The 5th Edition of the WHO Classification of Tumours: Digestive System Tumours “blue book” was released in mid-2019. Key updates are below.

General updates
• The classification of digestive neuroendocrine neoplasms is revised. They are categorized as neuroendocrine tumors (NETs, formerly “carcinoids”) or neuroendocrine carcinomas (NECs) based primarily on histology.
  • NETs can be grade 1, 2 or 3, with a Ki67 of less than 3% qualifying as grade 1 (formerly 0 - 2%). Mitotic rate is counted per 2 mm², not per 10 high power fields.
  • NECs are always high grade and therefore do not require numerical grading. Mixed adenoneuroendocrine carcinoma (MANEC) has been replaced with the more inclusive conceptual term of mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN); the actual diagnosis should indicate the lesion’s components.
  • Carcinoma grading is generally now two tier (low grade and high grade).
  • Poorly cohesive carcinoma is a diagnostic term incorporated into most organ system chapters, with signet ring cell carcinoma considered a subtype.
  • Hematolymphoid lesions, mesenchymal lesions and syndromes have been separated into their own respective chapters.
  • There is now a separate chapter on “other tumors” covering mucosal melanoma, germ cell tumors and metastases.

Esophagus
• Gastroesophageal junction carcinomas have been incorporated into the esophagus chapter.
• Undifferentiated carcinoma is separated into its own entity rather than a squamous cell carcinoma subtype. Lymphoepithelioma-like carcinoma is considered a subtype of this entity.

Stomach
• Undifferentiated carcinoma is now its own separate entity with many subtypes (large cell carcinoma with rhabdoid phenotype, pleomorphic carcinoma, sarcomatoid carcinoma and carcinoma with osteoclast-like giant cells).
• Micropapillary adenocarcinoma is added as an aggressive subtype of adenocarcinoma.
• Gastroblastoma is added as an entity.

Small bowel / Ampulla
• Ampullary carcinomas have been incorporated into the small bowel chapter, though the chapter distinguishes between ampullary and nonampullary carcinomas.
• Intra-ampullary papillary-tubular neoplasm has been added as a subtype of ampullary adenoma.

Appendix
• Low grade appendiceal mucinous neoplasm (LAMN) is formalized as a separate entity rather than a form of appendiceal adenocarcinoma.
• High grade appendiceal mucinous neoplasm (HAMN) is added as a diagnostic entity similar to LAMN but showing high grade dysplasia.
• Goblet cell carcinoid is renamed goblet cell adenocarcinoma, with a new grading system. High grade examples represent what was previously termed “adenocarcinoma ex goblet cell carcinoid” (Figure 1).

Figure 1: Goblet cell carcinoid of the appendix is renamed goblet cell adenocarcinoma.

Colorectum
• Sessile serrated adenoma / polyp is renamed to sessile serrated lesion, with the reasoning that they are not always polypoid on colonoscopy. Only one unequivocally distorted crypt is now needed to make this diagnosis.
• Adenoma-like adenocarcinoma is added as a subtype of colorectal carcinoma (CRC) with a good prognosis. Adenosquamous carcinoma is also now considered a CRC subtype.
• Cribriform-comedo type adenocarcinoma is removed as a CRC subtype.
• Spindle cell carcinoma is renamed to carcinoma with sarcomatoid components.
• Rather than grading CRC based on the predominant component,
the WHO now recommends grading based on the least differentiated component, regardless of amount.

**Liver / Intrahepatic bile ducts**

- Several subtypes of hepatocellular carcinoma (HCC) have been added: steatohepatitic, clear cell (formerly a “cytological variant”), macrotrabecular-massive, chromophobe and neutrophil-rich. The lymphoepithelioma-like subtype is renamed to lymphocyte-rich.
- Molecular features of HCC subtypes are emphasized, particularly the DNAJB1-PRKACA translocation of fibrolamellar HCC.
- Emphasis is placed on categorizing intrahepatic cholangiocarcinoma into large and small duct types.
- Hepatoblastoma subtypes have been reorganized, and calcifying nested stromal-epithelial tumor is separated out as a distinct entity rather than a variant / related neoplasm.
- The subtypes of combined HCC-cholangiocarcinoma are less strictly defined. Cholangiocarcinoma is moved from this classification scheme and is now considered a type of small duct cholangiocarcinoma instead.
- Primary neuroendocrine neoplasms of the liver have been formally added.

**Gallbladder / Extrahepatic bile ducts**

- Grading of biliary intraepithelial neoplasia (BilIN) is now two tier (low and high grade) rather than three tier.

**Pancreas**

- Acinar cystadenoma is officially renamed acinar cystic transformation.
- Pancreatic intraepithelial neoplasia (PanIN) is now two tier. Numerical grading (PanIN-1A, etc.) is no longer used.
- Intraductal oncocytic papillary neoplasm (IOPN) is established as a distinct entity separate from intraductal papillary mucinous neoplasm (IPMN), due to a different mutational profile (Figure 2).

**Lymphoma**

- Duodenal-type follicular lymphoma, intestinal T cell lymphoma NOS, indolent T cell proliferative disorder of the gastrointestinal tract and EBV positive inflammatory follicular dendritic cell sarcoma are added as distinct entities.
- Monomorphic CD56+ intestinal T cell lymphoma is renamed to monomorphic epitheliotrophic intestinal T cell lymphoma.

**Mesenchymal**

- Malignant gastrointestinal neuroectodermal tumor is added as a distinct entity. It may represent the same entity as clear cell sarcoma-like tumor of the gastrointestinal tract or a subtype.
- Molecular information on gastrointestinal stromal tumors (GISTs) is added, in particular the succinate dehydrogenase (SDH) deficient subtype.
- Epithelioid inflammatory myofibroblastic sarcoma is added as an aggressive subtype of inflammatory myofibroblastic tumor with RANBP2 rearrangement.
- New hemangioma subtypes are specified: anastomosing hemangioma, diffuse hepatic hemangiomatosis and hepatic small vessel neoplasm.
- Molecular data is added to epithelioid hemangioendothelioma, namely the characteristic WWTR1-CAMTA1 and YAP1-TFE3 translocations.

**Figure 2: IOPN of pancreas is officially distinct from IPMN.**

- The neuroendocrine section is markedly expanded, including discussion of each hormone producing subtype and emphasis on new molecular data.

**Genetics**

- Several new polyposis syndromes are added, including gastric adenocarcinoma and proximal polyposis syndrome (GAPPS), NTHLI associated polyposis, polymerase proofreading associated polyposis (caused by POLD1 or POLE mutation), AXIN2 associated polyposis and immune deficiency associated polyposis.
- Familial pancreatic cancer (caused by many potential germline mutations) is added.
- Criteria for serrated polyposis have been modified: either (1) ≥ 5 serrated lesions ≥ 5 mm in size proximal to the rectum, with at least 2 ≥ 10 mm, or (2) > 20 serrated lesions throughout the colorectum, with ≥ 5 proximal to the rectum.

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**Meet the Author**

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