Diagnosis of Digestive System Tumours.

[1]M Kay Washington MD; [2]Richard M Goldberg MD; [3]George J Chang MD, MS; [4]Paul Limburg MD, MPH; [5]Alfred K Lam MBBS, PhD, FRCPath; [6]Manuel Salto-Tellez MD; [7]Mark J Arends MBChB, PhD, FRCPath; [8]Iris D Nagtegaal MD, PhD; [9]David S Klimstra MD; [10]Massimo Rugge, MD; [11]Peter Schirmacher MD; [12]Alexander J Lazar MD, PhD; [13]Robert D Odze MD; [14]Fatima Carneiro MD; [15]Masashi Fukayama MD; [16]Ian A Cree MBChB, PhD, FRCPath on behalf of the WHO Classification of Tumours Editorial Board

[1]Vanderbilt University Medical Center, C-3321 MCN, Nashville, TN 37232, USA

[2]West Virginia University Cancer Institute and the Mary Babb Randolph Cancer Center, PO Box 9300 1805 Health Sciences Center South, Morgantown, WV 26506

[3]Department of Surgical Oncology, University of Texas M.D. Anderson Cancer Center, 1400 Pressler Street, FCT 17.5022, Houston, TX 77030, USA

[4]Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, MN 55905

[5]Pathology, School of Medicine, Gold Coast campus, Griffith University, Gold Coast, QLD 4222, Australia

[6]Queen's Precision Medicine Centre of Excellence, Queen's University Belfast, Belfast Health & Social Care Trust, 97 Lisburn Road, Belfast, BT9 7BL, UK

[7]Cancer Research UK Edinburgh Centre, MRC Institute of Genetics & Molecular Medicine, The University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XR, UK

[8]Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands

[9]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

[10]University of Padova, 61 Via Aristide Gabelli, 35121 Padua, Italy

[11]Institute of Pathology, University Hospital, Im Neuenheimer Feld 224, 69120 Heidelberg, Germany

[12]Departments of Pathology, Genomic Medicine, and Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 85, Houston, TX, USA

[13]110 Stuart Street, Boston, MA, USA

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[14]Faculty of Medicine, University of Porto, Porto, Portugal.

[15]Department of Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[16WHO] Classification of Tumours Group, International Agency for Research on Cancer (IARC), World Health Organization, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France

Correspondence to:

Dr Ian A Cree
Head, WHO Classification of Tumours Group and Section of Evidence Synthesis and Classification
International Agency for Research on Cancer (IARC),
World Health Organization,
150 Cours Albert Thomas,
69372 Lyon CEDEX 08,
France

Tel: +33 (0) 4 72 73 8534 (Direct)
Secretary: +33 (0) 4 72 73 8447
Email: creei@iarc.fr
Web: www.iarc.fr

List of abbreviations

ALK receptor tyrosine kinase (ALK)
APC, adenomatous polyposis coli gene
BRAF, B-Raf proto-oncogene
CDKN2A, Cyclin-Dependent Kinase Inhibitor 2A (P16)
CDH1, cadherin 1 gene
CTNNB1, beta-catenin 1 gene
EBV, Epstein-Barr virus
FAP, Familial adenomatous polyposis
FGFR2, fibroblast growth factor receptor 2
G1, Grade 1
G2, Grade 2
G3, Grade 3
GC, gastric carcinoma
GI, gastro-intestinal
GAPPS, Gastric adenocarcinoma and proximal polyposis of the stomach
GIST, Gastrointestinal stromal tumour
HER2, Human Epidermal Growth Factor Receptor 2
HGVS, Human Genome Variation Society-nomenclature
HHV8, Human herpesvirus 8

HPF, high power microscope fields
HPV, Human Papilloma Virus
iCCA, Intrahepatic cholangiocarcinoma
ICD-O, International Classification of Diseases for Oncology
IDH1/2, isocitrate dehydrogenase
IPMN(s), Intraductal papillary mucinous neoplasm(s)
KIT, KIT proto-oncogene receptor tyrosine kinase
KRAS, Kirsten rat sarcoma viral oncogene homolog
LCNEC, Large cell neuroendocrine carcinomas
LS, Lynch syndrome
MALAT1-GLI1, Metastasis Associated Lung Adenocarcinoma Transcript 1–Glioblastoma Associate Oncogene homologue 1
MANEC, Mixed adenoneuroendocrine carcinoma
MET, MET proto-oncogene
MiNEN(s), Mixed neuroendocrine – non-neuroendocrine neoplasms(s)
MSI, microsatellite instability
MSI-H, microsatellite-instability high
NEC(s), Neuroendocrine carcinomas(s)
NEN(s), Neuroendocrine neoplasm(s)
NET(s), Neuroendocrine tumour(s)
NOS, not otherwise specified
NRAS, Neuroblastoma rat sarcoma viral oncogene homolog
P16 protein product of Cyclin-Dependent Kinase Inhibitor 2A (*CDKN2A*)
P53, Tumour protein p53
PanNET(s), Pancreatic neuroendocrine tumour(s)
PDGFR, Platelet Derived Growth Factor Receptor
PDL1, Programmed Death-Ligand 1
PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PRKACA, Catalytic Subunit Alpha of Protein Kinase A
pTNM, pathological Tumour – Node – Metastasis staging
RB, retinoblastoma
RB1, retinoblastoma gene
SCNEC, Small cell neuroendocrine carcinoma
SI, Standardised international units.
SMAD4, SMAD family member 4
SSP/SSA, sessile serrated polyp or adenoma
SSL, sessile serrated lesion
TP53, Tumour Protein p53 gene
TCGA, The Cancer Genome Atlas
WHO, World Health Organization

Abstract (250 words)

The WHO Classification of Tumours provides the international standards for the classification and diagnosis of tumours. It enables direct comparisons to be made between different countries. In the new 5th Edition, the series has gone digital with the launch of a website as well as a series of books, known widely as the WHO Blue Books. The first volume to be produced is on the classification of Digestive System tumours, replacing the successful 2010 version. It has been rewritten and updated accordingly. This article summarises the major diagnostic innovations that have occurred over the last decade and that have now been incorporated in the classification. As an example, it incorporates the recently proposed classification of neuroendocrine tumours, based on the recognition that neuroendocrine tumours and carcinomas differ substantially in the genetic abnormalities that drive their growth, findings relevant to treatment selection and outcome prediction. Several themes have emerged during the production process. One is the importance of the progression from hyperplasia to dysplasia to carcinoma in the evolution of the malignant process. Advances in imaging techniques and endoscopy have resulted in enhanced access to precancerous lesions in the gastrointestinal and biliary tract, necessitating both changes in classification schema and clinical practice. Diagnosis of tumours is no longer the sole purview of pathologists, and some patients now receive treatment before tissue is obtained, based on clinical, radiological, and liquid biopsy results. This makes the classification relevant to many disciplines involved in the care of patients with tumours of the digestive system.

Keywords: tumour, classification, diagnosis, Digestive system, neoplasms, neuroendocrine, diagnosis.

Introduction

The potential to prevent, treat and cure many cancers has improved dramatically over the last 20 years and the pace of change continues to accelerate. There have been similar advances in our ability to reach a diagnosis and to refine a tumour's classification enabling pathologists and other clinicians to render a more complete diagnosis. Clinical investigations that leverage the new knowledge regarding tumour classifications have in turn accelerated progress towards improved treatments, while further informing more effective screening and surveillance strategies. With the recognition of the heterogeneity of tumours that share the same histology, the complexity of rendering a definitive diagnosis for individual patients is now more challenging than ever. Since 1963, the World Health Organization (WHO) has developed a classification that standardizes tumour diagnosis (http://whobluebooks.iarc.fr).[1-6] This means that cancer patients anywhere in the world can be diagnosed and then staged in a standardized fashion. This process leads to greater precision in categorizing their disease, allows more refinement in projecting their prognosis and permits them to enrol in and hopefully benefit from clinical trials predicated upon the treatment of patients with an individual cancer type and stage. The WHO Classification of Tumours provides the internationally accepted standards that pathologists and other clinicians employ to make diagnoses and categorize

the extent of disease. The classification is now in its 5th Edition and its reach has been extended with the publication of the first volume devoted exclusively to Digestive System Tumours (Figure 1),[2,7,8] which has also been made available in a searchable web format that permits rapid identification of gaps in knowledge (https://tumourclassification.iarc.who.int).[8]

The classification is organised by tumour site, category, family, and type (Table 1). It does change from time to time as new tumour types are discovered. The main driving force behind the refinement of tumour diagnosis and staging over the last ten years has been the discovery of specific genetic alternations that drive tumours and are relevant to their prognosis and therapy. The additional categorization can have one of two implications. The finding of one or more genetic alteration most may result in dichotomizing of what appear under the microscope to be one tumour type into two or more classifications. Occasionally it becomes clear that what appear to be two histologically dissimilar tumour types have the same molecular alterations and belong in the same category, despite widely differing histologic appearances. The classification schemes highlight the increasing importance of the multidisciplinary assessment and now incorporate information from many modalities, including clinical appearances, epidemiology, etiology and pathogenesis, imaging studies, genetics, epigenetics, and other molecular investigations, in addition to histopathology. The classification is increasingly complex and this has required the development of an accessible electronic database, although these data are still published as a series of books. Databases are ideal for creating websites, and the new WHO Classification of Tumours website should be of interest to all clinicians and investigators involved in cancer-related care (https://tumourclassification.iarc.who.int).

The new volume on the Digestive System includes a wealth of information relating to diagnosis of tumours from the oesophagus to the anus, including the pancreas, liver, and biliary system. Some of the major changes and advances in the field are described below, by relevant organ or region of the gastrointestinal tract.

Changes across the classification

The new classification of tumours of the digestive system has been updated completely[2] and, in line with most reference books in oncology, starts each chapter with benign lesions and finishes with the most aggressive malignancies. Consistency has been improved by collecting soft tissue and hematolymphoid tumours together into separate chapters. There is a separate chapter on inherited genetic tumour susceptibility syndromes, the recognition of which is of increasing importance to patients, their families and the practitioners that manage their illnesses. The use of the Human Genome Variation Society-nomenclature (HGVS) for genetics is now standard, as is the adoption of standardised international (SI) units. The adoption of SI units has caused problems in some areas of histopathology where mitotic counts are important in determining diagnosis or grade. For some tumour types, pathologists have long used high power microscope fields (HPF) without reference to their actual area, which can vary between microscopes.[9-13] We have therefore moved to the expression of mitoses per mm^2 across the series, with counts per HPF in parentheses for a given size of field where their use is ingrained in practice.

Soft tissue tumour pathology and diagnosis increasingly incorporates molecular parameters.[8] The importance of KIT proto-oncogene receptor tyrosine kinase (*KIT)* and Platelet Derived Growth Factor Receptor (*PDGFR)* mutations in defining the prognosis of gastrointestinal stromal tumour and its treatment is well known. Additional examples include the finding of ALK receptor tyrosine kinase (ALK) fusion genes in inflammatory myofibroblastic tumour,[14] and beta-catenin 1 (*CTNNB1*) mutations in desmoid fibromatosis,[15,16] to name but a few.

The development of a comprehensive classification of neuroendocrine tumours and carcinomas, malignancies that share a common histology but arise in disparate anatomic locations and have variable clinical courses, proved to be challenging. However a consensus-based new harmonized classification scheme was implemented following a multidisciplinary meeting in Lyon in November 2017.[13] The classification is based on the recognition that neuroendocrine tumours (NETs) and carcinomas (NECs) differ substantially in their genetics, with Retinoblastoma (*RB*) and Tumour Protein p53 (*TP53*) mutations commonly found in the latter. This helps to distinguish true neuroendocrine carcinomas (NEC) from grade 3 Neuroendocrine Tumours (NET), which can be problematic and the distinction has major management implications.

Malignancies arising in each of the organs in the digestive system are covered within this volume, and the key changes in these are as follows:

Neuroendocrine neoplasms (NENs)

NENs in various anatomical sites have been classified separately, and although the various classification systems have shared some common features,[17] differences in terminology and classification criteria between organ systems have caused considerable confusion. In 2018, WHO published a uniform classification framework for all NENs.[13] The key feature of the common classification is the distinction between well-differentiated neuroendocrine tumours (NETs), previously designated carcinoid tumours when occurring in the GI tract, and poorly differentiated neuroendocrine carcinomas (NECs), which share with NETs the expression of neuroendocrine markers, but are now known not to be closely related neoplasms based on genetic differences[18-21] as well as by clinical, epidemiological, histological, and prognostic differences.

NETs are graded as G1, G2, or G3 on the basis of proliferative activity as assessed by mitotic count and the Ki-67 proliferation index.[22] In the event that the two proliferation indicators suggest different grades, the higher grade is assigned; generally, when there is discordance, it is the Ki-67 proliferation index that indicates the higher grade.[23] NECs are high-grade by definition, and there is no need to grade them. NECs may occasionally have a Ki-67 proliferation index of 20–50%, especially after exposure to chemotherapy, so the Ki-67 proliferation index cannot be used to conclusively distinguish a NEC from a G3 NET.[24] Even G3 NETs of the pancreas retain the mutation profile of other well-differentiated neoplasms, providing a means to distinguish G3 NETs from NECs in challenging cases.[24,25] Genomic comparisons of NETs and NECs of other gastrointestinal sites are still emerging. NECs of these sites share frequent *TP53* and *RB1* mutations with NECs of the pancreas (and lung),[26,27] but extrapancreatic NETs generally lack frequent recurrent mutations,[28,29] reducing

the value of genomic analysis for diagnostic purposes, although extrapancreatic NETs do share abnormalities in chromatin remodelling pathways with their pancreatic counterparts.

There are also data supporting the distinction between G3 NETs and NECs from a clinical perspective. The common response of NECs to platinum-containing chemotherapy (which is dramatic in the case of SCNECs) led to the standard use of these regimens for the treatment of NECs of diverse anatomical origins.[30] However, it was recognized that a subset of patients, probably patients who in fact had G3 NETs, failed to respond but paradoxically survived longer than the others.[31] Alternative approved therapies are available for some subsets of NETs;[32] therefore, there is a clinical need to distinguish NETs from NECs within the high-grade category. Although all NETs are still considered to be malignant neoplasms, early-stage NETs of all anatomical sites have a low risk of metastasis if they are entirely removed. Larger or higher-grade NETs can metastasize and are difficult to treat, but survival for many years is still possible, even in advanced stages. Despite the unified treatment throughout the classification, NETs exhibit important organ-specific differences with different functionality, histology, and genomics. These distinctive clinical features mean that the surgical and medical treatment of NETs is highly dependent on the site of origin. Attempts to determine the origin of NETs presenting with distant metastases can involve both radiographical and pathological techniques.[33]

Mixed neuroendocrine – non-neuroendocrine neoplasms (MiNENs) are mixed epithelial neoplasms in which a neuroendocrine component is combined with a non-neuroendocrine component, each of which is morphologically and immunohistochemically recognizable as a discrete component and constitutes ≥ 30% of the neoplasm. Previously, these mixed neoplasms were classified under the category of “mixed adenoneuroendocrine carcinoma (MANEC)”. However, in recognition that the non-neuroendocrine component may not be adenocarcinoma, and to reflect the possibility that one or both components may not be carcinoma, the current term for this category is “mixed neuroendocrine – non-neuroendocrine neoplasm (MiNEN)”. MiNEN is regarded as a conceptual category of neoplasms rather than a specific diagnosis. Different types of MiNENs arise in different sites throughout the gastroenteropancreatic system, and each should be diagnosed using site-specific terminology that reflects the nature of the components. Carcinomas previously treated with neoadjuvant therapy should not be considered MiNENs either, unless the diagnosis of MiNEN is established based on a pretreatment specimen, because the neuroendocrine morphology exhibited by some treated carcinomas may not have the same prognostic significance as that seen in a de novo component of NEC.[34,35] The 30% rule is arbitrary, and the one exception is the finding of small cell NEC (SCNEC) which is a poor prognosis factor and should always be reported if present, even if making up less than 30% of the tumour.

Upper GI Tract

The processes involved in the development of common cancers in the esophagus and stomach are considerably better understood than was the case in previous editions, and this is reflected in the new volume. The sequential neoplastic progression from inflammation, through metaplasia (Barrett Esophagus) to adenocarcinoma of the esophagus is covered, with the role of gastro-oesophageal reflux disease acknowledged.[36,37] Less clear are the mechanisms underlying the marked differences

between countries in the incidence of esophageal squamous cell carcinoma and adenocarcinomas. While squamous dysplasia is a subject that requires further research, emerging insights regarding molecular alterations that occur early on in esophageal carcinogenesis provide considerable potential for new screening approaches. It should be noted that the staging of esophageal squamous cell carcinoma and adenocarcinoma differs.[38,39]

In the stomach, neoplastic progression begins with mucosal inflammation, usually caused by *Helicobacter pylori* infection, which renders this a potentially preventable cancer with the use of more effective antibacterial therapy.[40] Metaplasia and dysplasia precede the development of adenocarcinoma, allowing intervention, including secondary prevention and monitoring for disease progression to frank carcinoma. The genetic changes involved in the progression of gastric neoplasia area increasingly understood[41] and have direct relevance to the management of at least some patients.

The classification of gastric adenocarcinoma across the world was previously a matter of some debate, and inconsistencies in application caused some potential for incorrect diagnosis, management and cancer registration. These issues have been resolved in the 5th edition, providing clarity of diagnosis for gastric adenoma and adenocarcinoma in particular. Molecular profiling has provided a new framework for gastric carcinoma (GC) classification.[42-46] The key (epi)genetic molecular abnormalities associated with the four GC subtypes (EBV-positive, microsatellite-unstable, genomically stable, and chromosomally unstable) proposed by The Cancer Genome Atlas (TCGA) Research Network are described.[45,47-50] Specific alterations in rare tumours are increasingly required for diagnosis; the Metastasis Associated Lung Adenocarcinoma Transcript 1–Glioblastoma Associate Oncogene homologue 1 (*MALAT1-GLI1*) fusion gene in gastroblastoma being an example.[51] TP53 and RB1 expression can help distinguish high grade neuroendocrine tumours from neuroendocrine carcinomas.[13] Molecular pathology now guides treatment: patients with tumours that are noted to have germline or acquired defective mismatch repair also known as Microsatellite Instability High (MSI-H), manifest overexpression of Human Epidermal Growth Factor Receptor 2 (HER2, ERBB2), or have high expression of Programmed Death-Ligand 1 (PDL1) can benefit from the use of targeted therapies in the treatment of their gastric adenocarcinoma. *ERBB2* (*HER2*) amplification identifies GC subtypes susceptible to molecularly targeted therapy;[52-54] therefore, in high-income countries, oncology diagnostics may include sequencing.[55] However, at its core, the clinical management of GC still relies on traditional histology and pTNM staging.

Small intestine and ampulla

As a result of improvements in diagnostic procedures, the incidence of small bowel tumours is rising in North American and European countries; for example, the incidence in the United Kingdom more than doubled over the 25-year period of 1990–2015: from 1 to 2.5 cases per 100 000 person-years.[56] The increasing incidence of neoplastic cases is mainly due to an increase in duodenal tumors.[57] Potential associations with dietary risk factors are currently equivocal. Industrial exposures have also been linked to small bowel cancer.[58,59]

Since the 2010 edition,[60] there have been some important changes in the taxonomy of pre-invasive neoplasia of the small bowel and ampulla. Following the nomenclature in lesions from pancreatic and biliary ducts, the term "intra-ampullary papillary-tubular neoplasm" is now used for preinvasive neoplasms (adenomas and non-invasive papillary neoplasms) occurring almost exclusively within the ampulla. Fundamentally, these are intra-ampullary versions of intraductal papillary neoplasms or intraductal tubulopapillary neoplasms of the pancreas and bile ducts.

The prognosis of cancers arising deep within the ampulla (which have been termed "ampullary-ductal" carcinomas according to site/origin and are usually pancreatobiliary type by histology) differs from that of cancers originating from the duodenal surface of the ampulla (which have been termed "[peri]ampullary duodenal" carcinomas according to site/origin and are often intestinal type by histology), with 5-year survival rates of 29% and 52%, respectively.[61,62] Upper small intestine carcinomas sometimes exhibit pancreatobiliary or gastric differentiation, which suggests their origin from submucosal glandular units. The classification of ampullary carcinomas into four anatomically based subtypes has been adopted. This has some degree of histological correlation: intra-ampullary papillary-tubular neoplasm–associated carcinoma (carcinomas arising from intraluminal-growing preinvasive neoplasms), ampullary-ductal carcinoma (arising and growing along the walls of intra-ampullary ducts), (peri)ampullary-duodenal carcinoma (growing on the duodenal surface of the ampulla), and ampullary carcinoma NOS. This subdivision is driven by the anatomical complexity at that site and also affects the difficulty in tumour staging.

Lower GI Tract

Tumours of the appendix have been reclassified based on new evidence to reflect that of their colorectal counterparts. The term "serrated lesion" is preferred to "serrated adenoma" or "serrated polyp". The term "hyperplastic polyp" is retained. The term "low-grade mucinous neoplasm" is recommended for lesions formerly classified as mucinous tumour of uncertain malignant potential, mucinous cystadenocarcinoma, or mucinous cystadenoma; this recommendation is based on growing consensus regarding the nomenclature for these lesions[63] and their inclusion in current TNM staging systems.[38] High-grade appendiceal mucinous neoplasm is now recognized as a subtype of appendiceal mucinous neoplasm.

A major change in the new edition is reclassification of "goblet cell carcinoid" that arises in the appendix as "goblet cell adenocarcinoma" based on the finding that these tumours are largely adenocarcinomas with only a minor neuroendocrine component.[64,65] These tumours characteristically have a much more aggressive course than true neuroendocrine tumours (previously called carcinoids). The glandular lesions of the appendix have been renamed to correspond to characterization of colonic neoplasms.

In the colon and rectum, there is a detailed consideration of the pathways of carcinogenesis, and the biologic basis of adenoma formation. The terminology used in this fifth edition is a has changed from the previous edition. For instance, sessile serrated polyp or adenoma (SSP/SSA) is now termed "sessile serrated lesion (SSL)", for a variety of reasons – most notably, because not all lesions that fall into this category are necessarily polypoid in appearance and many the lack cytologic features of

typical adenomatous change.[66,67] In addition, to reflect the fact that some serrated lesions cannot always be classified reliably into one of the above three general categories after careful clinical/endoscopic and pathological evaluation, a fourth category has been added: unclassified serrated adenoma. For conventional adenomas, essential diagnostic criteria have been added.

The genetic classification of colorectal carcinomas is covered in detail and the biomarkers predictive of either drug resistance or drug sensitivity are listed. The importance of MSI, *BRAF*, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and Neuroblastoma rat sarcoma viral oncogene homolog (*NRAS*) is regarded as being established, while other predictive biomarkers are yet to become useful as determinants for choosing antineoplastic therapy. The changes are significant: in 2010 microsatellite-instability high (MSI-H) colorectal tumours were classified as poorly differentiated, high grade tumours whereas they are now regarded as relatively low grade CRCs with a better prognosis with differing chemosensitivity[68] and response to PD-1 blockade.[69,70] Newer, less commonly observed oncogenes (e.g. *PIK3CA, MET*) currently have insufficient evidence for inclusion; however, it is anticipated that additional biomarkers will make their way into the classification in the future, reflecting continued innovation in molecularly-targeted treatment and prevention.

The role of the pathologist in the diagnosis of anal tumours, particularly those of the anal margin, is changing. P16 immunohistochemistry and Human Papilloma Virus (HPV) typing can be helpful in defining patients at higher or lower risk of recurrence.

Liver and biliary system

Liver neoplasms provide several unusual aspects with clinical, diagnostic, and research impact. Not only is HCC one of the most frequent malignancies worldwide, it is the paradigm of cancer induced by infection and by metabolic and toxic agents linked to chronic necroinflammation. Although these findings have translated into primary and secondary preventive measures, as well as model systems of disease, the prognosis of clinically apparent HCC remains poor. Intrahepatic cholangiocarcinoma (iCCA) stands out as a malignancy with a high percentage of cases showing translocations that may also represent future therapeutic targets.

Knowledge of the molecular changes present in hepatocellular tumours has changed significantly in the 11 years since the previous edition of the classification of liver tumours. Indeed, several rare subtypes are now also defined by their molecular characteristics, for example fibrolamellar carcinoma, which has a diagnostic Catalytic Subunit Alpha of Protein Kinase A(*DNAJB1)-PRKACA* translocation.[71] iCCA is now understood to be a distinct entity with two functionally and clinically different subtypes:[72,73] a large duct type, which resembles extrahepatic cholangiocarcinoma, and a small duct type, which shares etiological, pathogenetic, and imaging characteristics with hepatocellular carcinoma. The two subtypes have very different etiologies, molecular alterations, growth patterns, and clinical behaviours, exemplifying the conflict between anatomically and histogenetically / pathogenetically based classifications. Clinical research and study protocols, including those focused on interception during the premalignant phase, will need to incorporate these findings in the near future. There is a new classification of hepatocellular adenomas, based on

the correlation of molecular pathology and histological appearances,[74] with implications for clinical management and the risk of the development of hepatocellular carcinoma.

Changes to the anatomical classification of disease are rare, but in the case of tumours of the biliary system, it has become clear that this is necessary, and new topographical ICD-O codes for intrahepatic, extrahepatic – distal, extrahepatic – perihilar, and overlapping lesions have been listed. Modern endoscopic methods allow access to in situ lesions of the biliary tract, and the description of biliary intraepithelial neoplasia is changing practice. It appears that many of these lesions are due to chronic biliary inflammation with *KRAS* mutation as early event, and *TP53* mutation as a late event.[74,75] Of other genetic alterations, isocitrate dehydrogenase (IDH1/2) and *BRAF* mutations, and fibroblast growth factor receptor 2 (*FGFR2*) fusions have been described in intrahepatic cholangiocarcinoma.[73]

Pancreas

Most adult pancreatic neoplasms are pancreatic ductal adenocarcinomas. There have been major advances in understanding of the underlying genetic drivers of these malignancies over the last decade, and particularly the role of germline mutations. The genetic basis of ductal adenocarcinoma was established more than a decade ago,[76] and the importance of germline mutations in its pathogenesis is becoming increasingly clear.[77] The subtypes of ductal adenocarcinoma now include invasive micropapillary carcinoma, which (as in other anatomical locations) has a particularly aggressive clinical course.

Precursor lesions are now recognized and in a change from the previous edition, are divided into two rather than three groups as either high or low grade lesions.[78] Most have *KRAS* mutations, but the transition to high grade lesions is characterised by Cyclin-Dependent Kinase Inhibitor 2A (*CDKN2A*), also known as P16, inactivation rather than *TP53* as previously thought, which is associated with invasion in frank carcinomas. Ductal carcinomas often have *KRAS* or *SMAD4* mutations, but the mutational landscape also includes a number of DNA repair genes. Opportunities exist to interrogate these DNA changes in a variety of biologic media (pancreatic secretions, cyst fluid, blood, etc.) for application to novel early detection assays. Numerous less common mutations also play an important role, some of which may be targetable therapeutically.[79-81] Molecular subcategories are also emerging based on genomic and transcriptomic analysis.[82,83]

The increased use of cross-sectional imaging has resulted in greater detection of cystic and intraductal neoplasms, as well as small PanNETs. Intraductal papillary mucinous neoplasms (IPMNs) now constitute 60% of cyst-forming neoplasms of the pancreas and are commonly detected incidentally, raising the issue of the preoperative features that should indicate surgical intervention.[84]

Haematolymphoid tumours

For the first time, to avoid repetition, these tumours are collected together in one chapter, as they can occur throughout the GI tract, albeit with some organ-specific differences. The GI tract is the most common site for occurrence of extranodal lymphomas, accounting for 30–40% of all extranodal lymphomas.[85-87] Only one change was made: EBV-positive inflammatory follicular dendritic cell sarcoma, was renamed from inflammatory pseudotumour-like follicular/fibroblastic dendritic cell sarcoma as it is now clear that this is EBV-related.[88]

Mesenchymal tumours

Soft tissue tumours are collected into one chapter allowing a more comprehensive description of the characteristics of each tumour type. The importance of genetics and viral etiologies is emphasised as appropriate, and in some molecular characterization is required for diagnosis. Viruses associated with soft tissue tumours include EBV (associated with some smooth muscle tumours in immunosuppressed patients)[89] and HHV8 (associated with Kaposi sarcoma).[90] Gastrointestinal stromal tumour (GIST) is the archetypal soft tissue tumour of the digestive system for which molecular investigation is a requirement for both diagnosis and treatment. GISTs are usually sporadic, although germline *KIT* or *PDGFRA* mutations (familial GIST), *NF1* mutations (neurofibromatosis type 1), and succinate dehydrogenase mutations (including Carney–Stratakis syndrome) account for a small subset of tumours.[91-93]

Genetic tumour syndromes

Several tumour syndromes primarily affect the digestive system, and new information is available for several. The section on Lynch syndrome (LS) includes a description of relevant new findings, including in the pathogenesis, progression, molecular pathology, molecular testing, and diagnosis. Exploitation of the immune response in mismatch repair–deficient tumours has paved the way to more-effective immunotherapies based on immune checkpoint blockade. Lynch-like syndrome, i.e. the occurrence of colorectal cancers with loss of mismatch repair that is not due to LS, is now being investigated via the sequencing of such cancers.[94,95] These investigations have demonstrated that the genes in which heritable mutations may predispose an individual to cancer are also prone to somatic mutation, in both LS and non-LS tumours.[95]

Familial adenomatous polyposis 1 and GAPPS, because of their distinct phenotypic features (e.g. GAPPS predominantly affects the stomach), are described in their own separate sections, despite the fact that GAPPS is currently considered to be a subtype of familial adenomatous polyposis because of the shared genetic etiology of causative mutations located in the promoter region of *APC*.[96] The section on other adenomatous polyposes describes several new conditions that are defined on the basis of their specific genetic aberrations.

The section on serrated polyposis presents new diagnostic criteria, updated from those included in the fourth edition. Only two clinical criteria are now included in the definition, corresponding to the two main phenotypes of serrated polyposis. The previous criterion of any number of serrated polyps

occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis has been discarded. Another change is the inclusion of the sigmoid colon in the criteria. The section addressing hereditary diffuse gastric cancer includes an improved characterization of the syndrome's clinicopathological and genetic features. Recent findings have confirmed the existence of an indolent phenotype in asymptomatic carriers of *CDH1* germline mutations, as well as an aggressive histological and immunohistochemical phenotype in aggressive, lethal cases.[97,98]

Conclusion

As knowledge expands classifications need to evolve and the WHO Classification of Tumours is no exception. The consensus arising from reviews by expert panels will continue to be periodically updated and published as a series of books. These reviews are now also available online, allowing the incorporation of whole slide images and clinical imaging in ways that are impossible to portray in book form. It is now underpinned by a database and can be much more easily updated as advances occur to accommodate new advances as these pass the scrutiny of the editorial board. Diagnosis of tumours is no longer the sole purview of pathologists, and some patients already receive therapeutic or preventive interventions before tissue is taken, based on clinical, radiological and liquid biopsy results. The Classification needs to adapt to encompass these methods, and in return is much more relevant to non-pathologists than ever before.

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Declarations
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Disclosures

Dr. Limburg serves as Chief Medical Officer for Exact Sciences through a contracted services agreement with Mayo Clinic. Dr. Limburg and Mayo Clinic have contractual rights to receive royalties through this agreement.

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Legends to Figures.

Figure 1. Cover of the WHO Classification of Tumours, 5th Edition, Digestive System Tumours.

Tables.

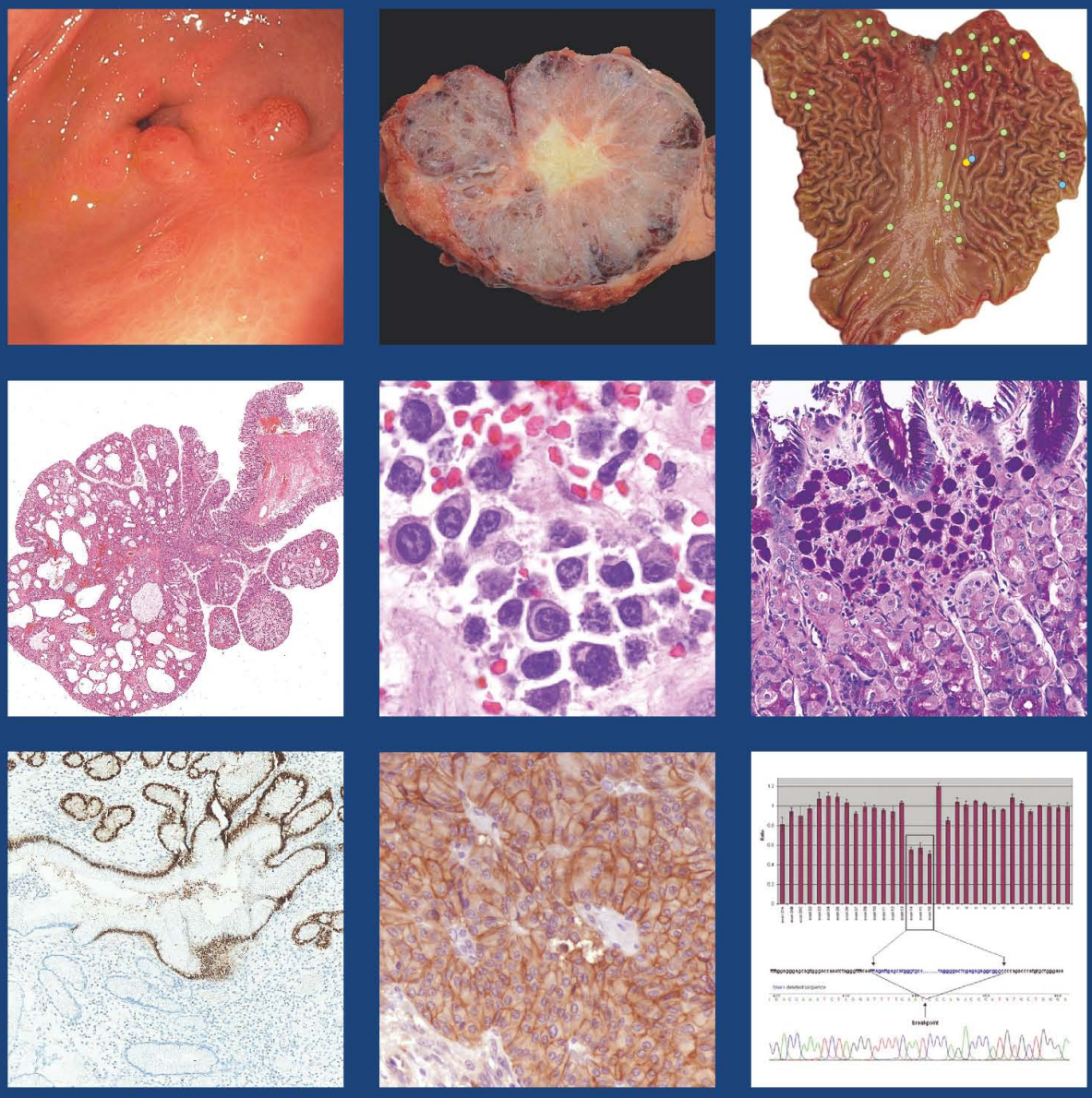
TABLE 1. The classification of tumours is organized by Site, Category, Family, Type and Subtype as shown in this example from the pancreas according to the new scheme for neuroendocrine neoplasms.[2]

CLASSIFICATION	NAME
Site	Pancreas
Category	Neuroendocrine neoplasm
Family	Neuroendocrine tumour
Type	Functioning pancreatic neuroendocrine tumour
Subtype	Glucagonoma

WHO Classification of Tumours • 5th Edition

Digestive System Tumours

Edited by the WHO Classification of Tumours Editorial Board



World Health Organization

Table 2. Major changes within the new classification of tumours of the Digestive System.

Topic	WHO 2010	WHO 2019
Mitotic counts	Expressed per HPF	Given per mm^2
Human Genome Variation Society-nomenclature (HGVS) for genetics	Variable usage	Required
Neuroendocrine neoplasms	Dealt with separately depending on site	Unified classification separating neuroendocrine tumours (carcinoids) from neuroendocrine carcinomas, on the basis of genetics, histology and clinical behaviour.
Neuroendocrine tumours	Graded 1 – 3 on the basis of mitotic count and Ki67	Graded 1 – 3 on the basis of mitotic count and Ki67. Ki67 alone insufficient.
Neuroendocrine carcinomas	Grade 3 by default	No longer graded as separately classified.
Mixed neuroendocrine neoplasms (MiNEN)	Previously called mixed adenoneuroendocrine carcinoma (MANEC)	MiNEN preferred as may arise from neoplasms other than carcinomas
Carcinogenesis of oesophageal and gastric carcinomas	Limited information available	Updated pathology, pathogenesis and molecular characteristics.
Gastric adenoma versus adenocarcinoma	Differences in practice developed since 4th edition	Inconsistencies clarified and diagnostic criteria added.
Gastric adenocarcinoma subtypes	Histology only	Molecular subtypes described – EBV, microsatellite instability, genomically stable, and chromosomally unstable.
Gastric and oesophageal adenocarcinomas, predictive biomarkers	Limited	Importance of ERBB2 (HER2) and PDL1 established.
Gastroblastoma	Histology only	Molecular diagnosis on basis of *MALAT1-GLI1* fusion gene
Small intestine	Limited	Increased recognition of importance and rising incidence
Ampullary pre-invasive neoplasms		'Intra-ampullary papillary-tubular neoplasm' is now used for preinvasive neoplasms (adenomas and non-invasive papillary neoplasms) occurring almost exclusively within the ampulla

Ampullary carcinoma	Treated together	Distinction of intestinal and ductal subtypes with prognostic significance
Appendix: Reclassification of tumours based on new evidence	Goblet cell carcinoid	Goblet cell adenocarcinoma
Appendix: Reclassification of tumours based on new evidence	Adenoma	Divided into serrated and mucinous lesions
Appendix: Reclassification of tumours based on new evidence	Mucinous tumour of uncertain malignant potential	Low-grade mucinous neoplasm
Benign colorectal neoplasia and precursors	Screening limited, insufficient data	Recognition of serrated pathway lesions, inflammatory bowel disease associated dysplasia,
Colorectal adenocarcinoma classification revised based on new molecular evidence	Limited impact on classification or treatment	Relevance to treatment recognised, prognostic factors and predictive biomarkers added.
Hepatocellular neoplasms	Classification mainly histological	Refinement on the basis of molecular information.
Cholangiolocarcinoma	Subtype of combined hepatocellular-cholangiocarcinoma	Now a subtype of small duct intrahepatic cholangiocarcinoma (iCCA), with all primary intrahepatic carcinomas with a ductal/tubular phenotype under the overarching category of iCCA
Pancreatic tumours	Limited molecular data	Classification revised in light of new molecular understanding
Pancreatic precursor lesion	Described in three groups	Divided into low and high grade lesions
Haematolymphoid tumours	Inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma	Renamed: EBV-positive inflammatory follicular dendritic cell sarcoma
Lynch syndrome		Updated with new findings and importance of MSI for immunotherapy.
Serrated polyposis		Revised diagnostic criteria
Familial adenomatous polyposis and GAPPS	Both part of FAP as caused by mutations in *APC* gene	Described in separate sections based on phenotypic differences
Hereditary diffuse gastric cancer		Improved characterization of the clinicopathological and genetic features