Histological tumour type (Core)

Colorectal cancers should be typed according to the World Health Organization (WHO) Classification of Tumours of the Digestive System, 5th edition, 2019.[1] Almost all are adenocarcinomas. Most colorectal adenocarcinomas are of no specific type (not otherwise specified (NOS)) but some subtypes of adenocarcinoma are defined as follows:

Mucinous adenocarcinoma classification requires greater than 50% of the tumour to comprise pools of extracellular mucin containing malignant glands or individual tumour cells. Microsatellite instability is present in a higher proportion compared to adenocarcinoma NOS. Tumours with less than 50% mucinous content are described as having a mucinous component.

Signet-ring cell adenocarcinoma classification requires greater than 50% of the tumour to demonstrate single malignant cells with intracytoplasmic mucin, displacing and typically indenting the nuclei, imparting signet-ring cell morphology. Signet-ring cell carcinoma has stage-independent adverse prognostic significance relative to conventional adenocarcinoma.[2] There is a strong association with microsatellite instability and with Lynch syndrome.[3] Tumours with less than 50% signet-ring cell content are described as having a signet-ring cell component.

Medullary carcinoma is characterised by sheets of malignant cells with indistinct cell boundaries, vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm and prominent intratumoural lymphocytes and neutrophils. These tumours almost invariably demonstrate microsatellite instability and are associated with a good prognosis.[4]

Serrated adenocarcinoma shares morphological similarities with precursor serrated polyps, demonstrating glandular serrations, which are often slit-like, abundant eosinophilic or clear cytoplasm, minimal necrosis and sometimes areas of mucinous differentiation.[5]

Micropapillary adenocarcinoma is characterised by small, rounded clusters of tumour cells lying within stromal spaces mimicking vascular channels. At least 5% of the tumour should demonstrate this feature to classify as micropapillary adenocarcinoma. This pattern is most frequently encountered alongside adenocarcinoma NOS. There is a strong association with adverse pathological features including a high risk of lymph node metastatic disease.[6]

Adenoma-like adenocarcinoma is defined as an invasive adenocarcinoma in which at least 50% of the invasive tumour has an adenoma-like appearance with villous architecture, low grade cytology, a pushing growth pattern and minimal desmoplastic stromal reaction.[7] Diagnosis of adenocarcinoma on endoscopic biopsy is exceedingly difficult. This variant is associated with a good prognosis.

Neuroendocrine neoplasms are classified into neuroendocrine tumours (NETs), neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs).[1] NETs are graded 1-3 using the mitotic count and Ki-67 proliferation index. Pure NETs are not considered within the scope of this dataset. NECs show marked cytological atypia, brisk mitotic activity, and are subclassified into small cell and large cell subtypes. NECs are considered high-grade by definition. A Ki-67 proliferation index <55% is associated with better overall survival.[8] MiNENs are usually composed of a poorly differentiated NEC component and an adenocarcinoma component.

Other epithelial tumours rarely encountered include adenosquamous carcinoma, carcinoma with sarcomatoid components, undifferentiated carcinoma, squamous cell carcinoma and non-signet-ring cell poorly cohesive adenocarcinoma. Many of these are extremely rare.

References

1 Nagtegaal ID, Arends MJ, Odze RD and Lam AK (2019). Tumours of the colon and rectum. In: *Digestive System Tumours. WHO Classification of Tumours, 5th Edition*, Lokuhetty D, White V, Watanabe R and Cree IA (eds), IARC Press, Lyon, France.

2 Kang H, O'Connell JB, Maggard MA, Sack J and Ko CY (2005). A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. *Dis Colon Rectum* 48(6):1161-1168.

3 Kakar S, Deng G, Smyrk TC, Cun L, Sahai V and Kim YS (2012). Loss of heterozygosity, aberrant methylation, BRAF mutation and KRAS mutation in colorectal signet ring cell carcinoma. *Mod Pathol* 25(7):1040-1047.

4 Pyo JS, Sohn JH and Kang G (2016). Medullary carcinoma in the colorectum: a systematic review and meta-analysis. *Hum Pathol* 53:91-96.

5 Garcia-Solano J, Perez-Guillermo M, Conesa-Zamora P, Acosta-Ortega J, Trujillo-Santos J, Cerezuela-Fuentes P and Makinen MJ (2010). Clinicopathologic study of 85 colorectal serrated adenocarcinomas: further insights into the full recognition of a new subset of colorectal carcinoma. *Hum Pathol* 41(10):1359-1368.

6 Haupt B, Ro JY, Schwartz MR and Shen SS (2007). Colorectal adenocarcinoma with micropapillary pattern and its association with lymph node metastasis. *Mod Pathol* 20(7):729-733.

7 Gonzalez RS, Cates JM, Washington MK, Beauchamp RD, Coffey RJ and Shi C (2016). Adenoma-like adenocarcinoma: a subtype of colorectal carcinoma with good prognosis, deceptive appearance on biopsy and frequent KRAS mutation. *Histopathology* 68(2):183-190.

8 Milione M, Maisonneuve P, Spada F, Pellegrinelli A, Spaggiari P, Albarello L, Pisa E, Barberis M, Vanoli A, Buzzoni R, Pusceddu S, Concas L, Sessa F, Solcia E, Capella C, Fazio N and La Rosa S (2017). The Clinicopathologic Heterogeneity of Grade 3 Gastroenteropancreatic Neuroendocrine Neoplasms: Morphological Differentiation and Proliferation Identify Different Prognostic Categories. *Neuroendocrinology* 104(1):85-93.