL). This is consistent with the naming of a morphologically similar lesion in the colorectum (see below) but differs from the Peritoneal Surface Oncology Group International’s recommended term of serrated polyp.\(^34\) These lesions are at risk of developing cytologic dysplasia and progressing to adenocarcinoma. Low-grade appendiceal mucinous neoplasm is formalized as a separate entity, rather than being bundled in with appendiceal adenocarcinoma; the terms *mucinous cystadenoma* and *mucinous tumor of uncertain malignant potential* are listed as not recommended for use. Low-grade appendiceal mucinous neoplasm is noteworthy for its ability to progress to pseudomyxoma peritonei, which has a slightly different grading scheme than primary lesions, as discussed in a table (table 5.02). Rare lesions that resemble low-grade appendiceal mucinous neoplasm but have unequivocal foci of high-grade dysplasia are now officially recognized as high-grade appendiceal mucinous neoplasm (Figure 7).\(^34\) *KRAS* mutations are frequently found in appendiceal SSL, low-grade appendiceal mucinous neoplasm, and appendiceal adenocarcinoma.\(^35\) GNAS mutations also occur regularly in low-grade appendiceal mucinous neoplasm\(^35\) and have been reported in appendiceal adenocarcinoma.\(^36\)
Finally, tubular carcinoid and L-cell carcinomas have been renamed to tubular NET and L-cell NET, respectively. With this change and the renaming of goblet cell adenocarcinoma, carcinoid is no longer used in any official/preferred diagnostic terminology in the digestive tract, though it remains listed as “acceptable” related terminology, and the clinical term carcinoid syndrome persists. Appendiceal NETs are otherwise unchanged (aside from the grading revision described earlier) and remain often-incidental, often-innocent lesions.

**COLORECTUM**

Most changes in the colorectum chapter relate to grading and classification of colorectal carcinoma (CRC), though a few changes were made to precursor lesions as well; these will be discussed first. Additionally, several topics on polyposis syndromes were moved to the chapter on genetic tumor syndromes.

Sessile serrated adenoma/polyp has been renamed to SSL, with provided reasoning that it is not always polypoid on colonoscopy. Diagnosis is based on unequivocally distorted crypts showing L- or T-shaped growth and full-length serration. In the 4th edition, more than 2 or 3 contiguous distorted crypts were needed; in the 5th edition, only one is needed to confirm the diagnosis (Figure 8). An expanded range of dysplastic changes in SSL has been added, including a subtle form best recognized by loss of MLH1 expression. The text indicates not to stratify SSL dysplasia into low-grade or high-grade, though ICD-O coding does make this distinction. Finally, dysplasia related to inflam-
LIVER AND INTRAHEPATIC BILE DUCTS

The pathologic and molecular classification of hepatocellular adenoma (HCA) continues to be refined and expanded. The major categories included in the 5th edition remain HNF1α-inactivated, inflammatory, β-catenin–activated, and β-catenin–activated inflammatory. The clinical, radiologic, molecular, and pathologic features are summarized in a table (table 8.02). The unclassified category, which accounts for 5% to 10% of all HCAs, has been de-emphasized because of poorly defined features.

There have been further efforts to characterize β-catenin–activated HCA and β-catenin–activated inflammatory HCA, which together account for approximately 20% to 25% of HCAs. Different mutations in CTNNB1 have been associated with varying degrees of Wnt signaling activation. Large deletions and hot-spot mutations in exon 3 are associated with high levels of activation (high risk of progression to hepatocellular carcinoma [HCC]), whereas exon 3 S45 mutations are associated with moderate activation and exon 7/8 mutations with weak activation (low risk of progression to HCC).

The β-catenin and glutamine synthetase (GS) IHC correlates for CTNNB1 mutation involving exon 3 (other than S45) versus S45 versus exon 7/8 are addressed. Importantly, the absence of β-catenin nuclear staining and faint GS in HCA with exon 7/8 mutations is highlighted, contrasting with lesions with exon 3 (other than S45) mutation, where β-catenin nuclear staining and diffuse GS are typical (Figure 10, A through D). Exon 3 S45-mutated lesions have intermediate features with little or no nuclear β-catenin staining and a diffuse but heterogeneous starry-sky GS pattern. Given the high risk of progression to HCC in HCAs with high levels of β-catenin activation, the term atypical hepatocellular neoplasm has been recommended by some, especially for lesions with diffuse (highest risk) staining, in which focal loss of reticulin (a feature of HCC) may be seen alongside heterogeneous GS patterns.

In addition to discussing pathogenesis of the β-catenin–activated HCA, the new edition also expands on the molecular pathogenesis of inflammatory HCA. The importance of IL-6/JAK/STAT pathway activation in the pathogenesis of inflammatory HCA has been emphasized.

A new molecular subtype of HCA has been described, which shows activation of the sonic hedgehog signaling pathway (sh-HCA) due to fusion of the promoter region of INHBE with GLI1. These tumors were reported to account for 4% of HCAs in one series and were associated with bleeding and obesity. Prostaglandin-H2 D-isomerase (PTGDS) IHC may be useful in identifying these cases. Argininosuccinate synthase 1 (ASS1) has also recently emerged as a possible biomarker in HCAs (ASS1+ HCA) and may be associated with clinically significant hemorrhage. Overexpression of ASS1 also appears to correlate strongly with the recently described sh-HCA category. This awaits validation in other studies.

Since 2010, there have been considerable efforts to characterize the molecular pathogenesis of HCC. The most frequent mutation in HCC, regardless of underlying etiology, involves the TERT promoter, which encodes the protein telomerase. Other common mutations involve TP53 and CTNNB1. Fibrolamellar HCC has been characterized by a unique DNAJB1-PRKACA somatic gene fusion, which leads to constitutive activation of protein kinase A.
Figure 10.  
A, Hepatocellular adenoma with β-catenin mutation has subtypes within this variant, which can be identified immunohistochemically with β-catenin and glutamine synthetase staining. B, β-Catenin mutation involving exon 3 other than S45 is more likely to show nuclear staining. C, It is also more likely to show strong, diffuse glutamine synthetase staining. D, Lesions with S45 exon 3 mutation have a heterogeneous diffuse starry-sky pattern for glutamine synthetase and could show rare or absent nuclear localization of β-catenin (hematoxylin-eosin, original magnification ×200 [A]; β-catenin immunohistochemical stain, original magnification ×200 [B]; glutamine synthetase immunohistochemical stain, original magnification ×200 [C and D]).

Figure 11.  
Hepatocellular carcinoma morphologic variants with independent prognostic significance are included in the current World Health Organization classification. A, The macrotrabecular-massive type, with 10 or more cells in trabecula, is associated with poorer prognosis. B, The clear cell variant has a better prognosis than traditional type (hematoxylin-eosin, original magnification ×200).
The 5th edition\(^1\) has officially recognized a number of HCC variants (Figure 11, A and B) with unique clinical, molecular, and histopathologic features. These variants include steatohepatitic HCC (5%–20% of HCC), clear cell HCC (3%–7% of HCC), macrotrabecular-massive HCC (defined as more than half of the tumor showing macrotrabecular growth [trabeculae >10 cells thick], often associated with high serum AFP and TP53 mutations),\(^55\) scirrhous HCC (found to demonstrate TSC1/2 mutations and increased TGF-β signaling),\(^55,56\) and chromophobe HCC.\(^57\) Of these, only scirrhous HCC was also formally recognized in the 4th edition.\(^2\) Two rare inflammatory variants—neutrophil rich and lymphocyte rich—are also included.\(^58\) The prognostic significance of these variants is not always clear except for the macrotrabecular-massive and neutrophil-rich variants, both associated with poorer outcome compared with more conventional types, and the
clear cell and lymphocyte-rich variants, which have been associated with better prognosis.

Recognizing usual practice by most experienced hepatopathologists, a simplified 3-tier grading system for HCC based on resemblance to normal liver has been proposed. Lesions that raise a differential diagnosis with HCA or benign (dysplastic) nodules but demonstrate reticulin loss and other features of malignancy are well differentiated. Those with architectural features of hepatocytes but clearly malignant cytology, including thicker plates and nuclear atypia, are moderately differentiated. Lesions that would typically require IHC proof of hepatocellular differentiation are poorly differentiated (Figure 12, A through F). Undifferentiated HCC is no longer included and is now described separately.

Precursor lesions (ie, dysplastic foci and dysplastic nodules) continue to be described within the HCC section, along with early and small progressed HCC. A new table (Table 8.04) highlights the multistep progression of molecular mutations within the precursor lesions from low-grade dysplastic nodules up to progressed HCC. Lastly, there is a new table (Table 8.06) describing the individual staining patterns and sensitivities for markers of hepatocellular differentiation, including arginase1, HepPar1, polyclonal CEA, CD10, and AFP.

The 5th edition emphasizes the subclassification of intrahepatic cholangiocarcinoma (iCCA) into small duct and large duct types. The small duct type occurs in the periphery of the liver and tends to form mass lesions. It occurs more commonly in patients with nonbiliary cirrhosis and chronic viral hepatitis. Histologically, it may show small ductal components without mucin production or identifiable precursor lesions. It shares etiologic and imaging features with HCC, and this subtype includes cholangiolar carcinoma (see below). In contrast, the large duct type arises within the larger-caliber bile ducts near the hilum and proximal to the (see below). In contrast, the large duct type arises within the larger-caliber bile ducts near the hilum and proximal to the.

The section on mucinous cystic neoplasm (MCN) has been updated with a new table (Table 8.14) describing the various cystic liver lesions. New molecular data are included in this section, highlighting the importance of KRAS mutations in the pathogenesis of MCN.

Primary hepatic neuroendocrine neoplasms occupy a new section in the 5th edition. They are rare tumors; metastases to the liver from other primary sites are far more common. Most reported cases are from Asian populations. In keeping with terminology from elsewhere in the gastrointestinal tract, primary hepatic neuroendocrine neoplasms are classified as well-differentiated NETs (grades 1–3), poorly differentiated NECs (small and large cell), and mixed neuroendocrine–nonneuroendocrine neoplasms.

**GALLBLADDER AND EXTRAHEPATIC BILE DUCTS**

Pyloric gland adenoma has been designated as a separate entity from other types of adenomas (intestinal, foveolar, biliary) and from intracholecystic papillary neoplasm (ICPN) because of advances in the molecular underpinnings of these lesions, which show pyloric gland adenoma is molecularly distinct. In contradistinction to the other adenomas, pyloric gland adenomas show increased IHC expression of β-catenin and mutations in CTNNB1 in 60%, rather than mutations in TP53 or CDKN2A, which are seen in the other adenomas. It is therefore thought that pyloric gland adenoma plays a minor role in carcinogenesis of the gallbladder and extrahepatic biliary tree.

Biliary intraepithelial neoplasia (BiliN) was described in the 4th edition as an epithelial dysplastic lesion of the
PANCREAS

Previously called acinar cell cystadenoma, acinar cystic transformation of the pancreas has been renamed to reflect the latest understanding as a nonneoplastic entity. Studies since the release of the 4th edition have shown chromosomal gains, but a follow-up study found random X chromosome inactivation for 5 cases, suggesting this is a nonneoplastic entity, and it has been renamed accordingly.

Pancreatic intraepithelial neoplasia (PanIN) has been restructured into a 2-tier system for grading of dysplasia. PanIN-1 and PanIN-2 are now classified as low-grade PanIN, whereas PanIN-3 is classified as high-grade PanIN. Additionally, in contrast to prior reports, TP53 mutations have since been shown to be rare or absent, and there are no mutations or homozygous deletions of SMAD4 in high-grade PanIN without associated invasive carcinoma, suggesting these 2 genes are inactivated only in truly invasive carcinomas.

Intraductal papillary mucinous neoplasm of the pancreas continues to have an ill-defined size criterion, with both larger than 0.5 cm and larger than 1.0 cm described in the 5th edition. For lesions 0.5 to 1.0 cm in size, falling in the "gray zone" between PanIN and IPMN, the term incipient IPMN is introduced. Since the 4th edition, the understanding of the genetic alterations in IPMN has advanced, with newer studies showing GNAS mutations at codon 201 in 50% to 70% of all IPMN, especially the intestinal variant. This is a relatively specific alteration not found in ductal adenocarcinoma. Another change is the reclassification and renaming of intraductal oncocytic papillary neoplasm as a unique entity from other variants of IPMN. Intraductal oncocystic papillary neoplasms lack KRAS, GNAS, and RNF43 mutations, which are commonly found in ductal adenocarcinoma and IPMN.

Pancreatic intraductal tubulopapillary neoplasm (ITPN) has been reclassified and reorganized as a separate entity from IPMN because of its genetic features: ITPN lacks KRAS mutations, which are typically found in IPMN and ductal adenocarcinoma. Of note, a subset shows FGFR2 fusions, which may represent a pharmacologic target. The long-term outcome of ITPN is excellent, and 5-year survival of ITPN with invasive carcinoma is 71%. Histologically, ITPN shows cuboidal cells with minimal cytoplasm arranged predominantly in tubules, in contrast to IPMN, which shows papillae of usually columnar cells with a variety of epithelial types but typically prominent intracellular mucin.

The most notable updates to MCN (a cystic mucin-producing lesion with surrounding ovarian-type stroma) involve the grading of dysplasia and staging of carcinomas arising from MCN. Like other entities within the pancreas and other organ systems, MCN with dysplasia is now graded using a 2-tier schema, with low- and intermediate-grade dysplasia now categorized as "low-grade dysplasia," whereas high-grade dysplasia remains "high-grade dysplasia." Additionally, for MCNs with invasion 2 cm or less, the Union for International Cancer Control introduced the substages pT1a (<0.5 cm), pT1b (>0.5 to <1 cm), and pT1c (≥1 cm).

The 5th edition places special emphasis on certain morphologic subtypes of pancreatic ductal adenocarcinoma (PDAC), the most important being the large duct pattern, with neoplastic ducts measuring more than 0.5 mm and having deceptively bland features. This pattern may mimic IPMN. The foamy gland pattern (Figure 13) can be difficult to diagnose, particularly on limited samples (hematoxylin-eosin, original magnification ×200).

Figure 13. As the World Health Organization notes, the foamy gland pattern of pancreatic ductal adenocarcinoma can be difficult to diagnose, particularly on limited samples (hematoxylin-eosin, original magnification ×200).
This subtype is a particular diagnostic pitfall on frozen section or small biopsies. A clear cell subtype may mimic metastatic renal cell carcinoma. Lastly, a cystic papillary pattern of PDAC may mimic IPMN but behaves like a poorly differentiated PDAC. The molecular foundation of PDAC has been well established, with mutations in KRAS, CDKN2A (p16), SMAD4 (DPC4), and TP53 found in 90% of all PDAC. New to the 5th edition are the contributions of BRCA2, PALB2, ATM, CHEK2, and RAD51 mutations involved in DNA repair, which are found in 15% to 20% of all PDAC. These may be targetable with platinum-based drugs or PARP inhibitors. New defects in epigenetic drivers are found in 40% of all cancers (COMPASS-like complex and the SWI/SNF complex) and may also represent a potentially targetable group. New genetic alterations in acinar cell carcinoma have been described, including occasional abnormalities in SMAD4, CDKN2A, CDKN2B, ID3, ARAIA1A, and APC. This lesion can have overlapping histology with pancreatic NETs and may show some IHC positivity for synaptophysin and chromogranin; positivity for trypsin, chymotrypsin, and/or BCL10 helps confirm the diagnosis.

There have been several changes in the field of pancreatic neuroendocrine neoplasms, including those mentioned at the beginning of this article. Studies have shown significantly worse prognosis in patients whose tumors show Ki67 labeling 5% or higher but at this time, there are no differences in clinical management for patients whose tumors show 5% labeling as opposed to 3%. In the pancreas, grade 3 NET has been shown to be molecularly distinct from grade 3 NEC, retaining the molecular features of lower-grade NETs; namely, they can show mutations in MEN1, DAXX, and ATRX, and they lack mutations in TP53 and RB1, which are seen in pancreatic NECs. As a result, aberrant IHC staining for p53 or RB1 indicates a diagnosis of NEC over NET. It is therefore thought that grade 3 pancreatic NETs represent a gradual transformation of lower-grade NETs; namely, they can show mutations in lower-grade NETs; namely, they can show mutations in MEN1, DAXX, and ATRX, and they lack mutations in TP53 and RB1, which are seen in pancreatic NECs. As a result, aberrant IHC staining for p53 or RB1 indicates a diagnosis of NEC over NET. It is therefore thought that grade 3 pancreatic NETs represent a gradual transformation from lower-grade NETs, whereas pancreatic NECs show genetic similarity to PDAC and therefore may represent radical, de novo mutations from other types of preexisting carcinomas.

**HEMATOLYMPHOID TUMORS**

The 5th edition aggregates all hematopoietic neoplasms under a single chapter, whereas in the 4th edition, different lymphomas were spread out and listed in the different anatomic sites.

Duodenal-type follicular lymphoma is recognized as a distinct entity (Figure 14, A through F). It is a generally indolent lymphoma with behavior more like in situ follicular lymphoma or extranodal marginal zone lymphoma. Patients appear to have an excellent outcome, including some cases managed with a watch-and-wait strategy instead of with chemotherapy. The neoplastic cells resemble those of follicular lymphoma with a centrocyte morphology and are arranged in nodules in the mucosa and submucosa. The nodules do not have tingible body macrophages or mantle zones. The neoplastic cells have a CD20+/CD10−, BCL2+, BCL6+ immunophenotype, similar to follicular lymphoma, and a low proliferative rate. The follicular dendritic mesh-works (CD21+/CD23+/CD35+) are pushed to the periphery of the nodules. Even though molecular testing will demonstrate the same t(14;18)(q32;q21) that is seen in follicular lymphoma, comparative genomic hybridization studies suggest similarities to extranodal marginal zone lymphoma.

The diffuse large B-cell lymphoma (DLBCL) content is greatly expanded in the 5th edition, dividing DLBCL into germinal center B-cell and activated B-cell profiles, noting that germinal center B-cell DLBCLs are more often CD10+, GCET1, and LMO2 positive, unlike the activated B-cell type, which more frequently expresses MUM1 and FOXP1. The most common site of extranodal DLBCL is the gastrointestinal tract, most commonly the stomach and ileocecal region. Double-expressor DLBCLs express both BCL2 and CMYC by IHC, which is an adverse prognostic indicator. What were previously designated as double-hit and triple-hit lymphoma are now classified as high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 gene rearrangement. Double-hit DLBCLs have MYC gene rearrangements with either BCL2 or BCL6 gene. Triple-hit DLBCLs have MYC, BCL2, and BCL6 gene rearrangements.

Immunoproliferative small intestinal disease is reclassified as a subtype of MALT lymphoma. This subtype secretes defective α-heavy chain without light chains, because the defective structure is unable to assemble with light chains. The process shows marked plasma cell differentiation, including Dutcher bodies, Russell bodies, immunoglobulin crystals, and globules.

Enteropathy-associated T-cell lymphoma previously was separated into type I (associated with gluten-sensitive enteropathy) and type II (not associated with gluten-sensitive enteropathy). Type II enteropathy-associated T-cell lymphoma was described in the 4th edition as monomorphic CD5+ intestinal T-cell lymphoma and has in the 5th edition been renamed as monomorphic epitheliotropic intestinal T-cell lymphoma.

Enteropathy-associated T-cell lymphoma is most often found in the jejunum of individuals with refractory celiac disease. The intraepithelial lymphocytes found in celiac disease are CD3+CD8+ T cells. Refractory celiac disease is defined as persistent villous atrophy and failure to improve clinically despite a strict gluten-restricted diet and is divided into 2 types. Refractory celiac disease type I has the same CD3+CD8+ T cells as found in celiac disease, but without clonal TCR gene rearrangements, and generally has an indolent clinical course. Refractory celiac disease type II has CD3+ intraepithelial T cells with loss of CD8 in at least 50% of the same T cells, and the majority have clonal TCR gene rearrangements. Refractory celiac disease type II can be considered enteropathy-associated T-cell lymphoma in situ, and up to 50% of patients will progress to enteropathy-associated T-cell lymphoma within 5 years. Enteropathy-associated T-cell lymphoma usually comprises atypical lymphocytes, some of which may be anaplastic. Mucosa adjacent to and away from the neoplasm will have the typical findings of celiac disease. An inflammatory background composed of eosinophils, lymphocytes, plasma cells, and histiocytes usually is present. Prognosis usually is poor. The neoplastic cells have a CD3+, CD7+, CD103+, CD5−, CD4+, CD8+, CD56+ immunophenotype. TCR-α and TCR-β may be expressed. Cytotoxic markers (TIA1, granzyme B, and perforin) frequently are expressed. CD30 may be positive, but ALK1 is negative. Epstein-Barr virus testing by in situ hybridization (EBER) is negative.

Monomorphic epitheliotropic intestinal T-cell lymphoma comprises large ulcerating masses throughout the gastrointestinal tract and is not associated with gluten-sensitive
Figure 14. A, Duodenal-type follicular lymphoma shows nodules of lymphoid cells in the duodenum lacking tingible body macrophages and well-formed mantle zones. B, CD20 is positive in the B cells. C, There are only few scattered reactive T cells. D, BCL6 is expressed in the B cells. E, BCL2 is also coexpressed in the B cells. F, The proliferative rate by Ki67 is moderate, ~25% in this case (hematoxylin-eosin, original magnification ×20 [A]; CD20 immunohistochemical stain, original magnification ×100 [B]; CD3 immunohistochemical stain, original magnification ×100 [C]; BCL6 immunohistochemical stain, original magnification ×100 [D]; BCL2 immunohistochemical stain, original magnification ×100 [E]; Ki67 immunohistochemical stain, original magnification ×200).
enteropathy (Figure 15, A through D). Generally, the neoplasm is aggressive and has a poor prognosis. The neoplastic cells are monomorphic, small to medium in size, and have round to oval nuclei with dispersed chromatin and clear cytoplasm. Scattered larger cells may be present. The adjacent mucosa will have neoplastic intraepithelial lymphocytes and villous blunting, but mucosa away from the tumor will not have increased intraepithelial lymphocytes. The neoplastic cells have a CD2⁺, CD3⁺, CD7⁺, CD8⁺, CD56⁺ immunophenotype. TCR-γ or TCR-β may be expressed. The cytotoxic marker TIA1 frequently is positive; granzyme B and perforin are less commonly expressed. aberrant expression of nuclear MATK and CD20 is reported in up to 20%. Intestinal T-cell lymphoma, not otherwise specified, has been carved out as a distinct, aggressive T-cell lymphoma multifocally involving the gastrointestinal tract without diagnostic features of other T-cell lymphomas. Intraepithelial lymphocytosis is uncommon. The neoplastic cells are medium- to large-sized, with frequently pleomorphic cells. The neoplastic cells have a CD2⁺, CD3⁺, CD5⁺, CD7⁻ immunophenotype, and usually are either CD4⁺/CD8⁻ or CD4⁻/CD8⁺. The majority of neoplastic cells express cytotoxic marker TIA1, but granzyme B is less common. CD30 may be expressed, and a small subset is positive for EBER.

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract is also a new diagnosis in the 5th edition, defined as an indolent clonal T-cell lymphoproliferative process of mature small lymphocytes in the lamina propria without intraepithelial lymphocytosis, usually involving the small bowel and colon. The neoplastic cells are small and expand the lamina propria with some extension into the muscularis mucosae and submucosa (Figure 16, A through E). An admixed inflammatory infiltrate is uncommon, but small epithelioid granulomas, similar to those seen in Crohn disease, may be present. The clinical course usually is indolent, with chronic relapsing disease. The neoplastic cells have a CD2⁺, CD3⁺, CD5⁺, CD7⁺ immunophenotype. Most express CD8, as well as TIA1, but a small subset express CD4 instead. CD56 is negative. TCR-α/β is positive and TCR-γ/δ is negative.

Extranodal NK/T-cell lymphoma is a neoplasm of cytotoxic natural killer (NK) T cells with extranodal involvement, angioinvasion, and a strong association with EBV infection. The nasal cavity and skin are more...
commonly involved than the gastrointestinal tract, where it can occur as single or multiple ulcerated mass lesions. Liver involvement is rare. Patients may present with gastrointestinal tract bleeding or perforation. The disease more frequently occurs in Asia and Central and South America; it is uncommon in Europe and North America. The neoplasm is aggressive, with a poor prognosis. The infiltrate usually is diffuse and has an angiocentric and
angiodestructive pattern with coagulative necrosis and prominent apoptosis. The neoplastic cells are medium in size and have irregular nuclei with pale to clear cytoplasm. They have a CD2+, cytoplasmic CD3+, CD56+ immunophenotype and express TIA1, granzyme B, and perforin, as well as EBER. They may express CD7, but they are negative for surface CD3, CD4, CD5, CD8, CD16, and CD57. A small subset of extranodal NK/T-cell lymphoma can be positive for surface CD3, CD5, CD8, and/or TCR.  

A related, but benign and indolent, NK proliferation is lymphomatoid gastropathy/NK-cell enteropathy. This presents as multiple small mucosal lesions in the stomach or intestine. The lesions occur and regress spontaneously without treatment or progression. On biopsy, the neoplastic cells infiltrate and destroy glandular epithelium, mimicking lymphoepithelial lesions seen in extranodal marginal zone lymphoma. The cells are medium in size and have irregular nuclei, cytoplasmic clearing, and red cytoplasmic granules. The immunophenotype is the same as for extranodal NK/T-cell lymphoma, but EBER is negative.

Epstein-Barr virus–positive inflammatory follicular dendritic cell (FDC) sarcoma of the digestive tract is an indolent neoplasm of spindled FDCs associated with EBV and a lymphoplasmacytic infiltrate. This previously was recognized as an EBV-associated inflammatory pseudotumor with FDCs. This tumor usually involves the spleen or liver. Patients usually are young to middle-aged and Asian. They present with constitutional B symptoms of weight loss, fever, and malaise, as well as anemia, elevated C-reactive protein, hypoalbuminemia, hypergammaglobulinemia, increased CA125, and peripheral eosinophilia. The FDCs are spindled and have nuclei with vesicular chromatin and small nucleoli and form whorled fascicles. Some may resemble Reed-Sternberg cells, and histiocytic/granulomatous inflammation may be present. Blood vessels in the lesion often have fibrinoid deposits with associated necrosis and hemorrhage. The neoplastic cells are variably positive for FDC markers CD21, CD23, CD35, CXCL13, D2-40, CNA4.2, and clusterin. Because staining can be weak or patchy, a large panel of FDC markers may be needed to identify the neoplastic cells. The neoplastic cells may also express smooth muscle actin. Epstein-Barr virus LMP1 expression is present in 70% of lesions.

A less common but related process is FDC sarcoma. This also is a low- to intermediate-grade neoplasm of FDC, not associated with EBV. The tumor cells variably express FDC markers and also may express PD-L1, EMA, S100, and CD68. They are negative for cytokeratins, CD1a, langerin, lysozyme, and myeloperoxidase.

Gastrointestinal tract involvement by Langerhans cell histiocytosis usually occurs in pediatric patients with multisystem disease, and in these patients usually is an aggressive disease with high mortality. Involvement in adults is rare and usually solitary, with an indolent course. Liver involvement can present with cholestasis and a sclerosing cholangitis injury pattern. The neoplastic cells are oval and have grooved nuclei with fine chromatin and indistinct nucleoli, as well as a moderate amount of pink cytoplasm and distinct cell membranes. The cells express the Langerhans cell markers S100, CD1a, and langerin (CD207). Molecular studies show BRAF V600E and MAP2K1 mutations. Eosinophils and macrophages are admixed with the neoplastic cells.

Histioytic sarcoma is a rare, aggressive neoplasm with morphologic and immunophenotypic histiocytic differentiation. The gastrointestinal tract is a common extranodal location for histiocytic sarcoma. The neoplastic cells are round to oval with oval, grooved, or reniform nuclei and abundant eosinophilic finely vacuolated cytoplasm. Hemophagocytosis can be seen. At least one histiocytic marker—CD163, CD68, or lysozyme—is expressed. S100 may be positive in some cells, but they are negative for CD1a, langerin, CD21, CD35, myeloperoxidase, and CD13.

Plasmablastic lymphoma is an aggressive lymphoma comprising large B cells with plasmablastic or immunoblastic morphology. The majority of patients are immunodeficient from a variety of causes, including HIV, immunosuppressive therapy, or posttransplantation. The neoplastic cells have a loss of usual B-cell markers CD20 and PAX5, MUM1 is positive, and CD79a can be positive. Plasma cell markers CD38, CD138, VS38c, Blimp1, and XBP1 are positive. MYC may be positive by IHC, although MYC translocation may not be present. Ki67 proliferative index is high. A small percentage of cases may express CD10, CD56, and CD30. In HIV patients, EBER may be positive. ALK1 and HHV8 are usually negative.

Discussion of the 5 categories of posttransplant lymphoproliferative disorders—nondestructive, polymorphic, monomorphic, classic Hodgkin lymphoma, and mucocutaneous ulcer—is included in the 5th edition. The majority of posttransplant lymphoproliferative disorders are of B-cell origin and associated with EBV, although T/NK and plasma cell variants are recognized. Additional risk factors include EBV-negative status prior to transplant, cytomegalovirus-negative status, posttransplantation, type of immunosuppression, sex, and age of recipient.

**MESENCHYMAL TUMORS**

This new chapter collects all the mesenchymal tumors that were previously scattered throughout the organ-specific chapters. Most changes involve descriptions of new subtypes and updated molecular data. The main “new entity” is malignant gastrointestinal neuroectodermal tumor, a rare, aggressive malignancy with poor prognosis. It shows IHC positivity for S100, SOX10, and neuroendocrine markers, as well as frequent EWSR1 translocations (Figure 17). It remains unclear whether this represents the same entity as gastrointestinal clear cell sarcoma (which was briefly discussed in the 4th edition) or a subtype of it.

New subtypes have been added the text and/or the classification box for numerous entities, including inflammatory myofibroblastic tumor (epithelioid inflammatory myofibroblastic sarcoma, an aggressive variant with RANBP2 rearrangement; Figure 18, A and B), glomus tumor (glomangiomatosis, glomus tumor of uncertain malignant potential, malignant glomus tumor), schwannoma (microcystic/reticular schwannoma, mucosal Schwann cell hamartoma, PEComa (sclerosing PEComa), angiomylipoma (inflammatory angiomylipoma), and hemangioma (anastomosing hemangioma, diffuse hepatocellular hemangiomatosis, hepatic small vessel neoplasm). In the discussion of gastrointestinal lipomas, intramucosal lipoma was added as a subtype that may suggest the patient has Cowden syndrome.

In keeping with other chapters throughout the text, important molecular data were added on several tumors, including a discussion of the succinate dehydrogenase—
deficient subtypes of gastrointestinal stromal tumor (Figure 19), discussion of the characteristic, mutually exclusive WWTR1–CAMTA1 and YAP1–TFE3 translocations in epithelioid hemangioendothelioma,155,156 and new molecular information regarding plexiform fibromyxoma (MALAT1–GLI1 fusion157), granular cell tumor (frequent mutations in ATP6AP1 and ATP6AP2158), and calcifying nested stromal-epithelial tumor of the liver (CTNNB1 mutation;159 helpful but not diagnostic).

GENETIC TUMOR SYNDROMES

This new chapter discusses updated findings in and classification of all of the known genetic syndromes that have lesions in the gastrointestinal tract. A 2-page table (table 14.01) lists all the currently known heritable syndromes with gastrointestinal lesions with their associated inheritance, mutations, loci, proteins, and protein function. The chapter also includes data regarding gene mutation, age, sex, and tumor type in Lynch syndrome, as well as a discussion regarding the use of mismatch repair protein expression to guide therapeutic choices. The notion that genes involved in germline mutations in familial syndromes also are prone to somatic mutations is included, and the transition to defining syndromes based on genetic findings rather than on clinical findings is recognized. Several new polyposis syndromes are added, including gastric adenocarcinoma and proximal polyposis syndrome,160 NTHL1-associated polyposis,161 polymerase proofreading–associated polyposis (caused by POLD1 or POLE mutation),162 AXIN2-associated polyposis,163 and immune deficiency–associated polyposis.164 Criteria for diagnosis of serrated polyposis and gastric adenocarcinoma and proximal...
The 5th edition of the WHO Classification of Digestive System Tumours offers a wide variety of updates across the digestive system, including revisions of nomenclature, delineations of newly described or clarified entities, and expanded data on defining and/or clinically relevant molecular abnormalities. Pathologists should make efforts to adopt these changes going forward. Some (in particular changes in nomenclature) may require discussions with clinical colleagues to prevent initial confusion. Still, the vast majority of changes represent incremental advancements rather than drastic overhauls, hopefully minimizing disruptions as the updates are integrated into daily practice.

CONCLUSIONS

The 5th edition of the WHO Classification of Digestive System Tumours offers a wide variety of updates across the digestive system, including revisions of nomenclature, delineations of newly described or clarified entities, and expanded data on defining and/or clinically relevant molecular abnormalities. Pathologists should make efforts to adopt these changes going forward. Some (in particular changes in nomenclature) may require discussions with clinical colleagues to prevent initial confusion. Still, the vast majority of changes represent incremental advancements rather than drastic overhauls, hopefully minimizing disruptions as the updates are integrated into daily practice.

References

37. Liu C, Walker NI, Leggett BA, Whitehall VL, Bettington ML, Rosty C. Evaluation in patients with juvenile polyposis is included. The contribution from and importance of both clinical and genetic findings to expand knowledge of familial and hereditary pancreatic carcinoma is stressed. The information on hamartomatous polyposis syndromes is extensively updated, with a discussion on distinctive morphologic findings in colonic lesions in juvenile polyposis and Peutz-Jeghers syndrome, as well as the spectrum of findings in Cowden syndrome–related lesions. The recent recognition of SMAD4 immunostaining as a guide for clinical and genetic evaluation in patients with juvenile polyposis is included.165 The criteria for serrated polyposis have been modified to the following: either (1) 5 or more serrated lesions 5 mm or more in size proximal to the rectum, with at least two 10 mm or more, or (2) more than 20 serrated lesions throughout the colorectum, with 5 or more proximal to the rectum. The number of serrated lesions identified is cumulative and hence may be identified over a number of endoscopies. The final section lists miscellaneous genetic syndromes causing neoplasms in the gastrointestinal tract and their relationships to and similarities with other known heritable syndromes.


Arch Pathol Lab Med WHO Digestive Tract Tumors Update—Gonzalez et al 19


