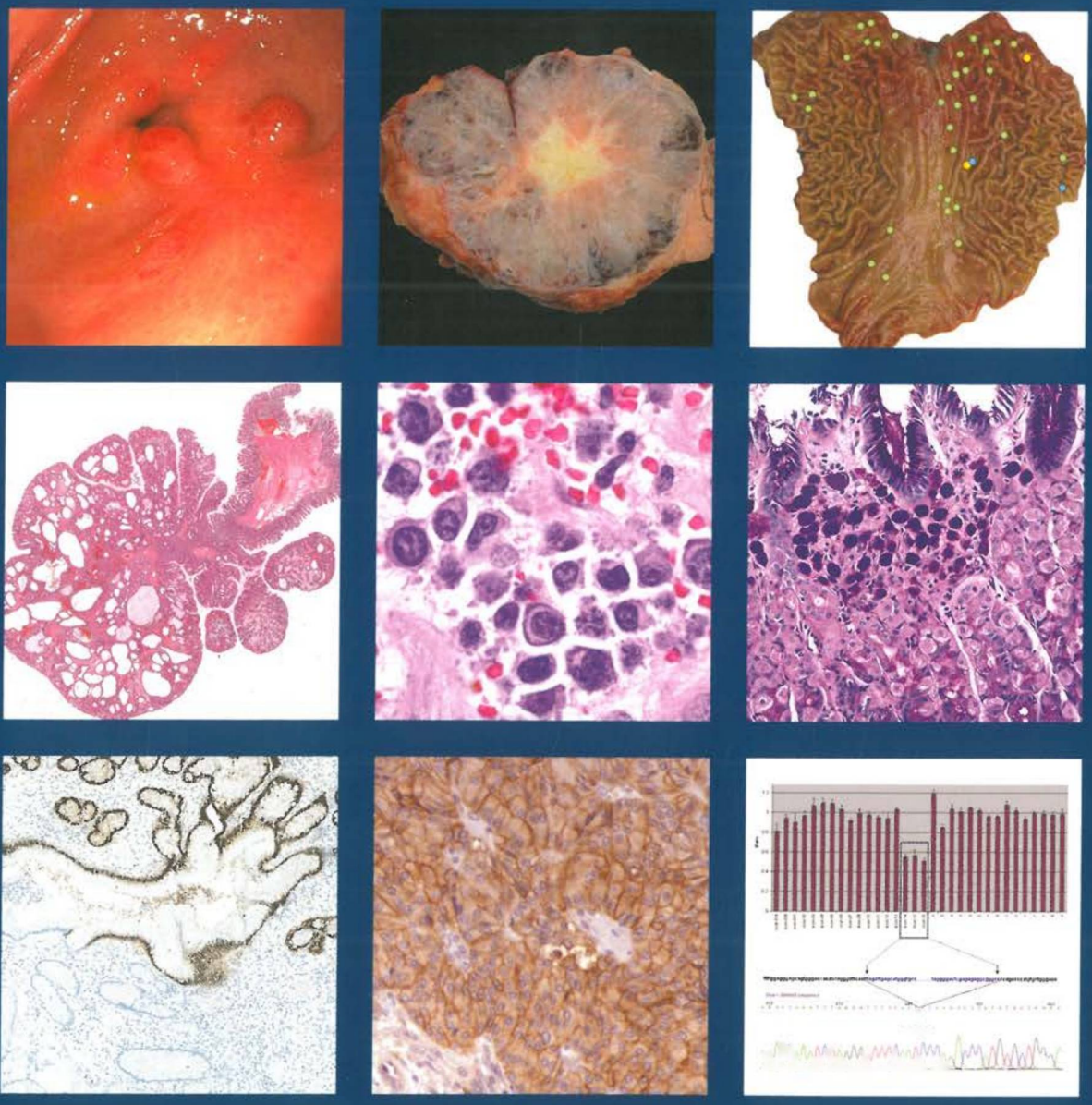
WHO Classification of Tumours • 5th Edition

Digestive System Tumours

Edited by the WHO Classification of Tumours Editorial Board



World Health Organization

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List of abbreviations

3D	three-dimensional
ABC	activated B cell
ACRG	Asian Cancer Research Group
ADP	adenosine diphosphate
AJCC	American Joint Committee on Cancer
ATP	adenosine triphosphate
CI	confidence interval
CIMP	CpG island methylator phenotype
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
dMMR	mismatch repair-deficient
DNA	deoxyribonucleic acid
EBER	EBV-encoded small RNA
EBV	Epstein-Barr virus
EC cell	enterochromaffin cell
ECL cell	enterochromaffin-like cell
EHBD	extrahepatic bile duct
EMVI	extramural vascular invasion
ER	estrogen receptor
EUS	endoscopic ultrasonography
FDC	follicular dendritic cell
FDG PET	18F-fluorodeoxyglucose positron emission tomography
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
GCB	germinal-centre B cell
GI tract	gastrointestinal tract
GPC3	glypican-3
GS	glutamine synthetase
H&E	haematoxylin and eosin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
ICD-11	International Classification of Diseases, 11th Revision
ICD-0	International Classification of Diseases for Oncology
IEL	intraepithelial lymphocyte
ig	immunoglobulin
IMVI	intramural vascular invasion
InSiGHT	International Society for Gastrointestinal Hereditary Tumours
IQ	intelligence quotient
JGCA	Japanese Gastric Cancer Association
kb	kilo base pair
M:F ratio	male-to-female ratio
MALT	mucosa-associated lymphoid tissue
MF pattern	mass-forming pattern
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MSS	microsatellite stability
N:C ratio	nuclear-to-cytoplasmic ratio
NK cell	natural killer cell
NSAID	non-steroidal anti-inflammatory drug
PAS	periodic acid—Schiff
PASD	periodic acid-Schiff with diastase
PCR	polymerase chain reaction
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PI pattern	periductal infiltrating pattern
PR	progesterone receptor
RNA	ribonucleic acid
SCNA	somatic copy-number alteration
SDH	succinate dehydrogenase
SEER Program	Surveillance, Epidemiology, and End Results Program
SNP	single nucleotide polymorphism
TACE	transarterial chemoembolization
TCGA	The Cancer Genome Atlas
TNM	tumour, node, metastasis
TRG	tumour regression grade
UICC	Union for International Cancer Control
UV	ultraviolet

Foreword

The WHO Classification of Tumours, published as a series of books (also known as the WHO Blue Books), is an essential tool for standardizing diagnostic practice worldwide. The WHO classification also serves as a vehicle for the translation of cancer research into practice. The diagnostic criteria and standards these books contain are underpinned by evidence evaluated and debated by experts in the field. About 200 authors and editors participate in the production of each book, and they give their time freely to this task. I am very grateful for their help: it is a remarkable team effort.

This first volume of the fifth edition of the WHO Blue Books incorporates several important changes to the series as a whole. For example, this is the first WHO Blue Book to be led by an editorial board. The WHO Classification of Tumours Editorial Board is composed of standing members nominated by pathology organizations and expert members selected on the basis of informed bibliometric analysis. The diagnostic process is increasingly multidisciplinary, and we are delighted that several radiology and clinical experts have already joined us to address specific needs. The editorial board also includes a patient representative.

The most conspicuous change to the format of the books in the fifth edition is that tumour types common to multiple systems are dealt with together - so there are separate chapters on haematolymphoid tumours and mesenchymal tumours. There is also a chapter on genetic tumour syndromes. Genetic disorders are of increasing importance to diagnosis in individual patients, and the study of these disorders has undoubtedly informed our understanding of tumour biology and behaviour over the past 10 years. The inclusion of a chapter dedicated to genetic tumour syndromes reflects this importance.

We have attempted to take a more systematic approach to the multifaceted nature of tumour classification; each tumour type is described on the basis of its localization, clinical features, epidemiology, etiology, pathogenesis, histopathology, diagnostic molecular pathology, staging, and prognosis and prediction. Where appropriate we have also included information on macroscopic appearance and cytology, as well as essential and desirable diagnostic criteria. This standardized, modular approach is in part to ready the books to be accessible online, but it also enables us to call attention to areas in which there is little information, and where serious gaps in our knowledge remain to be addressed.

The organization of the WHO Blue Books content now follows the normal progression from benign to malignant - a break with the fourth edition, but one we hope will be welcome.

The volumes are still organized on the basis of anatomical site (digestive system, breast, soft tissue and bone, etc.), and each tumour type is listed within a taxonomic classification that follows the format below, which helps to structure the books in a systematic manner:

- Site; e.g. stomach
- Category; e.g. epithelial tumours
- Family (class); e.g. adenomas and other premalignant neoplastic lesions
- Type; e.g. adenoma
- Subtype; e.g. foveolar-type adenoma

The issue of whether a given tumour type represents a distinct entity rather than a subtype continues to exercise pathologists, and it is the topic of many publications in the scientific literature. We continue to deal with this issue on a case-by-case basis, but we believe there are inherent rules that can be applied. For example, tumours in which multiple histological patterns contain shared truncal mutations are clearly of the same type, despite the differences in their appearance. Equally, genetic heterogeneity within the same tumour type may have implications for treatment. A small shift in terminology as of this new edition is that the term "variant" in reference to a specific kind of tumour has been wholly superseded by “subtype[1]’, in an effort to more clearly differentiate this meaning from that of “variant” in reference to a genetic alteration.

The WHO Blue Books are much appreciated by pathologists and of increasing importance to cancer researchers. The new editorial board and I certainly hope that the series will continue to meet the need for standards in diagnosis and to facilitate the translation of diagnostic research into practice worldwide. It is particularly important that cancers continue to be classified and diagnosed according to the same standards internationally so that patients can benefit from multicentre clinical trials, as well as from the results of local trials conducted on different continents.

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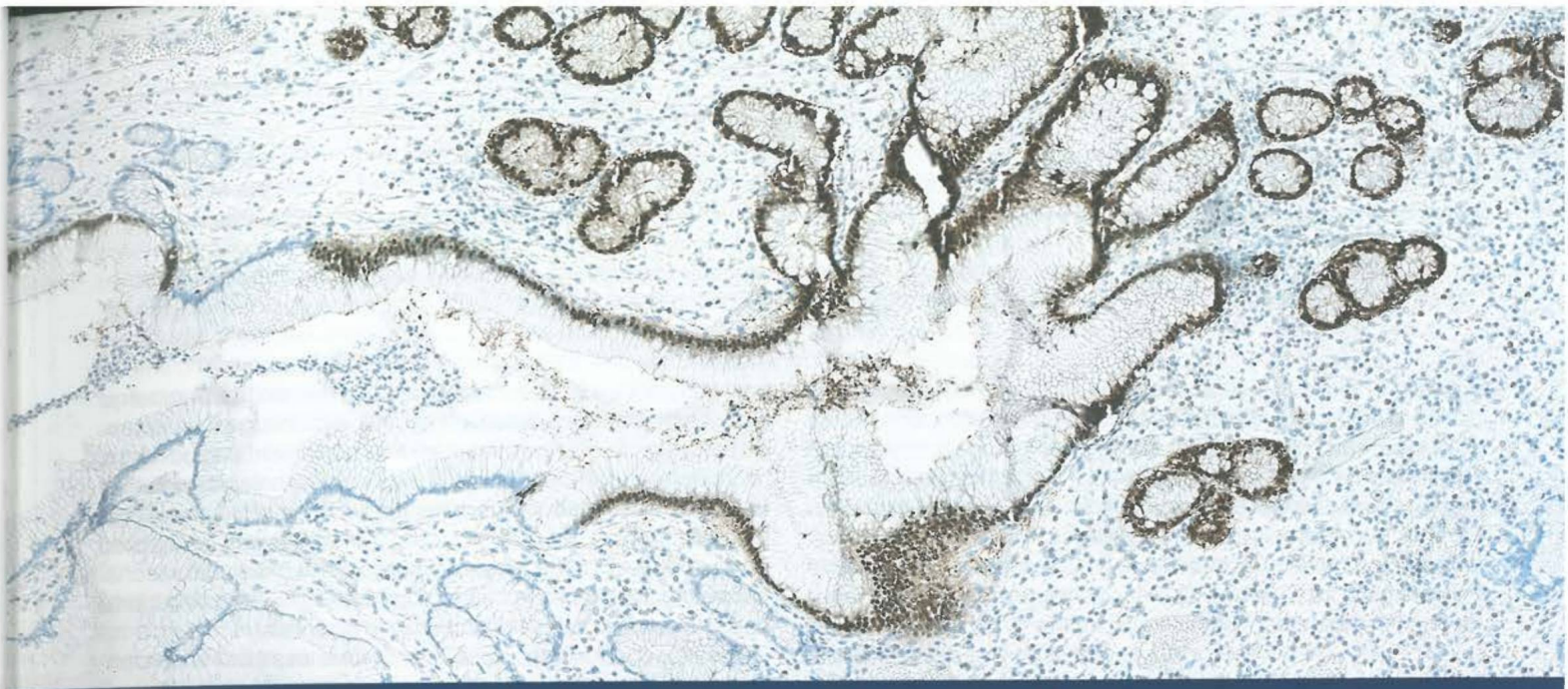

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Introduction to tumours of the digestive system

Edited by: Washington MK

General introduction
Classification of neuroendocrine neoplasms of the digestive system

Introduction to tumours of the digestive system

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The WHO classification of digestive system tumours presented in this volume of the WHO Classification of Tumours series' fifth edition reflects important advancements in our understanding of tumours of the digestive system. For the first time, certain tumour types are defined as much by their molecular phenotype as their histological characteristics; however, histopathological classification remains the gold standard for diagnosis in most instances. The WHO Classification of Tumours series is designed to be used worldwide, including those settings where a lack of tissue samples or of specific technical facilities limits the pathologist's ability to rely on molecular testing.

Since the publication of the fourth-edition digestive system tumours volume in 2010 {379}, there have been important developments in our understanding of the etiology and pathogenesis of many tumours. However, the extent to which this new information has altered clinical practice has been quite variable. For some of the tumours described in this volume, there is little molecular pathology in clinical use, despite the fact that we now have a more detailed understanding of their molecular pathogenesis. A tumour's molecular pathology, as defined for the purposes of this publication, concerns the molecular markers that are relevant to the tumour's diagnosis, biological behaviour, outcome, and treatment, rather than its molecular pathogenesis. The role of molecular pathology is expanding. For some tumour entities, molecular analysis is now essential for establishing an accurate diagnosis. Some of these analyses require investigation of somatic (acquired) genetic alterations, gene or protein expression, or even circulating tumour markers. For certain tumour types, specific analytical tests are needed to predict prognosis or tumour progression, and these tests are carefully outlined in this volume. In the following paragraphs, we have summarized some of the more notable changes since the fourth edition. More detailed descriptions can be found in the introductions to the chapters on each main tumour category and/or in the tumour-specific sections themselves. In instances where the editorial board determined that there was insufficient evidence of the diagnostic or clinical relevance of new information about a particular tumour entity, the position held in the fourth edition has been maintained as the standard in the current volume.

There has been substantial progress in our understanding of the development of oesophageal neoplasia and the sequential neoplastic progression from inflammation to metaplasia (Barrett oesophagus), dysplasia, and ultimately adenocarcinoma. This process is initially driven by gastro-oesophageal reflux disease, which leads to reprogramming of cell differentiation and proliferation in the oesophagus.

The molecular pathway of cancer progression in the stomach is less clear Most so-called epidemic gastric cancers are now considered to be inflammation-driven, and their etiology is characteristically environmental - usually related to *Helicobacter pylori* infection. It is because of this infectious etiology that gastric cancer is included among the limited number of highly lethal but preventable cancers. Chronic gastric inflammation leads to changes in the microenvironment (including the microbiome) that result in mucosal atrophy/metaplasia, which may progress to neoplasia after further molecular alterations. Metaplastic changes in the upper GI tract are well recognized as early cancer precursors, but their precise molecular mechanisms and the exact role of the progenitor cells in the oncogenic cascade are still subjects of intense investigation.

The pathogenesis of precursor lesions is less clear in oesophageal squamous carcinogenesis than in gastric carcinogenesis. Environmental factors are believed to play an important role, but the mechanisms of neoplastic change as a result of specific factors, such as tobacco use and alcohol consumption, are poorly understood. For example, HPV infection was initially believed to play a key role in squamous carcinogenesis, but recent evidence suggests that there is no such association in most cases of oesophageal squamous cell carcinoma. This finding contrasts with our current knowledge of the etiology and pathogenesis of anal squamous lesions, in which HPV infection does appear to play an important etiological role, driving genetic alterations similar to those seen in cervical cancer.

The pathogenesis of adenocarcinomas of the intestines (the small and large bowel and the appendix) is now much better delineated than it was a decade ago. The introduction of population-based screening for colorectal cancer has laid the foundation for a better understanding of neoplastic precursor lesions and the molecular pathways associated with each type of tumour. For example, our knowledge of the molecular pathways and biological behaviour of conventional adenomas and serrated precursor lesions, including the recently renamed sessile serrated lesion (formerly called sessile serrated polyp/adenoma), has grown rapidly in the past decade, and this has enabled clinicians to provide tailored, evidence-driven screening and surveillance programmes. Our understanding of appendiceal tumours has also improved. For example, we now know that many tumours of the appendix develop via neoplastic precursor lesions similar to those in the small and large intestines, and the biological potential and molecular pathways of appendiceal tumours are therefore much better appreciated. The recently renamed goblet cell adenocarcinoma (formerly called goblet cell carcinoid/carcinoma) of the appendix is a prime example of a tumour whose biological potential and histological characteristics have been better described, resulting in improvements in the pathological approach to these tumours.

For some rare tumours, distinctive driver mutations have been identified, for example, the characteristic *MALAT1-GLI1* fusion gene in gastroblastoma and *EWSR1* fusions in gastrointestinal clear cell sarcoma and malignant gastrointestinal neuroectodermal tumour. In both examples, demonstration of the fusion gene is now required for the diagnosis.

One particularly important change in the fifth edition is in the classification of neuroendocrine neoplasms (NENs), which occur in multiple sites throughout the body. In this volume, NENs are covered within each organ-specific chapter, including the chapter on tumours of the pancreas, where detailed sections describing each functioning and non-functioning subtype are provided. Previously, these neoplasms were covered in detail only in the volume on tumours of endocrine organs (1936). The general principles guiding the classification of all NENs are presented in a separate introduction to this topic *(Classification of neuroendocrine neoplasms of the digestive system,* p. 16). To consolidate our increased understanding of the genetics of these neoplasms, a group of experts met for a consensus conference at the International Agency for Research on Cancer (IARC) in November 2017 and subsequently published a paper in which they proposed distinguishing between well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) in all sites where these neoplasms arise {2717). Genomic data have also led to a change in the classification of mixed NENs, which are now grouped into the conceptual category of "mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs)''. Mixed adenoneuroendocrine carcinomas (MANECs), which show genetic alterations similar to those of adenocarcinomas or NECs, rather than NETs, probably reflect clonal evolution within the tumours, which is a rapidly growing area of interest. The study of these mixed carcinomas may also lead to an improved understanding of other facets of clonality in tumours of the digestive system and other parts of the body.

Unfortunately, mixed tumours in other anatomical sites (e.g. oesophageal adenosquamous carcinoma and mucoepidermoid carcinoma, as well as hepatic carcinomas with mixed hepatocellular and cholangiolar differentiation) also remain subjects of uncertainty. The relative importance of the various lineages of differentiation within these neoplasms remains unknown. It is also uncertain how these neoplasms develop and how they should be treated clinically. These issues are a matter of debate because hard evidence is lacking, but improvements in the pathological criteria and classification of these neoplasms should help to standardize the diagnostic approach and facilitate better clinical and genomic research.

There are certain terms in current day-to-day use about which many pathologists continue to disagree. The editorial board carefully considered our current understanding of carcinogenesis pathways when considering the use of specific terms and definitions. In general, the overall consensus was that established terms, definitions, and criteria should not be changed unless there was strong evidence to support doing so and the proposed changes had clinical relevance. For some tumours, our understanding of the progression from normal epithelium to metastatic carcinoma remains inadequate. For example, in certain tumours the line between benign and malignant can be ambiguous, and in some cases the distinction is more definitional than biological. These are some of the many areas of tumour biology that need to be more fully investigated in the future.

In the fifth edition, the terminology for precursors to invasive carcinoma in the GI tract has been standardized somewhat, although the terms “dysplasia" and "intraepithelial neoplasia" are both still considered acceptable for lesions in certain anatomical locations, in acknowledgement of their ongoing clinical acceptance. For example, the term "dysplasia" is preferred for lesions in the tubular gut, whereas "intraepithelial neoplasia" is preferred for those in the pancreas, gallbladder, and biliary tree. For all anatomical sites, however, a two-tiered system (low-grade vs high-grade) is considered the standard grading system for neoplastic precursor lesions. This has replaced the three-tiered grading scheme previously used for lesions in the pancreatobiliary system (267). The term "carcinoma in situ" continues to be strongly discouraged in clinical practice for a variety of reasons, most notably its clinical ambiguity. This term is encompassed by the category of high-grade dysplasia / intraepithelial neoplasia. Genomic findings have helped to determine that some tumours, such as pancreatic intraductal neoplasms (i.e. intraductal oncocytic papillary neoplasm and intraductal tubulopapillary neoplasm) are distinct from pancreatic intraductal papillary mucinous neoplasms, and these tumours are now classified as separate entities. Additional clinical and genomic information has also helped in the identification of carcinoma subtypes that are distinct enough to warrant separate classification.

Many refinements of the fourth-edition classification have been made concerning liver tumours, supported by novel molecular findings. For example, a comprehensive picture of the molecular changes that occur in common hepatocellular carcinoma has recently emerged from large-scale molecular profiling studies. Meanwhile, several rarer hepatocellular carcinoma subtypes, which together may account for 20-30% of cases, have been defined by consistent morphomolecular and clinical features, with fibrolamellar carcinoma and its diagnostic *DNAJB1-PRKACA* translocation being one prime example. Intrahepatic cholangiocarcinoma is now understood to be a distinct entity with two very specific subtypes: 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 will need to incorporate these findings in the near future. Also supported by molecular findings, the definition of combined hepatocellular-cholangiocarcinoma and its distinction from other entities have recently become clearer. Cholangiolocellular carcinoma is no longer considered a subtype of combined hepatocellular-cholangiocarcinoma, but rather a subtype of small duct intrahepatic cholangiocarcinoma, meaning that all intrahepatic carcinomas with a ductal or tubular phenotype are now included within the category of intrahepatic cholangiocarcinoma. A classic example of morphology-based molecular profiling leading to a new classification based on a combination of biological and molecular factors is the classification of hepatocellular adenomas, which has gained a high degree of clinical relevance and has fuelled the implementation of refined morphological criteria and molecular testing in routine diagnostics.

In this fifth-edition volume, haematolymphoid tumours and mesenchymal tumours that occur in the GI tract, some of which are very distinctive, have been grouped together in their own separate chapters, to ensure consistency and avoid duplication. The importance of genetic tumour syndromes has also been highlighted in this edition by their inclusion in a dedicated chapter, consolidating the increased knowledge of these disorders in a way that we hope will be helpful to all readers.

Classification of neuroendocrine neoplasms of the digestive system

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General characteristics of NENs

Neuroendocrine neoplasms (NENs) can arise in most epithelial organs of the body and include many varieties, with widely differing etiologies, clinical features, morphological and genomic findings, and outcomes. Historically, NENs of the various anatomical sites have been classified separately, and although the various classification systems have shared some common features (1630), differences in terminology and classification criteria between organ systems have caused considerable confusion. In 2018, WHO published a uniform classification framework for all NENs (2717), based on a consensus conference held in November 2017. The key feature of this new, common classification is the distinction between well-differentiated neuroendocrine tumours (NETs), which were 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. The morphological classification of NENs into NETs and NECs is supported by genetic evidence, 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 rate and the Ki-67 proliferation index (3431). Mitotic rates are to be expressed as the number of mitoses/2 mm^2 (equalling 10 high-power fields at 40x magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2 mm^2 (i.e. in a total area of 10 mm^2), although it is recognized that an accurate rate may not be possible to determine when only a small sample is available. The Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hotspots), which are identified at scanning magnification. 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 (2096). NECs are considered high-grade by definition. The current classification and grading system is largely based on the 2017 WHO classification of neoplasms of the neuroendocrine pancreas (1936), which formally introduced the concept that well-differentiated neoplasms could be high-grade (272). In earlier classifications of both pancreatic and gastrointestinal NENs, the G3 category was considered to be synonymous with poor differentiation (i.e. NEC). However, after the publication of data related to pancreatic NETs (PanNETs), it became clear that NETs of other organs can also have a proliferative rate in the G3 range (3256), justifying the extension of the pancreatic classification system in the current edition of the WHO classification to NENs occurring throughout the GI tract.

The rationale for a sharp separation of NETs and NECs into different families comes from a variety of sources. Although they share neuroendocrine differentiation based on immunolabelling for chromogranin A and synaptophysin, most NETs are morphologically distinct from NECs, which are subtyped as small cell NEC (SCNEC) and large cell NEC (LCNEC). NETs have an organoid architecture (e.g. nests, cords, and ribbons), uniform nuclear features, coarsely stippled chromatin, and minimal necrosis. NECs have a less nested architectural pattern, often growing in sheets, and they have either tightly packed fusiform nuclei with finely granular chromatin (SCNEC) or more-rounded, markedly atypical nuclei, sometimes with prominent nucleoli (LCNEC); necrosis is usually abundant. NETs may show grade progression, either within an individual tumour at presentation or between different sites of disease (e.g. primary vs metastasis) during the course of tumour progression. The presence of

Table 1.01 Classification and grading criteria for neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs

Terminology	Differentiation	Grade	Mitotic rate" (mitoses/2 mm^2)	Ki-67 index'
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2-20	3-20%
NET, G3		High	>20	>20%
NEC, small cell type (SCNEC)	Poorly differentiated	High"	>20	>20%
NEC, large cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated®	Variable®	Variable®	Variable®

LCNEC, large cell neuroendocrine carcinoma; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; SCNEC, small cell neuroendocrine carcinoma.

•Mitotic rates are to be expressed as the number of mitoses/2 mm^2 (equalling 10 high-power fields at 40* magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2 mm^2 (i.e. in a total area of 10 mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hotspots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher grade category. [b]Poorly differentiated NECs are not formally graded but are considered high-grade by definition. [c]In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated: when feasible, each component should therefore be graded separately.

both low-grade and high-grade components within an individual NET provides strong evidence that the high-grade component remains a well-differentiated neoplasm. In contrast, NECs do not commonly arise in association with NETs, but instead arise from precursor lesions that typically give rise to non-neuroendocrine carcinomas of the respective organs, such as adenomas in the colorectum or squamous dysplasia in the oesophagus. NECs may also contain non-neuroendocrine carcinoma elements such as adenocarcinoma or squamous cell carcinoma. Mixed neoplasms in which both components (neuroendocrine and non-neuroendocrine) are substantial (each accounting for ≥ 30% of the neoplasm), are classified into the general category of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), and they only exceptionally contain a well-differentiated (NET) component in addition to the non-neuroendocrine neoplasm. Emerging genomic data have provided further evidence that NETs and NECs are unrelated. In the pancreas in particular, frequent mutations in *MEN1, DAXX,* and *ATRX* are entity-defining for well-differentiated NETs (1463) and are not found in poorly differentiated NECs, which instead have mutations in *TP53, RB1,* and other carcinoma-associated genes (3632,1681,1682). Sporadic PanNETs are also associated with germline mutations in the DNA repair genes *MUTYH, CHEK2,* and *BRCA2*(3500). Even the 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 (3055,3253). Genomic comparisons of NETs and NECs of other gastrointestinal sites are still emerging. NECs of these sites share frequent *TP53and RB1* mutations with NECs of the pancreas (and lung) (3577,1450), but extrapancreatic NETs generally lack frequent recurrent mutations (233,961), 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 (3153). 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 (3104). Alternative approved therapies are available for some subsets of NETs (1716); therefore, there is a clinical need to distinguish NETs from NECs within the high-grade category.

One difference between the current WHO classification and the fourth-edition classification of tumours of the pancreas concerns the assignment of a grade for NECs. Previously, all NECs were graded G3, like high-grade NETs. The current proposal is not to assign a grade to NECs (they are all high-grade by definition), in order to avoid confusion about neoplasms within the G3 category.

The recently published proposal for a uniform classification of NENs (2717) is now formally adopted in this WHO classification of tumours arising throughout the entire GI tract and in the hepatopancreatobiliary organs. The terminology and grading criteria are presented in Table 1.01). The specific features of NETs, NECs, and MiNENs of individual organs are described in each organ's respective chapter. It is important to remember that despite the use of uniform terminology, there are important organ-specific differences among NENs in terms of hormonal function, clinical presentation, prognosis, morphology, and genomics; the current classification system is intended to standardize the approach to diagnosis and grading, but not to replace the key additional information to be included in pathological diagnoses reflecting the unique features of each NEN.

Well-differentiated NENs: NETs

Neuroendocrine tumours (NETs) are well-differentiated epithelial neoplasms with morphological and immunohistochemical features of neuroendocrine differentiation, most typically showing organoid architecture, uniform nuclei, and coarsely granular chromatin. NETs can be low-grade (G1), intermediate-grade (G2), or high-grade (G3).

NETs are a broad family of related neoplasms that can arise in any organ in the GI tract and hepatopancreatobiliary system. Former terms include "carcinoid tumour" and (for pancreatic tumours) "islet cell tumour" and "pancreatic endocrine neoplasm". The well-differentiated nature of NETs means that the neoplastic cells bear a strong resemblance to non-neoplastic neuroendocrine cells, usually including strong immunoexpression of general neuroendocrine markers (chromogranin A and synaptophysin) along with variable expression of specific peptide hormones. The morphological features of NETs are highly varied, and some organ-specific subtypes have characteristic histological patterns (see the individual sections in each organ's respective chapter). However, NETs generally display characteristic architectural patterns including nests, cords, and ribbons. Gland formation by the neoplastic cells is common, especially in the ileum and pancreas, as well as in a subset of appendiceal and duodenal NETs. The nuclei often contain coarsely clumped chromatin, giving rise to the classic salt-and-pepper appearance, but some NETs show more diffusely granular chromatin and others have prominent nucleoli. The cytoplasm may show intense granularity, reflecting abundant neurosecretory granules that are oriented towards the vascular pole of the cells. Most NETs have a low proliferative rate, defined in the fourth-edition digestive system tumours volume by a mitotic rate of < 20 mitoses/2 mm^2 and a Ki-67 proliferation index of < 20% (379). Although the mitotic rate is indeed found to be within this range in almost all cases, it is now clear that some NETs, in particular those arising in the pancreas, have a Ki-67 proliferation index of > 20%, and values as high as 70-80% have been observed in some cases. Therefore, the Ki-67 proliferation index alone cannot be used to conclusively distinguish NETs from neuroendocrine carcinomas (NECs).

An important clinical distinction among NETs relates to their hormonal functionality. Functioning NETs are defined as those associated with characteristic clinical syndromes related to the abnormal production of hormones by the neoplasm. Clinically non-functioning NETs may also produce hormones, which can be detected in the serum or in the tumour cells using immunohistochemistry, but the hormones do not result in clinical symptoms. The nomenclature for functioning NETs often includes the name of the specific hormone causing the syndrome (insulinoma, gastrinoma, glucagonoma, etc.). The pancreas gives rise to the greatest variety of functioning NETs (see *Functioning pancreatic neuroendocrine tumours,* p. 353). Functioning gastrin-producing NETs (gastrinomas) typically occur in the duodenum, and NETs that cause carcinoid syndrome usually arise

¡n the ileum. Most gastric NETs are non-functioning, although the conditions associated with hypergastrinaemia (including gastrinomas themselves) can induce NETs composed of enterochromaffin-like (ECL) cells in the oxyntic mucosa of the stomach. NETs of the bile ducts, liver, and colorectum are also usually non-functioning. Another characteristic feature of NETs is the expression of somatostatin receptors (in particular, abundant SSTR2), which can be detected by immunohistochemistry or using functional radiographical imaging, such as octreoscan and 68Ga-DOTATOC/DOTATATE/DOTANOC PET-CT. NETs are usually not detectable by FDG PET, with the exception of rare high-grade examples. Another distinctive clinical feature of NETs is their indolent natural history. Although all NETs are 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.

The uniformity of the classification and grading system for gastroenteropancreatic NETs presented in this volume should not be interpreted as suggestive that NETs are a homogeneous group of closely related neoplasms; this is far from the case. Each organ gives rise to different types of NETs, with different functionality, different histological features, and different genomic underpinnings. Certain types of NETs (e.g. pancreatic and duodenal) occur commonly in patients with multiple endocrine neoplasia type 1 and are associated with frequent somatic mutations in *MEN1,* whereas other NETs (e.g. ileal and rectal) are not associated with this syndrome or with mutations in *MEN1.* There are also prognostic differences among NETs of different sites. 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 (e.g. immunohistochemistry for site-specific transcription factors (3674)).

Poorly differentiated NENs: NECs

Neuroendocrine carcinomas (NECs) are poorly differentiated epithelial neoplasms with morphological and immunohistochemical features of neuroendocrine differentiation. NECs can be small cell NEC (SCNEC), which displays fusiform nuclei with finely granular chromatin, scant cytoplasm, and nuclear moulding, or large cell NEC (LCNEC), which has round nuclei, sometimes with prominent nucleoli, and moderate amounts of cytoplasm. All NECs are high-grade neoplasms.

Like neuroendocrine tumours (NETs), NECs can arise in most sites within the gastroenteropancreatic system and may be pure or mixed with variable amounts of adenocarcinoma, squamous cell carcinoma, or other components. Previously, the term "neuroendocrine carcinoma" was also used for well-differentiated NETs with evidence of malignant behaviour (i.e. metastasis), but in the current classification the term "carcinoma" is reserved for poorly differentiated neoplasms. NECs are generally subclassified as SCNEC or LCNEC; however, this distinction can be challenging at some sites within the GI tract {2995}. NECs are considered to be high-grade by definition, with a mitotic rate of > 20 mitoses/2 mm^2 and a Ki-67 proliferation index of > 20%. In most instances, these thresholds are substantially exceeded; however, 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 (3253). Necrosis is commonly extensive. Demonstration of neuroendocrine differentiation is necessary to confirm the diagnosis of NEC. For the diagnosis of LCNEC, expression of either synaptophysin or chromogranin A must be present. The exact extent and intensity of staining required for the diagnosis have not yet been explicitly defined, but more than scattered positive cells should be present, and the morphology should also be suggestive of neuroendocrine differentiation.

NECs are somewhat more homogeneous among different sites of origin than are NETs. The morphological patterns overlap, as do the genomic alterations, which include common mutations in *TP53* and *RB1.* Additional organ-specific mutations that typify non-neuroendocrine carcinomas of the same site may also be found (3632,3587). NECs lack mutations in the genes most commonly involved in the pathogenesis of NETs.

NECs are highly aggressive neoplasms, usually even more so than the more common types of carcinoma to arise at the same site. Advanced stage at presentation is common; therefore, chemotherapy is often the primary therapeutic approach, and it may be the initial treatment choice even for surgically resectable cases (3153). Considerable evidence supports the treatment of extrapulmonary SCNEC with a platinum-containing regimen; anecdotal evidence of responses to similar regimens in LCNECs has promoted the widespread practice of treating all NECs with platinum-containing regimens, but there are no randomized clinical trials showing superior efficacy compared with the alternative regimens used for non-neuroendocrine carcinomas. Defining the molecular basis for responsiveness to platinum remains an area of active investigation.

Mixed neoplasms: MiNENs

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.

Most epithelial neoplasms in the GI tract and hepatopancreatobiliary system are classified as either pure glandular or squamous neoplasms (or their precursors) or pure neuroendocrine neoplasms (NENs). Glandular (and to a lesser extent squamous) neoplasms may have a minor population of interspersed neuroendocrine cells that can be identified by immunohistochemistry, but this finding does not affect the classification. Less commonly, epithelial neoplasms are composed of quantitatively considerable neuroendocrine and non-neuroendocrine cell populations. Previously, when each component represented ≥ 30% of the neoplasm, 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,

Box 1.01 Specific subtypes of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) of the GI tract and hepatopancreatobiliary organs

Oesophagus and oesophagogastric junction
. Mixed SCC-NEC (SCNEC or LCNEC)
• Mixed adenocarcinoma-NEC (SCNEC or LCNEC)
• Mixed adenocarcinoma-NET (1249)

Stomach
• Mixed adenocarcinoma-NEC (SCNEC or LCNEC)
• Mixed adenocarcinoma-NET (1758.1754)

Small intestine and ampulla
• Mixed adenocarcinoma-NEC (SCNEC or LCNEC)

Appendix
• Mixed adenocarcinoma-NEC (SCNEC or LCNEC)
• Mixed adenocarcinoma-NET

Colon and rectum
• Mixed adenocarcinoma-NEC (SCNEC or LCNEC)
• Mixed adenocarcinoma-NET

Anal canal
• Mixed SCC-NEC (SCNEC or LCNEC)

Liver
• Mixed hepatocellular carcinoma-NEC
• Mixed cholangiocarcinoma-NEC

Gallbladder and bile ducts
• Mixed adenocarcinoma-NEC (SCNEC or LCNEC)

Pancreas
• Mixed ductal carcinoma-NEC (SCNEC or LCNEC)
• Mixed ductal adenocarcinoma-NET
• Mixed acinar cell carcinoma-NEC (distinct components)
• Mixed acinar cell carcinoma-ductal carcinoma-NEC (distinct components)

LCNEC, large cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; SCC, squamous cell carcinoma; SCNEC, small cell neuroendocrine carcinoma.

and each should be diagnosed using site-specific terminology that reflects the nature of the components. Box 1.01 lists the specific neoplasms that are included in the MiNEN category, by anatomical site.

For a neoplasm to qualify as MiNEN, both components should be morphologically and immunohistochemically recognizable. The presence of neuroendocrine differentiation in the neuroendocrine component should be confirmed by immunolabelling for synaptophysin and/or chromogranin. In MiNENs arising in the GI tract and hepatopancreatobiliary system, both components are usually carcinomas; therefore, the neuroendocrine component is usually poorly differentiated neuroendocrine carcinoma (NEC) and can be either large cell NEC (LCNEC) or small cell NEC (SCNEC). Rarely, the neuroendocrine component of a MiNEN may be well differentiated. NENs can arise in association with carcinoma precursors such as adenomas of the tubular GI tract or intraductal or cystic neoplasms of the pancreas. However, neoplasms in which the non-neuroendocrine component consists solely of a precursor (preinvasive) neoplasm are not considered MiNENs. Similarly, independent neuroendocrine and non-neuroendocrine neoplasms arising in the same organ should not be classified as MiNEN, even if they abut one another (true collision tumours), because the MiNEN category applies only to neoplasms in which the two components are presumed to be clonally related. 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 (2996,2993).

By arbitrary convention, each component should constitute ≥ 30% of a neoplasm for the neoplasm to be included in the MiNEN category; the presence of focal (< 30%) neuroendocrine differentiation may be mentioned in the diagnosis (in particular when the component is poorly differentiated) but does not affect the diagnostic categorization. However, an important consideration is the finding of focal (< 30%) SCNEC associated with a non-neuroendocrine neoplasm. Because of the clear clinical significance of SCNEC, even minor components should be mentioned in the diagnosis. When feasible, the two components of MiNENs should be graded individually; some data suggest that the grade of the neuroendocrine component correlates with prognosis (2163). The non-neuroendocrine component should be classified as adenocarcinoma, acinar cell carcinoma (in the pancreas), squamous cell carcinoma, or any other definable tumour category as appropriate. In general, MiNENs composed of an adenocarcinoma with a NEC component, for which the designation MANEC can be retained, show poor prognosis (overlapping with that of pure NEC), independent of the non-neuroendocrine component (2163). MiNENs composed of adenocarcinoma and neuroendocrine tumour (NET) have been reported, but their prognostic significance requires further study (1758,1754). The intensity and degree of the immunolabelling of the neuroendocrine component for synaptophysin and chromogranin A should be documented.

TNM staging of well-differentiated neuroendocrine tumours of the gastrointestinal tract

Well-Differentiated Neuroendocrine Tumours of the Gastrointestinal Tract

Rules for Classification

This classification system applies to well-differentiated neuroendocrine tumours (carcinoid tumours and atypical carcinoid tumours) of the gastrointestinal tract, including the pancreas. Neuroendocrine tumours of the lung should be classified according to criteria for carcinoma of the lung. Merkel cell carcinoma of the skin has a separate classification.

High-grade (Grade 3) neuroendocrine carcinomas are excluded and should be classified according to criteria for classifying carcinomas at the respective site.

Well-Differentiated Neuroendocrine Tumours (G1 and G2) - Gastric, Jejunum/Ileum, Appendix, Colonic, and Rectal

Regional lymph nodes

The regional lymph nodes correspond to those listed under the appropriate sites for carcinoma.

TNM Clinical Classification

Stomach

T - Primary Tumour
TX Primary tumour cannot be assessed
TO No evidence of primary tumour
T1 Tumour invades mucosa or submucosa and 1 cm or less in greatest dimension
T2 Tumour invades muscularis propria or is more than 1 cm in greatest dimension
T3 Tumour invades subserosa
T4 Tumour perforates visceral peritoneum (serosa) or invades other organs or adjacent structures

Note
For any T, add (m) for multiple tumours.

N - Regional Lymph Nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Distant Metastasis
MO No distant metastasis
M1 Distant metastasis
M1a Hepatic metastasis only
M1 b Extrahepatic metastasis only
M1c Hepatic and extrahepatic metastases

Stage

Stage I	T1	NO	MO
Stage II	T2.T3	NO	MO
Stage III	T4	NO	MO
	Any T	N1	MO
Stage IV	Any T	Any N	M1

TNM Clinical Classification

Duodenal/Ampullary Tumours

T - Primary Tumour
TX Primary tumour cannot be assessed
TO No evidence of primary tumour
T1 *Duodenal:* Tumour invades mucosa or submucosa and 1 cm or less in greatest dimension
Ampullary: Tumour 1 cm or less in greatest dimension and confined within the sphincter of Oddi
T2 *Duodenal:* Tumour invades muscularis propria or is more than 1 cm in greatest dimension
Ampullary: Tumour invades through sphincter into duodenal submucosa or muscularis propria, or more than 1 cm in greatest dimension
T3 Tumour invades the pancreas or peripancreatic adipose tissue
T4 Tumour perforates visceral peritoneum (serosa) or invades other organs

Note
For any T, add (m) for multiple tumours.

N - Regional Lymph Nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Distant Metastasis
MO No distant metastasis
M1 Distant metastasis
M1a Hepatic metastasis only
M1b Extrahepatic metastasis only
M1c Hepatic and extrahepatic metastases

Stage

Stage I	T1	NO	MO
Stage II	T2.T3	NO	MO
Stage III	T4	NO	MO
	Any T	N1	MO
Stage IV	Any T	Any N	M1

TNM Clinical Classification

Jejunum/Ileum

T - Primary Tumour
TX Primary tumour cannot be assessed
TO No evidence of primary tumour
T1 Tumour invades mucosa or submucosa and 1 cm or less in greatest dimension
T2 Tumour invades muscularis propria or is greater than 1 cm in greatest dimension
T3 Tumour invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal)
T4 Tumour perforates visceral peritoneum (serosa) or invades other organs or adjacent structures

Note
For any T, add (m) for multiple tumours.

N - Regional Lymph Nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Less than 12 regional lymph node metastasis without mesenteric mass(es) greater than 2 cm in size
N2 12 or more regional nodes and/or mesenteric mass(es) greater than 2 cm in maximum dimension

M - Distant Metastasis
MO No distant metastasis
M1 Distant metastasis
M1 a Hepatic metastasis only
M1b Extrahepatic metastasis only
M1c Hepatic and extrahepatic metastases

Stage

Stage I	T1	NO	MO
Stage II	T2.T3	NO	MO
Stage III	T4	Any N	MO
	Any T	N1.N2	MO
Stage IV	Any T	Any N	M1

TNM Clinical Classification

Appendix

T - Primary Tumour®
TX Primary tumour cannot be assessed
TO No evidence of primary tumour
T1 Tumour 2 cm or less in greatest dimension
T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumour more than 4 cm or with subserosal invasion or involvement of the mesoappendix
T4 Tumour perforates peritoneum or invades other adjacent organs or structures, other than direct mural extension to adjacent subserosa, e.g., abdominal wall and skeletal muscle[0]

Notes
[a] High-grade neuroendocrine carcinomas, mixed adenoneuroendocrine carcinomas and goblet cell carcinoid, are excluded and should be classified according to criteria for classifying carcinomas.
[0] Tumour that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumour is present in the adhesion, microscopically, the tumour should be classified as pT1-3 as appropriate.

N - Regional Lymph Nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Distant Metastasis
MO No distant metastasis
M1 Distant metastasis
M1a Hepatic metastasis only
M1 b Extrahepatic metastasis only
M1c Hepatic and extrahepatic metastases

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pNO Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pNO.

pM - Distant Metastasis*
pM1 Distant metastasis microscopically confirmed

Note
* pMO and pMX are not valid categories.

Stage

Stage I	T1	NO	MO
Stage II	T2.T3	NO	MO
Stage III	T4	NO	MO
	Any T	N1	MO
Stage IV	Any T	Any N	M1

TNM Clinical Classification

Colon and Rectum

T - Primary Tumour
TX Primary tumour cannot be assessed
TO No evidence of primary tumour
T1 Tumour invades lamina propria or submucosa or is no greater than 2 cm in size
T1a Tumour less than 1 cm in size
T1b Tumour 1 or 2 cm in size
T2 Tumour invades muscularis propria or is greater than 2 cm in size
T3 Tumour invades subserosa, or non-peritonealized pericolic or perirectal tissues
T4 Tumour perforates the visceral peritoneum or invades other organs

Note
For any T, add (m) for multiple tumours.

N - Regional Lymph Nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Distant Metastasis
MO No distant metastasis
M1 Distant metastasis
M1a Hepatic metastasis only
M1b Extrahepatic metastasis only
M1c Hepatic and extrahepatic metastases

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pM - Distant Metastasis*
pM1 Distant metastasis microscopically confirmed

Note
* pMO and pMX are not valid categories.

Stage

Stage I	T1	NO	MO
Stage IIA	T2	NO	MO
Stage IIB	T3	NO	MO
Stage 11IA	T4	NO	MO
Stage 11 IB	Any T	N1	MO
Stage IV	Any T	Any N	M1

Well-Differentiated Neuroendocrine Tumours - Pancreas (G1 and G2)

Rules for Classification
This classification system applies to well-differentiated neuroendocrine tumours (carcinoid tumours and atypical carcinoid tumours) of the pancreas.
High-grade neuroendocrine carcinomas are excluded and should be classified according to criteria for classifying carcinomas of the pancreas.

Regional Lymph Nodes
The regional lymph nodes correspond to those listed under the appropriate sites for carcinoma.

TNM Clinical Classification

Pancreas

T - Primary Tumour[3]
TX Primary tumour cannot be assessed
TO No evidence of primary tumour
T1 Tumour limited to pancreas,[0] 2 cm or less in greatest dimension
T2 Tumour limited to pancreas[0] more than 2 cm but less than 4 cm in greatest dimension
T3 Tumour limited to pancreas,[0] more than 4 cm in greatest dimension or tumour invading duodenum or bile duct.
T4 Tumour invades adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (coeliac axis or the superior mesenteric artery)

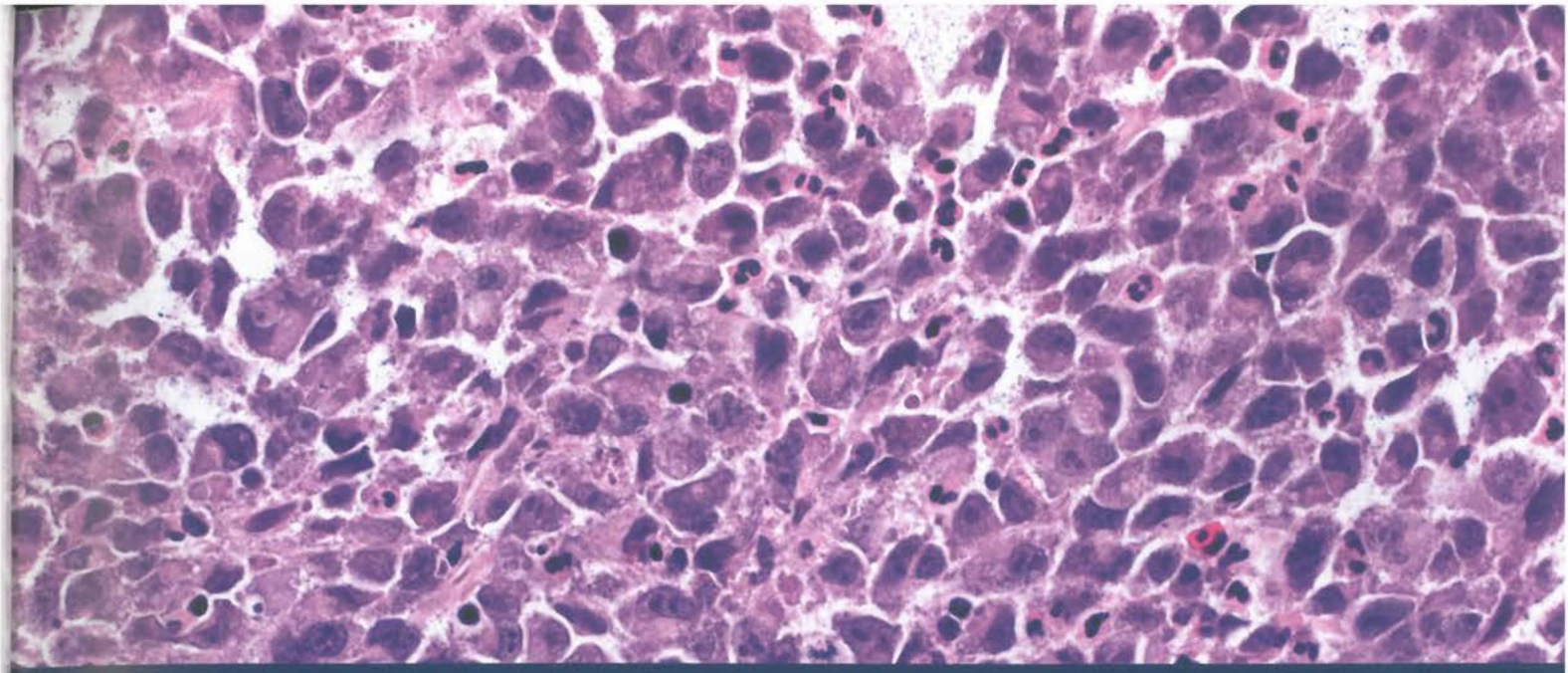
Notes
• For any T, add (m) for multiple tumours.
[0] Invasion of adjacent peripancreatic adipose tissue is accepted but invasion of adjacent organs is excluded.

N - Regional Lymph Nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Distant Metastasis
MO No distant metastasis
M1 Distant metastasis
M1a Hepatic metastasis only
M1b Extrahepatic metastasis only
M1c Hepatic and extrahepatic metastases

Stage

Stage I	T1	NO	MO
Stage II	T2.T3	NO	MO
Stage III	T4	NO	MO
	Any T	N1	MO
Stage IV	Any T	Any N	M1



2

Tumours of the oesophagus

Edited by: Odze RD, Lam AK, Ochiai A. Washington MK

WHO classification of tumours of the oesophagus

Benign epithelial tumours and precursors
8052/0 Squamous cell papilloma NOS
8060/0 Squamous papillomatosis
8148/0 Oesophageal glandular dysplasia (intraepithelial neoplasia), low grade
8148/2 Oesophageal glandular dysplasia (intraepithelial neoplasia), high grade
8077/0 Oesophageal squamous intraepithelial neoplasia (dysplasia), low grade
8077/2 Oesophageal squamous intraepithelial neoplasia (dysplasia), high grade

Malignant epithelial tumours
8140/3 Adenocarcinoma NOS
8200/3 Adenoid cystic carcinoma
8430/3 Mucoepidermoid carcinoma
8560/3 Adenosquamous carcinoma
8070/3 Squamous cell carcinoma NOS
8051/3 Verrucous squamous cell carcinoma
8074/3 Squamous cell carcinoma, spindle cell
8083/3 Basaloid squamous cell carcinoma
8020/3 Carcinoma, undifferentiated. NOS
8082/3 Lymphoepithelioma-like carcinoma
8240/3 Neuroendocrine tumour NOS
8240/3 Neuroendocrine tumour, grade 1
8249/3 Neuroendocrine tumour, grade 2
8249/3 Neuroendocrine tumour, grade 3
8246/3 Neuroendocrine carcinoma NOS
8013/3 Large cell neuroendocrine carcinoma
8041/3 Small cell neuroendocrine carcinoma
8154/3 Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)
8045/3 Combined small cell-adenocarcinoma
8045/3 Combined small cell-squamous cell carcinoma

These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2) {1378A} Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia, /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site Behaviour code /6 is not generally used by cancer registries.

This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions

TNM staging of tumours of the oesophagus

Oesophagus

(ICD-0-3 C15) Including Oesophagogastric Junction (C16.0)

Rules for Classification

The classification applies only to carcinomas and includes adenocarcinomas of the oesophagogastric/gastroesophageal junction. There should be histological confirmation of the disease and division of cases by topographic localization and histological type. A tumour the epicentre of which is within 2 cm of the oesophagogastric junction and also extends into the oesophagus is classified and staged using the oesophageal scheme. Cancers involving the oesophagogastric junction (OGJ) whose epicentre is within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as oesophageal cancers.

The following are the procedures for assessing T, N, and M categories.

T categories	Physical examination, imaging, endoscopy (including bronchoscopy), and/or surgical exploration
N categories	Physical examination, imaging, and/or surgical exploration
M categories	Physical examination, imaging, and/or surgical exploration

Anatomical Subsites

1. Cervical oesophagus (C15.0): this commences at the lower border of the cricoid cartilage and ends at the thoracic inlet (suprasternal notch), approximately 18 cm from the upper incisor teeth.
2. Intrathoracic oesophagus
   a) The upper thoracic portion (C15.3) extending from the thoracic inlet to the level of the tracheal bifurcation, approximately 24 cm from the upper incisor teeth
   b) The mid-thoracic portion (C15.4) is the proximal half of the oesophagus between the tracheal bifurcation and the oesophagogastric junction. The lower level is approximately 32 cm from the upper incisor teeth
   c) The lower thoracic portion (C15.5), approximately 8 cm in length (includes abdominal oesophagus), is the distal half of the oesophagus between the tracheal bifurcation and the oesophagogastric junction. The lower level is approximately 40 cm from the upper incisor teeth
3. Oesophagogastric junction (C16.0). Cancers involving the oesophagogastric junction (OGJ) whose epicentre is within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as oesophageal cancers. Cancers whose epicentre is more than 2 cm distal from the OGJ will be staged using the Stomach Cancer TNM and Stage even if the OGJ is involved.

Regional Lymph Nodes

The regional lymph nodes, irrespective of the site of the primary tumour, are those in the oesophageal drainage area including coeliac axis nodes and paraesophageal nodes in the neck but not the supraclavicular nodes.

TNM Clinical Classification

T - Primary Tumour
TX Primary tumour cannot be assessed
TO No evidence of primary tumour
Tis Carcinoma in situ/high-grade dysplasia
T1 Tumour invades lamina propria, muscularis mucosae, or submucosa
  T1a Tumour invades lamina propria or muscularis mucosae
  T1b Tumour invades submucosa
T2 Tumour invades muscularis propria
T3 Tumour invades adventitia
T4 Tumour invades adjacent structures
  T4a Tumour invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
  T4b Tumour invades other adjacent structures such as aorta, vertebral body, or trachea

N - Regional Lymph Nodes
NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Metastasis in 1 to 2 regional lymph nodes
N2 Metastasis in 3 to 6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes

M - Distant Metastasis
MO No distant metastasis
M1 Distant metastasis

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pNO Histological examination of a regional lymphadenectomy specimen will ordinarily include 7 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pNO.

pM - Distant Metastasis*
pM1 Distant metastasis microscopically confirmed

Note
* pMO and pMX are not valid categories.

Stage and Prognostic Group - Carcinomas of the Oesophagus and Oesophagogastric Junction*

Squamous Cell Carcinoma

Clinical Stage

Stage 0	Tis	NO	MO
Stage I	T1	N0.N1	MO
Stage II	T2	N0.N1	MO
	T3	NO	MO
Stage III	T1.T2	N2	MO
	T3	N1.N2	MO
Stage IVA	T4a,T4b	N0.N1.N2	MO
	Any T	N3	MO
Stage IVB	Any T	Any N	M1

Pathological Stage

Stage 0	Tis	NO	MO
Stage IA	T1a	NO	MO
Stage IB	T1b	NO	MO
Stage IIA	T2	NO	MO
Stage I IB	T1	N1	MO
	T3	NO	MO
Stage IIIA	T1	N2	MO
	T2	N1	MO
Stage IIIB	T2	N2	MO
	T3	N1.N2	MO
	T4a	N0.N1	MO
Stage IVA	T4a	N2	MO
	T4b	Any N	MO
	Any T	N3	MO
Stage IVB	Any T	Any N	M1

Adenocarcinoma

Clinical Stage

	T	N	**M**
Stage 0	Tis	NO	MO
Stage I	T1	NO	MO
Stage IIA	T1	N1	MO
Stage IIB	T2	NO	MO
Stage III	T2	N1	MO
	T3,T4a	N0.N1	MO
Stage IVA	T1-T4a	N2	MO
	T4b	N0.N1.N2	MO
	Any T	N3	MO
Stage IVB	Any T	Any N	M1

Pathological Stage

Stage 0	Tis	NO	MO
Stage IA	T1a	NO	MO
Stage IB	T1b	NO	MO
Stage IIA	T2	NO	MO
Stage IIB	T1	N1	MO
	T3	NO	MO
Stage IIIA	T1	N2	MO
	T2	N1	MO
Stage IIIB	T2	N2	MO
	T3	N1.N2	MO
	T4a	N0.N1	MO
Stage IVA	T4a	N2	MO
	T4b	Any N	MO
	Any T	N3	MO
Stage IVB	Any T	Any N	M1

Pathological Prognostic Group

Group	T	N	**M**	Grade	Location
Group 0	Tis	NO	MO	N/A	Any
Group IA	T1a	NO	MO	1.X	Any
Group IB	T1a	NO	MO	2-3	Any
	T1b	NO	MO	Any	Any
	T2	NO	MO	1	Any
Group IIA	T2	NO	MO	2-3,X	Any
	T3	NO	MO	Any	Lower
	T3	NO	MO	1	Upper, middle
Group IIB	T3	NO	MO	2-3	Upper, middle
	T3	NO	MO	Any	X
	T3	NO	MO	X	Any
	T1	N1	MO	Any	Any
Group IIIA	T1	N2	MO	Any	Any
	T2	N1	MO	Any	Any
Group IIIB	T2	N2	MO	Any	Any
	T3	N1.N2	MO	Any	Any
	T4a	N0,N1	MO	Any	Any
Group IVA	T4a	N2	MO	Any	Any
	T4b	Any N	MO	Any	Any
	Any T	N3	MO	Any	Any
Group IVB	Any T	Any N	M1	Any	Any

Pathological Prognostic Group

	T	**N**	**M**	Grade
Group 0	Tis	NO	MO	N/A
Group IA	T1a	NO	MO	1.X
Group IB	T1a	NO	MO	2
	T1b	NO	MO	1.2.X
Group IC	T1a,Tlb	NO	MO	3
	T2	NO	MO	1.2
Group IIA	T2	NO	MO	3.X
Group IIB	T1	N1	MO	Any
	T3	NO		Any
Group IIIA	T1	N2	MO	Any
	T2	N1	MO	Any
Group IIIB	T2	N2	MO	Any
	T3	N1.N2	MO	Any
	T4a	N0,N1	MO	Any
Group IVA	T4a	N2	MO	Any
	T4b	Any N	MO	Any
	Any T	N3	MO	Any
Group IVB	Any T	Any N	M1	Any

Note

' The AJCC publishes prognostic groups for adenocarcinoma and squamous cell carcinoma after neoadjuvant therapy (categories with the prefix "y").

Tumours of the oesophagus: Introduction

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Odze RD

This chapter describes benign and malignant oesophageal tumours of epithelial differentiation and their precursor lesions. The ICD-0 topographical coding for the anatomical sites covered in this chapter is presented in Box 2.01. The most common benign lesion, squamous papilloma, is addressed in a dedicated section. Throughout this fifth edition of the series, precursor lesions are typically described in separate sections from malignant tumours - a change from the fourth edition. The decision to make this change was based on the considerable expansion of our understanding of the biological and pathological features of precursor lesions and their relevance to clinical practice.

There are two main types of precursor lesions in the oesophagus; Barrett dysplasia and squamous dysplasia. Over the past 10 years or so, we have seen an important shift from surgery towards ablation for the treatment of Barrett oesophagus in patients with high-grade dysplasia. The same shift may eventually occur in the treatment of low-grade dysplasia, but this is currently a controversial issue. Therefore, the two-tiered (low-grade vs high-grade) system remains clinically useful for the time being, but this may change if ablation becomes the standard treatment for low-grade dysplasia as well. Regardless, we now have a much better understanding of the molecular pathways and pathological characteristics of carcinogenesis in Barrett oesophagus and its precursor lesions. The two most common types of dysplasia - intestinal and foveolar (gastric-type) - are now far better understood in terms of their pathological characteristics, biological behaviours, and clinical associations than a decade ago, but their distinction from non-neoplastic regenerative lesions remains a challenge and requires further research. Sampling error remains an issue of concern in surveillance programmes, but the increasing use of brush sampling and cytology-based diagnosis in the surveillance of Barrett oesophagus has already resulted in substantial improvements in the detection of goblet cells and dysplasia within both general and high-risk patient populations. There is ongoing controversy regarding the definition of Barrett oesophagus in different parts of the world: in the USA, goblet cells are an essential criterion for diagnosis, whereas this feature is not considered essential in Asian and European countries.

Squamous dysplasia remains a less well understood form of neoplasia in the oesophagus and a topic of disagreement between pathologists in different parts of the world. It is an uncommon entity, except in areas with high incidence of oesophageal squamous cell carcinoma where screening programmes are in place. One notable change since the fourth edition of this volume is that there is now wider agreement that a two-tiered grading system is preferable (because it is more reproducible and clinically more relevant) than a three-tiered system. However, oesophageal squamous dysplasia's pathological features and their variability, as well as the molecular characteristics, remain areas in need of further research.

Box 2.01 ICD-0 topographical coding for the anatomical sites covered in this chapter

C15 Oesophagus
- C15.0 Cervical oesophagus
- C15.1 Thoracic oesophagus
- C15.2 Abdominal oesophagus
- C15.3 Upper third of the oesophagus
- C15.4 Middle third of the oesophagus
- C15.5 Lower third of the oesophagus
- C15.8 Overlapping lesion of the oesophagus
- C15.9 Oesophagus NOS

C16 Stomach
- C16.0 Oesophagogastric junction
- C16.0 Overlapping lesion of the digestive system

The two most common types of malignant epithelial tumours of the oesophagus are adenocarcinoma and squamous cell carcinoma. Subtypes of these entities have become better understood in recent years, and these new insights are covered in the tumours' respective sections. The incidence of these two types of oesophageal carcinomas varies in different parts of the world, and there have been improvements in our understanding of the reasons for this, such as certain environmental and dietary factors. One important change is that for patients who have not received neoadjuvant chemoradiation, the TNM staging criteria for these two carcinomas are now different. In recent years, neoadjuvant chemoradiotherapy has become a mainstay in the treatment of oesophageal carcinomas; as a result, there is increasing awareness of the effects of therapy on the morphology and molecular biology of carcinomas and their regression patterns, which are now incorporated into staging systems in recognition of their clinical relevance. For both squamous cell carcinoma and adenocarcinoma of the oesophagus, the two-tiered grading system for tumour differentiation is now strongly recommended.

In this fifth-edition volume, adenocarcinomas of the oesophagus and of the oesophagogastric junction are discussed together in a single section, because recent data suggest that these tumours share many etiological, histological, and biological features. However, readers should be aware of a change in the definition of adenocarcinoma of the oesophagogastric junction, which now includes any adenocarcinoma whose epicentre is within 2 cm of the junction.

There have recently been important advances in oesophageal carcinoma treatment related to the development of immunotherapy and targeted therapy. For example, ERBB2 (HER2) status is now considered a useful predictor of response to anti-ERBB2 therapy in adenocarcinoma of the oesophagogastric junction.

A subject of continued confusion is the definition and diagnostic criteria of mixed tumours, such as adenosquamous and mucoepidermoid carcinomas. These are rare tumours, but our poor understanding of their biological characteristics is mainly due to the lack of well-defined diagnostic criteria and lack of

understanding of their pathogenesis. For example, there is controversy as to whether these two carcinomas are histological subtypes of squamous cell carcinoma or adenocarcinoma, although they seemingly arise in both conditions (at various rates in different parts of the world). Some may also arise from the oesophageal gland ducts, but it is unclear how such cases differ from those that arise from the mucosal epithelium.

Undifferentiated carcinoma is a tumour that lacks squamous, glandular, or neuroendocrine differentiation. In this fifth-edition volume, undifferentiated carcinoma is now considered a distinct entity rather than a subtype of squamous cell carcinoma.

Neuroendocrine neoplasms (NENs) of the oesophagus are uncommon. They are now classified according to the same criteria used for NENs in the pancreas and other parts of the GI tract. These classification criteria are described in more detail in the introductory section *Classification of neuroendocrine neoplasms of the digestive system* (p. 16).

Oesophageal squamous papilloma

Lam AK

Definition
Squamous papilloma of the oesophagus is a benign oesophageal epithelial polyp composed of squamous epithelium, usually with a papillary growth pattern.

ICD-0 coding
8052/0 Squamous cell papilloma NOS

ICD-11 coding
2E92.0 & XH50T2 Benign neoplasm of oesophagus & Squamous cell papilloma

Related terminology
None

Subtype(s)
Squamous papillomatosis (8060/0)

Localization
In a large US series, 58% of squamous papillomas were located in the lower oesophagus {2502}. In Asian populations, squamous papilloma is more frequently found in the middle oesophagus. In a series from Taiwan, China, slightly more than half (54%) of squamous papillomas were located in the middle oesophagus {3594}.

Clinical features
Most patients with squamous papilloma are asymptomatic. Endoscopically, squamous papilloma appears as a small white exophytic growth with vessels crossing on a wart-like surface (3594).

Epidemiology
Squamous papilloma is uncommon. The prevalence in endoscopic series ranges from 0.01% to 0.45% (705). In a large endoscopy series from north-eastern France, the M:F ratio was 1.3:1 (705). In many other populations, squamous papilloma is more common in females (with M:F ratios ranging from 0.2:1 to 0.8:1) (3594,3195). Squamous papilloma typically presents in middle age (median age: 50 years) (705). Squamous papillomatosis may present in paediatric (3050) or elderly (927) patients. Approximately 30 cases have been reported in the English-language literature (927,3050).

Etiology
The causes of squamous papilloma include chronic mucosal irritation, HPV infection, and genetic syndromes. Chronic mucosal irritation can result from chemical factors (e.g. gastro-oesophageal reflux, alcohol consumption, cigarette smoking, and caustic injury) or mechanical factors (e.g. minor trauma, variceal sclerotherapy, self-expandable metal stents, chronic food impaction, nasogastric intubation, and bougie-assisted oesophageal dilation) (705). The etiological role of gastro-oesophageal reflux in squamous papilloma may explain why these lesions are frequently located in the lower oesophagus (705). The observed prevalence of HPV infection in patients with squamous papilloma is as high as 87.5% in some series (705). Squamous papillomatosis may occur in patients with focal dermal hypoplasia (also known as Goltz-Gorlin syndrome) (2540,313,1533) or angioma serpiginosum (347); both genetic disorders are rare genodermatotic conditions that affect the X chromosome.

Pathogenesis
Chronic mucosal irritation or HPV infection leads to mucosal injury. The resulting hyperregenerative responses stimulate proliferation of the squamous mucosa, resulting in squamous papilloma. Oesophageal papillomas are hypothesized to be related to the high incidence of early-onset gastro-oesophageal reflux in focal dermal hypoplasia (1074).

Macroscopic appearance
Macroscopically, squamous papillomas usually have a white, elevated, warty surface. The papillomas are often small (median diameter: 3 mm) (705), but giant squamous papillomas have been reported (3196).

Histopathology
Microscopic examination reveals a papillary proliferation of squamous epithelium with a fibrovascular core of lamina propria. Scattered vacuolated cells with morphological features of koilocytes are often seen. No atypical nuclear features and no viral inclusions are present. The proliferation patterns of squamous epithelium are most often exophytic (2408), but they can also be endophytic or spiked. Rarely, dysplasia has been reported in squamous papilloma (705,2701).

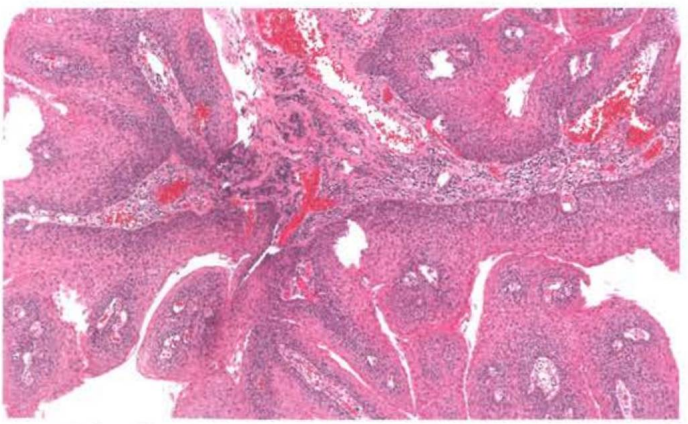

Fig. 2.01 Oesophageal squamous papilloma. Exophytic pattern of growth; the papillary fibrovascular core is surrounded by hyperplastic squamous epithelium with parakeratosis.

Squamous papilloma should be differentiated from fibrovascular polyp, which is typically located in the upper oesophagus and covered by stratified squamous epithelium, without papillary proliferation {1131}. Squamous papilloma must also be differentiated from squamous cell carcinoma, by excluding invasion.

Cytology
Not clinically relevant

Diagnostic molecular pathology
Not clinically relevant

Essential and desirable diagnostic criteria
Essential: papilloma consisting of squamous epithelium with fibrovascular cores.

Staging (TNM)
Not clinically relevant

Prognosis and prediction
Squamous papilloma does not recur after resection. Squamous cell carcinoma has been rarely reported to be associated with squamous papilloma or squamous papillomatosis {705,1465}.

Barrett dysplasia

Odze RD

Definition

Barrett dysplasia is defined by a morphologically unequivocal neoplastic epithelium without invasion, occurring in an area of metaplastic columnar epithelium in the oesophagus.

ICD-0 coding

8148/0 Oesophageal glandular dysplasia (intraepithelial neoplasia), low grade
8148/2 Oesophageal glandular dysplasia (intraepithelial neoplasia), high grade

ICD-11 coding

DA23.1 Dysplasia of Barrett epithelium
2E92.0 & XH3K13 Benign neoplasm of oesophagus & Oesophageal glandular dysplasia (intraepithelial neoplasia), low-grade
2E60.1 & XH36M5 Carcinoma in situ of oesophagus & Oesophageal glandular dysplasia (intraepithelial neoplasia), high-grade

Related terminology

Low-grade Barrett dysplasia
Not recommended: glandular dysplasia.

High-grade Barrett dysplasia
Not recommended: columnar dysplasia.

Subtype(s)

None

Localization

Barrett dysplasia is restricted to metaplastic oesophageal mucosa.

Clinical features

There are no distinct clinical, radiological, or serological manifestations of dysplasia in Barrett oesophagus. Patients typically present because of the underlying Barrett oesophagus, with symptoms such as gastro-oesophageal reflux disease. Dysplasia may be visible endoscopically, appearing as a flat, plaque-like or irregular area of mucosa distinct from the surrounding non-dysplastic Barrett oesophagus {1073}. Mucosal abnormalities such as ulceration, plaques, nodules, and strictures are associated with an increased risk of cancer.

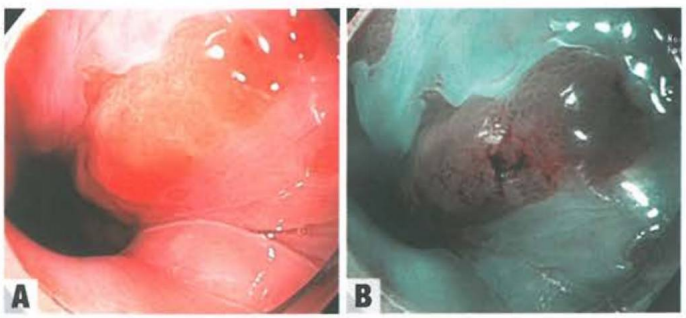

Fig. 2.02 High-grade Barrett dysplasia. A White-light endoscopy reveals a 2 cm tongue of Barrett oesophagus, with a focus of high-grade dysplasia appearing as a slightly irregular and plaque-like area of mucosa with slight loss of vascular pattern and congestion. B The focus of dysplasia is best visualized with narrow-band imaging, which helps delineate the area of abnormality.

Epidemiology

The risk factors for dysplasia in Barrett oesophagus are similar to those for oesophageal adenocarcinoma (see Box 2.02, p. 39). Dysplasia develops mainly in patients who have metaplastic intestinal-type epithelium characterized by the presence of goblet cells (2966,3306|. However, neoplasia can also develop in mucosa without goblet cells (2787). The true risk of neoplasia development in non-goblet columnar epithelium is unknown.

Etiology

See *Adenocarcinoma of the oesophagus and oesophagogastric junction NOS* (p. 38).

Pathogenesis

Cancer in Barrett oesophagus develops via sequential progression from inflammation to metaplasia, dysplasia, and ultimately carcinoma. As a result of chronic gastro-oesophageal reflux disease, the squamous epithelium converts to columnar epithelium, which is initially of the cardia type and devoid of goblet cells; it later develops goblet cell metaplasia and eventually dysplasia. Dysplasia has been shown to develop from clones of epithelium without goblet cells; both dysplasia and cancer have been shown to develop in patients without goblet cells anywhere in the oesophagus, and even in patients with short-segment columnar metaplasia. Dysplasia develops and progresses as a result of the accumulation of multiple genetic and epigenetic alterations, many of which occur before the onset of dysplasia (3539,3122). Many of the molecular events, in particular those that occur early, are related to alterations of the cell-cycle regulatory genes, apoptosis, cell signalling, and adhesion pathways (3539,3122,822). Late changes in Barrett oesophagus-associated neoplasia include widespread genomic abnormalities, losses and gains in chromosome function, and (most importantly) DNA instability characterized by an increased 4N (tetrapioid) cell fraction and aneuploidy. Dysplasia shows an increased Ki-67 proliferation index, which is typically highest in the bases of the crypts, but it may also be high in the surface epithelium in high-grade dysplasia. Other abnormalities include mutations in *PONA, CCND1. TP53, IGF2BP3,* and *AMACR* (3122,822,3444,3742). A more complete description of the molecular abnormalities in Barrett oesophagus is provided in the section *Adenocarcinoma of the oesophagus and oesophagogastric junction NOS* (p.38).

Macroscopic appearance
Not clinically relevant

Histopathology
Histologically, the two most common types of dysplasia are intestinal and foveolar; the latter is also referred to as non-intestinal dysplasia or gastric-type dysplasia (2278). Rarely, dysplasia may have a serrated pattern of growth. A mixture of intestinal and foveolar dysplasia is not uncommon. Intestinal dysplasia is composed of columnar cells with intestinal differentiation, including goblet cells and enterocyte-like cells.

Like inflammatory bowel disease, dysplasia can be classified as negative, indefinite, or positive (either low-grade or high-grade) according to the system proposed in 1988 by Reid et al. (2679); however, many pathologists instead use the modified Vienna classification of dysplasia (2886) (see Table 2.01, p. 34).

Low-grade dysplasia shows cytological abnormalities but little or no architectural atypia. The cells show elongation, nuclear enlargement, hyperchromasia, and stratification, but they largely retain their nuclear polarity. Stratification is typically limited to the basal portion of the cell cytoplasm. Goblet cells vary from few to numerous, generally decreasing in number with increasing grade of dysplasia.

High-grade dysplasia shows a greater degree of cytological atypia, often along with architectural abnormalities. The cells show markedly enlarged nuclei (as large as 3-4 times the size of lymphocytes), full-thickness nuclear stratification in the base and surface epithelium, marked nuclear pleomorphism, irregular nuclear contours, and substantial loss of polarity. Mitoses are usually increased in number in the surface epithelium, and atypical mitoses are common. Intraluminal necrosis may be present. In some cases, the dysplastic nuclei may be irregularly shaped and show a more rounded configuration, with vesicular nuclei and prominent nucleoli; this is more common in foveolar dysplasia. The crypts in high-grade dysplasia may show variability in size and shape, may appear crowded, and/or may contain marked budding or angulation. Back-to-back gland formation and cribriforming are not uncommon. The diagnosis of high-grade dysplasia can be established in the presence of either high-grade cytological or architectural aberrations alone, but most cases show a combination of both.

Foveolar (non-intestinal) dysplasia typically shows few, if any, goblet cells; instead, it is characterized by prominent cytoplasmic mucin. The cells are more uniformly columnar and are typically composed of a single layer. They have small or slightly enlarged, round to oval, basally located nuclei without stratification or pleomorphism. In some cases, the nuclei may be pencil-shaped. High-grade foveolar dysplasia shows cells with a markedly increased N:C ratio and more-irregular nuclear contours, often with an open chromatin pattern, prominent nucleoli, and an increased mitotic rate. Some cases may also show

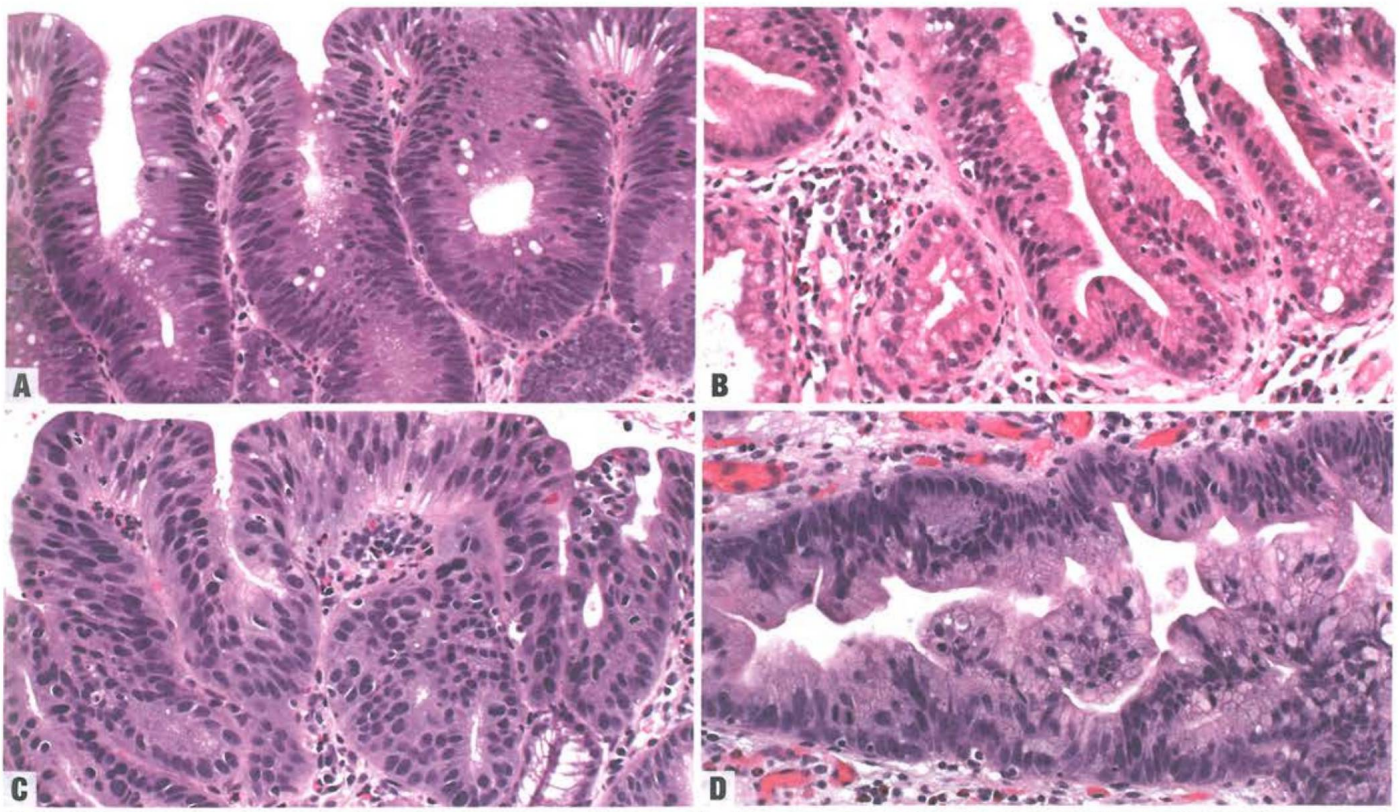

Fig. 2.03 Barrett dysplasia. A Low-grade, intestinal type. Evenly spaced tubules are lined with enlarged, hyperchromatic, elongated, slightly stratified atypical cells with increased numbers of mitoses and a lack of surface maturation. B Low-grade, foveolar type. The dysplastic epithelium shows mildly to moderately enlarged, hyperchromatic, round to oval-shaped nuclei, with slight stratification and increased numbers of mitoses but no goblet cells; the cytoplasm is mucinous. **C** High-grade, intestinal type. Compact crypts with markedly enlarged, oval to elongated, hyperchromatic nuclei with multiple nucleoli, showing full-thickness stratification, increased numbers of mitoses, loss of polarity, and pleomorphism. D High-grade, foveolar type. Markedly atypical epithelium composed of enlarged, hyperchromatic, elongated, irregularly shaped nuclei, with pleomorphism, full-thickness stratification, loss of polarity, and increased numbers of mitoses; the cytoplasm is mucinous but somewhat depleted.

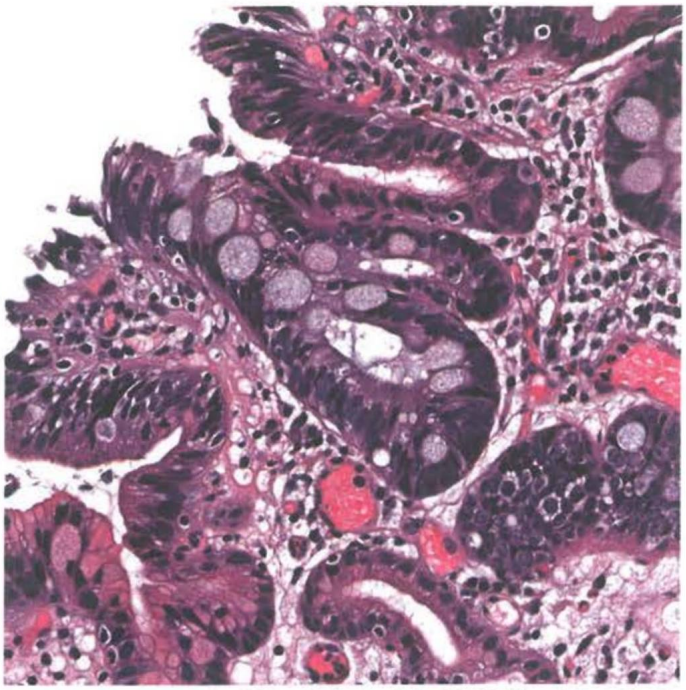

Fig. 2.04 Barrett dysplasia with intestinal metaplasia. Intestinal-type low-grade dysplasia with multiple goblet cells.

stratification of the nuclei. Foveolar dysplasia may develop in fields of metaplastic columnar mucosa without goblet cells.

Like inflammatory bowel disease, dysplasia can sometimes be detected at an early stage, when it is still restricted to the bases of the crypts; such cases are referred to as crypt dysplasia (1945). Crypt dysplasia most often shows low-grade cytological features, but some cases can show high-grade cytological changes as well.

Immunohistochemistry using antibodies to p53, AMACR, and IMP3 is sometimes useful for differentiating between non-dysplastic and dysplastic epithelium, but the results are variable and of mixed value {2136}. For example, one of the problems with p53 immunohistochemistry is that a non-mutant pattern does not exclude dysplasia.

Cytology

Cytology is increasingly used as an adjunct to biopsy in the diagnosis of Barrett oesophagus and associated neoplasms. In general, the degree of atypia depends on the grade of dysplasia, although well-accepted criteria for diagnosing low-grade and high-grade dysplasia on cytology samples have not been established (3512). The observed sensitivity of cytology in the diagnosis of low-grade dysplasia is as low as 31% in some studies (2806), but the cytological diagnosis of high-grade dysplasia is more accurate - comparable to diagnosis using mucosal biopsy samples, with a reported sensitivity of 82% and specificity as high as 95% (2806,1721). Cytologically, dysplasia shows some of the atypical features of malignancy, such as cellular diffusion, haphazard arrangement of cells, an increased N:C ratio, nuclear enlargement, hyperchromasia, nuclear membrane irregularity, and chromatin aberration (either clumping or clearing). The periphery of the cell groups is often irregular. In high-grade dysplasia, the cells are more discohesive, with a higher N:C ratio and moderate to markedly enlarged atypical nuclei.

Diagnostic molecular pathology

Not clinically relevant

Essential and desirable diagnostic criteria

Essential: unequivocal neoplastic alteration of the epithelium, without invasion.

Note: Unequivocal neoplastic alteration (dysplasia) most often consists of cells with enlarged hyperchromatic elongated, pleomorphic, and stratified nuclei with increased numbers of mitoses, lack of surface maturation, and loss of polarity. Architecturally, the neoplastic epithelium may show glands of abnormal size and shape, with branching, increased complexity, and/or a back-to-back pattern of growth with little or no intervening lamina propria when the dysplasia is of high grade.

Staging (TNM)

Not clinically relevant

Prognosis and prediction

In various studies, the observed rates of progression of low-grade dysplasia to high-grade dysplasia or cancer range from

Table2.01 The Vienna and Reid classifications of dysplasia in Barrett oesophagus

Vienna	Reid
Negative for neoplasia/dysplasia	Negative for dysplasia
Indefinite for neoplasia/dysplasia	Indefinite for dysplasia
Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia)	Low-grade dysplasia
Non-invasive high-grade neoplasia High-grade dysplasia Non-invasive carcinoma (carcinoma in situ) Suspicious for invasive carcinoma	High-grade dysplasia
Invasive neoplasia	Adenocarcinoma
Intramucosal adenocarcinoma	Intramucosal adenocarcinoma
Submucosal carcinoma or beyond	Invasive adenocarcinoma

3% to 23% (2752,2976}, undoubtedly as a result of interobserver variability. In one meta-analysis, the pooled annual incidence rate of progression to adenocarcinoma was 0.5% for adenocarcinoma alone and 1.7% for either high-grade dysplasia or adenocarcinoma (3049). In some studies, as many as 55% of high-grade dysplasias have been found to progress to cancer during 5 years of follow-up, and high-grade dysplasia is associated with a cancer incidence of ≥ 6% per year (2976,2680). In a recent European study, the risk of progression to adenocarcinoma associated with low-grade dysplasia was 5 times that associated with no dysplasia (732). Progression rates for both low-grade and high-grade dysplasia have been shown to correlate with the number of pathologists who agree on the diagnosis (3120). In one study, 15 of 25 patients (60%) with a dysplastic lesion associated with a nodule were diagnosed with oesophageal cancer (451). A similarly strong association has been observed between adenocarcinoma and polypoid dysplasia, ulceration, or stricture formation (3307,2204). Other markers of progression that have been evaluated include p53, p16, and DNA content abnormalities (941,3742,1549). Several studies have shown a positive association between aberrant p53 expression and an increased risk of neoplastic progression (3742,1549). Genomic instability is also a useful marker of progression (941).