International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Pathology of Colorectal Cancer

Mohamed El-arabi Abdallah El-attar, Wael Ibrahim Elshelfa, Joseph Rizk Israel and eslam G Abozaid

General Surgery & Surgical Oncology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Mohamed El-arabi Abdallah El-attar

Abstract:

Background: Colorectal cancer (CRC) is a heterogeneous and multifactorial malignancy resulting from complex interactions between environmental exposures, lifestyle factors, chronic inflammation, and genetic susceptibility. It develops through progressive accumulation of molecular alterations that transform normal colonic epithelium into invasive carcinoma. Multiple carcinogenic pathways have been identified, including chromosomal instability, microsatellite instability, and CpG island methylator phenotype, each associated with distinct clinicopathological features. Histologically, CRC exhibits diverse subtypes and grades that influence tumor behavior, prognosis, and response to therapy. In addition, pathological features such as lymphovascular invasion and perineural invasion play a critical role in tumor progression and metastatic potential. Obstructed colorectal cancer represents a more aggressive clinical entity, often associated with advanced stage, unfavorable pathological characteristics, and poorer outcomes. Understanding the pathological and molecular mechanisms of CRC is essential for accurate diagnosis, prognostic assessment, and guiding therapeutic strategies.

Keywords: Colorectal cancer, Pathology, Adenoma–carcinoma sequence, Microsatellite instability, Chromosomal instability, Histological types, Lymphovascular invasion, Perineural invasion, Tumor grading, TNM staging.

Introduction:

Colorectal cancer (CRC) is a multifactorial malignancy arising from complex interactions between environmental exposures, lifestyle factors, chronic inflammation, and inherited genetic susceptibility. The disease develops through progressive accumulation of genetic and epigenetic alterations that transform normal colonic epithelium into invasive adenocarcinoma **(Morgan et al., 2023).**

A. Environmental and Lifestyle Risk Factors

Dietary patterns play a significant role in colorectal carcinogenesis. High consumption of red and processed meats has been associated with increased CRC risk due to exposure to heterocyclic amines, N-nitroso compounds, and polycyclic aromatic hydrocarbons, which induce DNA damage and mutagenesis. Conversely, diets rich in fiber, fruits, and vegetables exert a protective effect by reducing transit time and modulating gut microbiota **(Dekker et al., 2019; Keum & Giovannucci, 2019).**

Obesity and metabolic syndrome are strongly associated with increased CRC incidence. Hyperinsulinemia and insulin-like growth factor-1 (IGF-1) signaling promote cellular proliferation and inhibit apoptosis. Chronic low-grade inflammation in obese individuals further contributes to genomic instability and tumor promotion **(Arnold et al., 2020; Sung et al., 2021).**

Cigarette smoking and heavy alcohol consumption are established risk factors. Tobacco carcinogens induce mutations in tumor suppressor genes, while alcohol metabolism produces acetaldehyde, a mutagenic compound that contributes to DNA damage and epigenetic alterations **(Morgan et al., 2023).**

B. Inflammatory Conditions

Chronic inflammatory bowel diseases (IBD), particularly ulcerative colitis and Crohn's disease, significantly increase CRC risk. Persistent mucosal inflammation generates reactive oxygen and nitrogen species, leading to DNA damage, epigenetic dysregulation, and accelerated epithelial turnover. Inflammation-associated CRC follows a distinct dysplasia–carcinoma sequence, often with early p53 mutations and less frequent APC mutations compared to sporadic CRC **(Ullman & Itzkowitz, 2018; Olén et al., 2020).**

C. Hereditary Syndromes

Approximately 5–10% of colorectal cancers arise from inherited syndromes characterized by germline mutations in tumor suppressor or DNA repair genes **(Dekker et al., 2019).**

1. **Familial adenomatous polyposis (FAP)** results from germline mutation in the APC gene, leading to constitutive activation of the Wnt/β-catenin pathway. Patients develop hundreds to thousands of adenomatous polyps with nearly 100% lifetime CRC risk if prophylactic colectomy is not performed **(Valle et al., 2019).**

2. **Lynch syndrome (hereditary nonpolyposis colorectal cancer)** is caused by germline mutations in mismatch repair (MMR) genes including MLH1, MSH2, MSH6, and PMS2. These tumors demonstrate microsatellite instability (MSI), are often right-sided, poorly differentiated, and frequently mucinous, with a strong lymphocytic infiltrate **(Lynch et al., 2015; Dekker et al., 2019).**

2. Molecular Pathogenesis of Colorectal Cancer:

Colorectal carcinogenesis is a multistep process involving accumulation of genetic and epigenetic alterations that confer growth advantage, resistance to apoptosis, and invasive potential. Three principal molecular pathways have been described: chromosomal instability **(CIN),** microsatellite instability **(MSI),** and CpG island methylator phenotype **(CIMP) (Sveen et al., 2020).**

A. The Adenoma–Carcinoma Sequence

The adenoma–carcinoma sequence is the classical model of colorectal carcinogenesis describing the stepwise transformation of normal colonic epithelium into invasive carcinoma through sequential genetic mutations. The process typically begins with inactivation of the APC tumor suppressor gene, leading to activation of the Wnt/β-catenin pathway and formation of early adenoma. Subsequent KRAS mutation promotes adenoma growth through activation of the RAS–MAPK signaling pathway. Loss of tumor suppressor genes such as SMAD2/SMAD4 impairs TGF-β–mediated growth inhibition, while late mutation of TP53 facilitates progression to invasive carcinoma. This pathway is strongly associated with chromosomal instability and is more common in left-sided colorectal cancers, which frequently present with annular growth and obstruction **(Dekker et al., 2019; Sveen et al., 2020).**

B. Chromosomal Instability (CIN) Pathway

The CIN pathway accounts for approximately 65–70% of CRC cases and is characterized by aneuploidy and chromosomal gains and losses. It typically involves APC mutation, KRAS activation, and TP53 inactivation **(Sveen et al., 2020).**

Clinically, CIN tumors are more frequently located in the left colon and tend to form circumferential constricting lesions with marked desmoplastic reaction. These features predispose to luminal narrowing and mechanical obstruction **(Dekker et al., 2019).**

C. Microsatellite Instability (MSI) Pathway

MSI results from deficiency in mismatch repair proteins, leading to accumulation of replication errors in microsatellite regions. MSI-high tumors account for approximately 15% of CRC cases **(Sveen et al., 2020).**

MSI tumors are typically right-sided, poorly differentiated, mucinous, and associated with prominent tumor-infiltrating lymphocytes. Despite poor differentiation, they often have a better prognosis and lower metastatic potential. Their growth pattern is frequently exophytic rather than circumferential, explaining a lower tendency for obstruction compared to CIN tumors **(Dekker et al., 2019; Morgan et al., 2023).**

D. CpG Island Methylator Phenotype (CIMP)

CIMP is characterized by widespread promoter hypermethylation leading to epigenetic silencing of tumor suppressor genes. It is frequently associated with BRAF mutation and overlaps with MSI tumors. CIMP-high tumors are more common in the right colon and often exhibit mucinous differentiation **(Sveen et al., 2020).**

F. BRAF Mutation

BRAF V600E mutation occurs in approximately 8–12% of CRCs and is commonly associated with MSI and CIMP-high tumors. It is linked to poor prognosis in metastatic disease and is more frequent in right-sided tumors **(Yaeger & Corcoran, 2019; Morgan et al., 2023).**

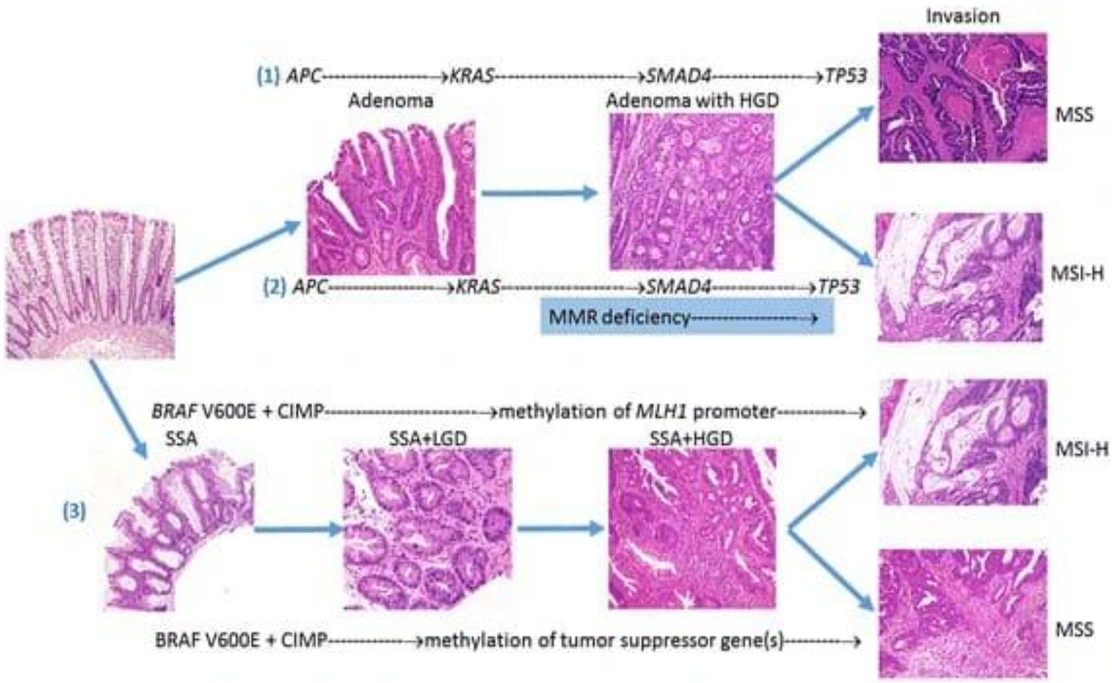

Figure 1: Molecular pathways in Colorectal Cancer **(Sveen et al., 2020).**

Gross Appearance

Colorectal cancers (CRC) exhibit diverse gross morphologies, which can influence both clinical presentation and risk of luminal obstruction. The tumors may appear as exophytic polypoid masses, ulcerating lesions, or circumferential strictures, depending on their anatomical location and growth pattern. Distal tumors, particularly in the rectosigmoid region, frequently present as annular "napkin-ring" constricting lesions, which are more likely to cause bowel obstruction. In contrast, tumors in the cecum and ascending colon often grow as polypoid or exophytic masses, allowing a larger luminal diameter and a lower likelihood of obstruction at the time of diagnosis.

Recent epidemiological studies confirm that tumor location significantly affects gross morphology and clinical outcomes, with obstructed tumors more commonly arising in the distal colon and rectum **(Lin et al., 2021; Wang et al., 2024).**

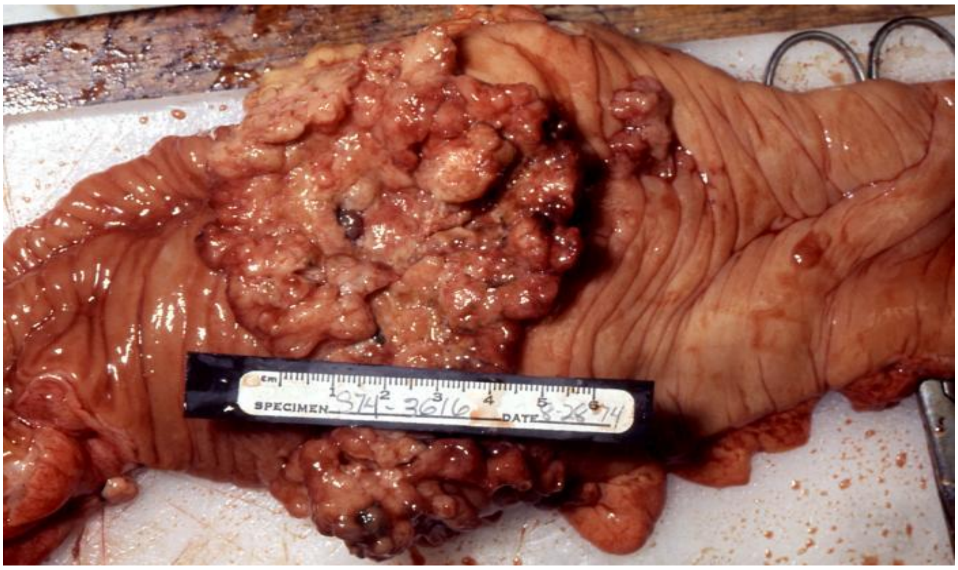

Figure 2: Gross surgical specimen showing an exophytic adenocarcinoma of the colon forming a polypoid, fungating mass protruding into the lumen**. (Ewing,Jr et al., 2021)**

Microscopic features

Histologic types of Colorectal Cancer

1- Conventional Adenocarcinoma (Adenocarcinoma, NOS):

Conventional adenocarcinoma, also known as adenocarcinoma not otherwise specified (NOS), represents approximately 85–90% of colorectal cancers. Microscopically, these tumors are characterized by infiltrating irregular glands lined by atypical columnar epithelial cells with enlarged hyperchromatic nuclei, nuclear stratification, loss of polarity, and increased mitotic activity. The tumor glands often exhibit architectural distortion with cribriform or fused glandular structures. A characteristic histological feature is "dirty necrosis," which consists of necrotic cellular debris and inflammatory cells within the glandular lumen. These tumors commonly arise from preexisting adenomatous polyps through the adenoma–carcinoma sequence and remain the most prevalent histological type encountered in colorectal malignancies **(Kumar et al., 2021).**

2- Mucinous Adenocarcinoma:

Mucinous adenocarcinoma is a distinct histological subtype accounting for approximately 10% of colorectal cancers. It is defined by the presence of extracellular mucin constituting more than 50% of the tumor volume. Histologically, large pools of mucin are seen in the tumor stroma with clusters or strips of malignant epithelial cells floating within the mucinous material. In some cases, tumor cells may exhibit signet-ring morphology due to intracellular mucin accumulation. Mucinous carcinomas are frequently associated with microsatellite instability (MSI) and mutations in genes such as KRAS and BRAF, and they often arise in the proximal colon. Clinically, these tumors tend to present at a more advanced stage and may demonstrate a different metastatic pattern compared with conventional adenocarcinoma **(Huang et al., 2021).**

3- Signet-Ring Cell Carcinoma:

Signet ring cell carcinoma is a rare but highly aggressive subtype, accounting for less than 1% of colorectal cancers. Histologically, the tumor is characterized by more than 50% signet-ring cells, which contain abundant intracytoplasmic mucin displacing the nucleus to the periphery, producing the characteristic signet-ring appearance. These tumors typically exhibit diffuse infiltration of the bowel wall with minimal gland formation and often spread extensively within the submucosa and muscularis propria. Clinically, signet ring cell carcinoma is associated with advanced stage at diagnosis, early peritoneal dissemination, and poor prognosis compared with conventional adenocarcinoma (**An et al., 2021).**

4- Medullary Carcinoma:

Medullary carcinoma is a rare histological variant characterized by solid sheets or nests of poorly differentiated tumor cells with vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. The tumor often demonstrates a syncytial growth pattern and is typically accompanied by prominent tumor-infiltrating lymphocytes, reflecting a strong host immune response. Medullary carcinoma is strongly associated with high levels of microsatellite instability (MSI-H) and is frequently seen in patients with Lynch syndrome. Despite its poor differentiation histologically, this tumor subtype paradoxically tends to have a relatively favorable prognosis compared with other poorly differentiated colorectal carcinomas **(Kumar et al., 2021).**

5- Serrated Adenocarcinoma

Serrated adenocarcinoma represents a distinct morphological subtype that arises from the serrated neoplasia pathway, which includes precursor lesions such as sessile serrated adenomas and traditional serrated adenomas. Histologically, these tumors display serrated or saw-tooth glandular architecture, similar to the morphology observed in serrated polyps. Tumor cells often show abundant eosinophilic cytoplasm and vesicular nuclei, and mucin production may also be present. Molecularly, serrated adenocarcinomas are frequently associated with BRAF mutations, CpG island methylator phenotype (CIMP), and microsatellite instability, indicating a carcinogenic pathway different from the classical adenoma–carcinoma sequence **(Kumar et al., 2021).**

6- Micropapillary Adenocarcinoma

Micropapillary adenocarcinoma is an uncommon but clinically important variant characterized by small clusters of tumor cells arranged in micropapillary structures within clear stromal spaces that mimic vascular channels. These clusters typically demonstrate reverse cell polarity, where the apical surface of tumor cells faces the surrounding stroma. This distinctive morphology is strongly associated with lymphovascular invasion, lymph node metastasis, and aggressive tumor behavior. Even when the micropapillary component represents only a small portion of the tumor, it may significantly influence the prognosis and clinical outcome **(Kumar et al., 2021).**

7- Adenosquamous Carcinoma

Adenosquamous carcinoma is a rare colorectal malignancy characterized by the presence of both glandular (adenocarcinoma) and squamous carcinoma components within the same tumor. Histologically, the adenocarcinoma component forms malignant glands similar to conventional colorectal adenocarcinoma, while the squamous component demonstrates keratinization, intercellular bridges, and squamous differentiation. These tumors are usually aggressive and associated with poor clinical prognosis compared with conventional adenocarcinoma **(Kumar et al., 2021).**

8- Undifferentiated Carcinoma

Undifferentiated carcinoma is a rare subtype characterized by lack of glandular or squamous differentiation. Microscopically, the tumor is composed of sheets of highly pleomorphic malignant cells with marked nuclear atypia and frequent mitotic figures. Because these tumors lack specific morphological features, immunohistochemical studies are often required to confirm epithelial origin. Undifferentiated colorectal carcinomas generally demonstrate highly aggressive biological behavior and poor prognosis **(Kumar et al., 2021).**

International Journal of Multiphysics
Volume 18, No. 3, 2024
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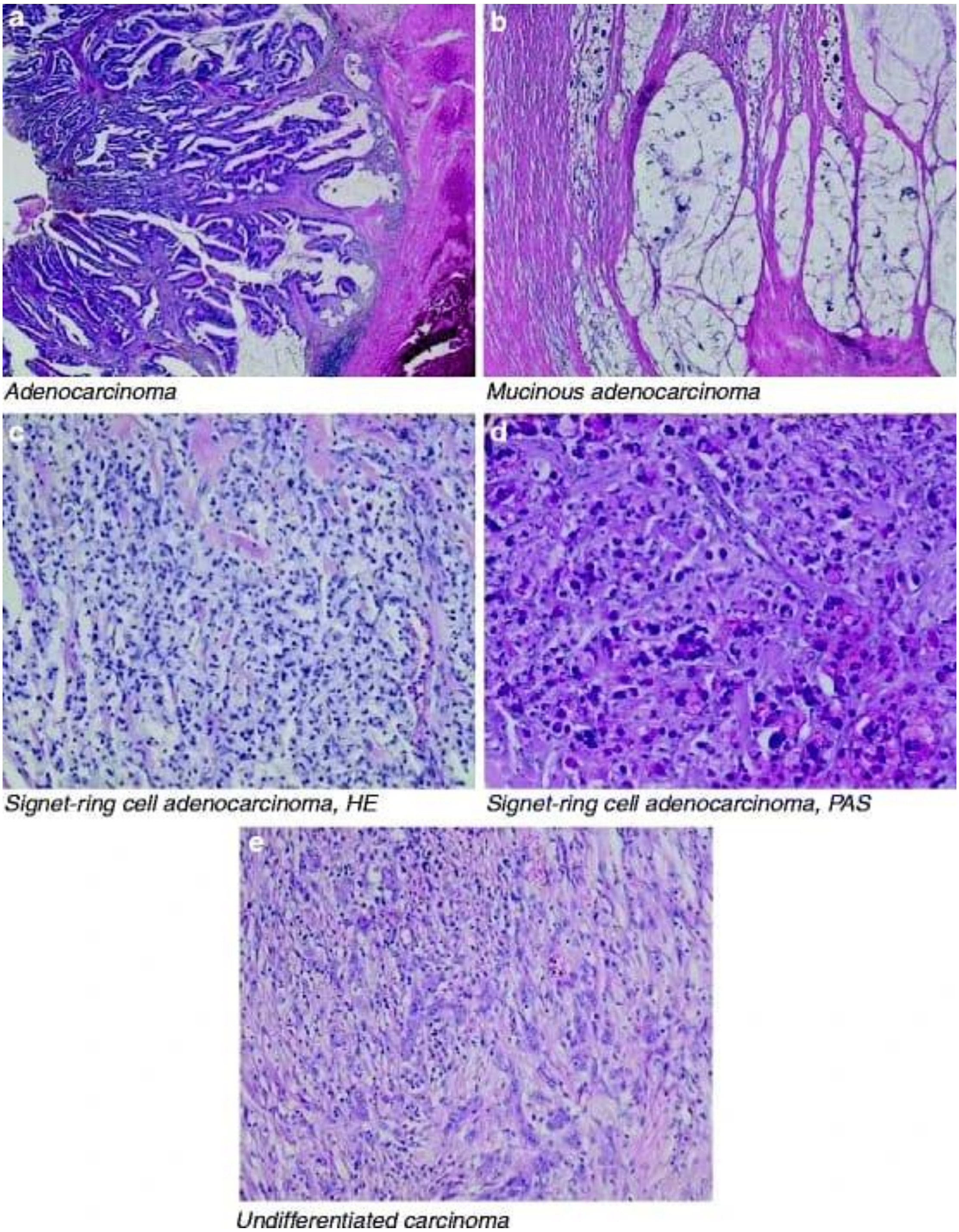

Figure 3: Histological types of Colorectal Carcinoma **(Kumar et al., 2021).**

Histological Grade

Histological grading of colorectal cancer (CRC) provides important prognostic information by assessing the degree of tumor differentiation. Tumors are typically classified as:

1- Well-differentiated (Grade 1):

Tumor cells closely resemble normal colonic epithelium and form well-defined glandular structures. These tumors usually exhibit slower growth and are less likely to cause luminal obstruction, especially in the proximal colon **(Wang et al., 2024).**

2- Moderately-differentiated (Grade 2):

Tumors show a mixture of well-formed glands and areas of less organized architecture. They represent the majority of CRCs and have intermediate aggressiveness and risk of obstruction.

3- Poorly-differentiated (Grade 3):

Tumor cells lose glandular architecture and display marked cytologic atypia. Poorly-differentiated tumors are often associated with high-grade histology, aggressive behavior, lymphovascular invasion, and an increased likelihood of causing obstruction, particularly in the distal colon and rectum **(Gulinac et al., 2024).**

4- Undifferentiated/Anaplastic (Grade 4, rare):

Tumor cells lack recognizable glandular structures and show extreme atypia. These are rare but highly aggressive tumors, frequently associated with poor prognosis and early presentation with obstruction **(Kumar et al., 2021).**

Histological grading is therefore a crucial component in predicting clinical outcomes and guiding surgical and adjuvant therapy decisions, especially in patients with obstructed colorectal cancer, where high-grade tumors are more commonly observed.

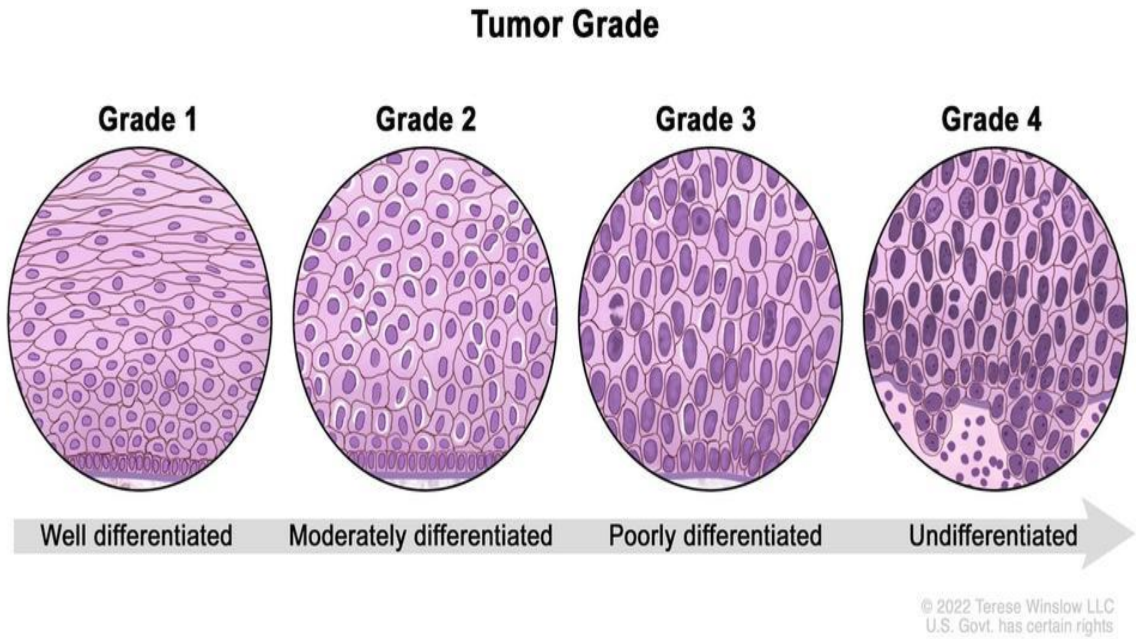

Figure 4: Tumor grade (Jones et al., 2022)

Staging of Colorectal Cancer

Tumor staging is a cornerstone in the management of colorectal cancer (CRC), as it provides critical information regarding tumor extent, guides therapeutic decision-making, and predicts prognosis. The most widely accepted staging system for colorectal cancer is the Tumor–Node–Metastasis (TNM) system, developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC).

TNM Staging of Colorectal Cancer (AJCC)

The Tumor–Node–Metastasis (TNM) staging system is an internationally accepted method for classifying the anatomical extent of colorectal cancer. It is based on evaluation of the primary tumor (T), regional lymph node involvement (N), and the presence of distant metastasis (M). Accurate TNM staging is essential for prognostic assessment, treatment planning, and standardized pathological reporting **(Amin et al., 2017)**

Primary Tumor (T)	
Tis	**Carcinoma in situ (intraepithelial or invasion of lamina propria)**
T1	**Tumor invades submucosa**
T2	**Tumor invades muscularis propria**
T3	**Tumor invades through muscularis propria into pericolorectal tissues**
T4a	**Tumor penetrates the visceral peritoneum**
T4b	**Tumor directly invades or adheres to adjacent organs or structures**
Regional Lymph Nodes (N)	
N0	**No regional lymph node metastasis**
N1a	**Metastasis in 1 regional lymph node**
N1b	**Metastasis in 2–3 regional lymph nodes**
N1c	**Tumor deposits in subserosa, mesentery, or non-peritonealized pericolic tissues without nodal metastasis**
N2a	**Metastasis in 4–6 regional lymph nodes**
N2b	**Metastasis in ≥7 regional lymph nodes**
Distant Metastasis (M)	
M0	**No distant metastasis**
M1a	**Metastasis confined to one distant organ or site (e.g., liver, lung)**
M1b	**Metastases in more than one distant organ or site**
M1c	**Metastasis to the peritoneal surface with or without other organ involvement**
Stage Grouping	
Stage	TNM Classification
Stage 0	**Tis N0 M0**
Stage I	**T1–T2 N0 M0**
Stage IIA	**T3 N0 M0**
Stage IIB	**T4a N0 M0**
Stage IIC	**T4b N0 M0**
Stage IIIA	**T1–T2 N1/N1c M0**
Stage IIIB	**T3–T4a N1/N1c M0**
Stage IIIC	**T4b N1/N2 M0 or any T N2 M0**
Stage IVA	**Any T Any N M1a**
Stage IVB	**Any T Any N M1b**
Stage IVC	**Any T Any N M1c**

Table 1 TNM staging system for colorectal carcinoma according to the American Joint Committee on Cancer (AJCC), 8th edition.

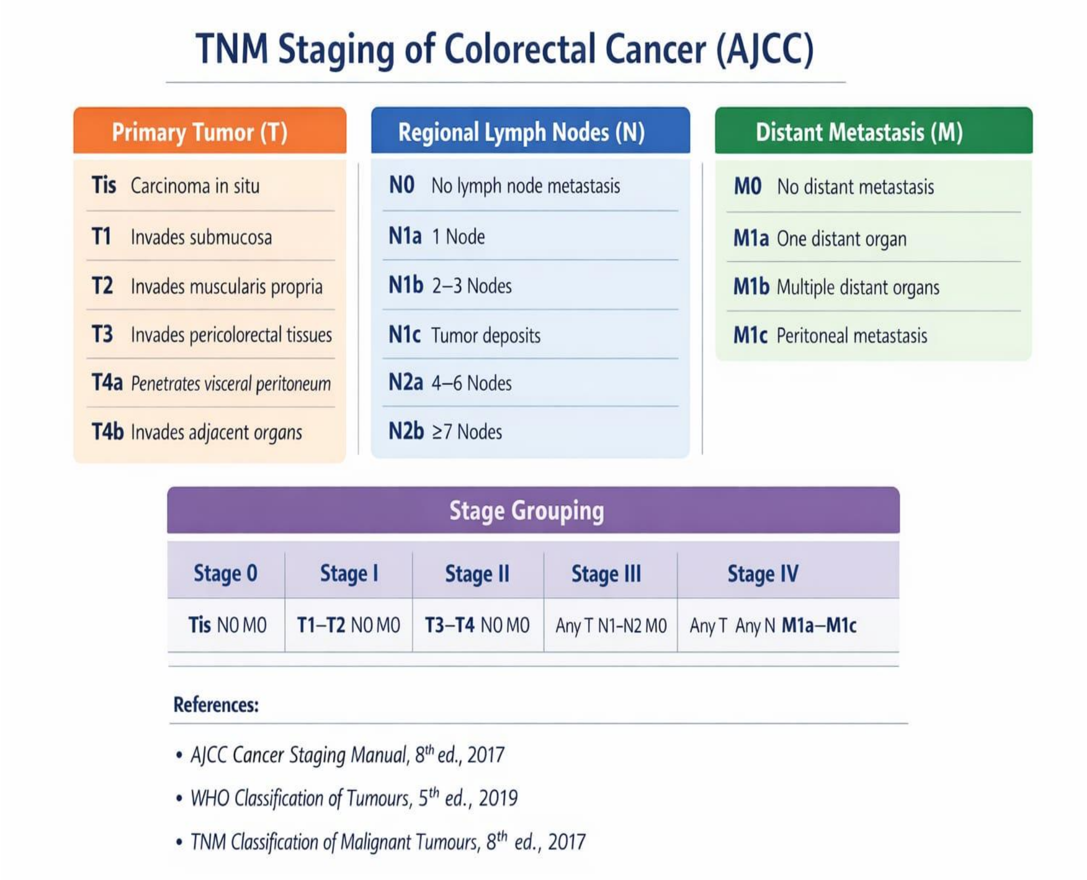

Figure 5: TNM staging of colorectal cancer (T, N, M) according to AJCC **(Amin et al., 2017)**

Perineural and Lymphovascular Invasion in Colorectal Cancer

A- Perineural Invasion (PNI)

Perineural invasion (PNI) is defined as the presence of tumor cells within any of the three layers of the nerve sheath (endoneurium, perineurium, or epineurium) or surrounding at least one-third of the nerve circumference. Microscopically, malignant cells may be seen tracking along nerve bundles, encasing nerve fibers, or infiltrating the perineural space. This pattern reflects a specific pathway of tumor spread distinct from lymphatic or hematogenous dissemination and represents an interaction between tumor cells and neural structures within the tumor microenvironment **(Knijn et al., 2016;. Nagtegaal et al., 2020).**

Perineural invasion is increasingly recognized as an independent adverse prognostic factor in colorectal cancer. Tumors exhibiting PNI have been associated with increased local recurrence, higher tumor stage, and decreased overall survival. The mechanism underlying this aggressive behavior is believed to involve molecular interactions between tumor cells and neural elements, including the production of neurotrophic factors that promote tumor cell migration along nerve sheaths. These interactions facilitate tumor spread beyond the primary site and may contribute to more aggressive disease progression **(Liebig et al., 2009; Knijn et al., 2016).**

Histologically, PNI may present in several forms, including intraneural invasion, where tumor cells penetrate the nerve fascicles, and perineural invasion, where malignant cells surround the nerve within the perineural space. In some cases, tumor cells may form concentric layers around nerves, producing a characteristic "targetoid" appearance. Identification of PNI may occasionally require careful examination of multiple tissue sections because the involved nerves may be small and scattered within the tumor stroma. The detection of PNI is therefore considered an important component of routine histopathological assessment in colorectal cancer specimens **(Nagtegaal et al., 2020).**

Clinically, the presence of perineural invasion is associated with more aggressive tumor biology, higher rates of local tumor recurrence, and poorer survival outcomes. Consequently, PNI is frequently included among the high-risk pathological features that guide postoperative management and the consideration of adjuvant therapy in patients with colorectal cancer. Reporting of PNI has therefore become a standard requirement in modern colorectal cancer pathology protocols, including those recommended by the World Health Organization and the College of American Pathologists **(Benson et al., 2021).**

B- Lymphovascular Invasion (LVI)

Lymphovascular invasion (LVI) refers to the presence of tumor cells within endothelial-lined lymphatic or blood vessels adjacent to or within the primary tumor. Microscopically, LVI is identified when clusters of malignant epithelial cells are seen within vascular spaces lined by endothelial cells, often accompanied by red blood cells in the lumen in the case of blood vessels. Retraction artifacts surrounding tumor glands may mimic vascular invasion; therefore, careful histopathological evaluation is required to confirm true invasion by identifying endothelial lining or using immunohistochemical stains such as CD31, CD34, or D2-40 to highlight vascular structures. LVI represents an important step in tumor dissemination because it allows malignant cells to spread through lymphatic channels to regional lymph nodes or through blood vessels to distant organs **(Nagtegaal et al., 2020).**

The presence of lymphovascular invasion is considered a significant adverse prognostic factor in colorectal cancer. Numerous studies have demonstrated that tumors exhibiting LVI have a significantly higher risk of regional lymph node metastasis and distant metastasis, particularly to the liver and lungs. Consequently, LVI is routinely evaluated and reported in pathology reports and is incorporated into clinical decision-making, especially in patients with stage II colorectal cancer where the presence of LVI may influence the decision to administer adjuvant chemotherapy **(Benson et al., 2021; Lugli et al., 2017).**

From a pathological perspective, LVI may be classified into lymphatic invasion and venous invasion, depending on the type of vascular channel involved. Lymphatic invasion typically involves thin-walled vessels without smooth muscle layers and is frequently associated with regional lymph node metastasis. In contrast, venous invasion involves thicker-walled vessels with smooth muscle layers and is more commonly associated with hematogenous spread, particularly hepatic metastases due to portal venous drainage of the colon. Extramural venous invasion (EMVI), defined as tumor invasion into veins beyond the muscularis propria, is especially important as it has been strongly correlated with poor prognosis and increased risk of distant metastasis **(Betge et al., 2012; Nagtegaal et al., 2020).**

Pathology of Obstructed Colon Cancer

Obstructed colon cancer represents a clinically significant subtype of colorectal cancer, often associated with delayed diagnosis, advanced local invasion, and worse prognosis compared to non-obstructed tumors. Obstruction occurs when the tumor lumen narrows sufficiently to impair passage of intestinal contents, leading to proximal bowel distension, ischemia, and mucosal compromise **(Matsuda et al., 2024).**

Gross Pathology

Macroscopically, obstructed tumors frequently present as exophytic, circumferential lesions, often termed “apple-core” or “napkin-ring” tumors, which encircle the bowel lumen. The stenotic nature of these tumors causes proximal dilation of the colon and occasionally small bowel. Obstructed tumors tend to be larger in size, more infiltrative, and located preferentially in the left colon, particularly the sigmoid and descending segments **(Sarela et al., 2023).**

Histopathological Features

Tumor Grade and Differentiation:

Obstructed tumors often exhibit poorly to moderately differentiated adenocarcinoma, with higher rates of mucinous or signet-ring subtypes compared to non-obstructed cancers. Poor differentiation is associated with increased invasiveness, higher risk of lymph node metastasis, and early hematogenous dissemination **(Zhang et al., 2024).**

Depth of Invasion (T-Stage):

The delayed presentation of obstructed tumors correlates with advanced T-stage, with frequent penetration into the muscularis propria, subserosa, or serosa. This extensive local invasion increases the likelihood of adjacent organ involvement and surgical complexity **(Van Cutsem et al., 2016).**

Lymph Node Involvement and Lymphovascular Invasion (LVI):

Obstructed tumors demonstrate higher rates of lymph node metastases, reflecting both tumor aggressiveness and prolonged intraluminal pressure that may promote lymphatic and vascular invasion. LVI is commonly observed in pathology specimens, serving as a predictor for distant metastasis and recurrence **(Boland & Goel, 2010).**

Perineural Invasion (PNI):

PNI is frequently reported in obstructed colon cancers and is associated with deeper local invasion, pain, and higher recurrence rates. The presence of PNI is an independent adverse prognostic factor and may influence decisions regarding adjuvant therapy **(Boland & Goel, 2010).**

Inflammatory Changes and Ischemic Damage:

Chronic obstruction leads to mucosal ulceration, crypt distortion, and focal ischemic necrosis. The proximal bowel may show marked dilation, edema, and congestion, sometimes with secondary bacterial overgrowth or microperforation. These changes complicate surgical resection and can increase postoperative morbidity **(Sarela et al., 2023).**

Molecular and Genetic Features

Obstructed colon cancers often exhibit molecular alterations associated with aggressive behavior, including:

High microsatellite instability (MSI-H) in a subset of cases, particularly in right-sided tumors.

KRAS, NRAS, and BRAF mutations, which may correlate with poor differentiation and chemoresistance.

p53 overexpression and loss of APC function, promoting uncontrolled proliferation and deeper invasion **(Boland & Goel, 2010).**

These molecular features may guide targeted therapy and prognostic stratification in patients presenting with obstruction.

Clinical Implications

The pathological characteristics of obstructed colon cancer directly influence clinical management. Advanced T-stage, LVI, PNI, and nodal metastases necessitate extended surgical resections and often adjuvant chemotherapy. Obstruction itself may require emergency surgery, sometimes with staged procedures such as proximal diversion or stenting prior to definitive colectomy. Recognizing the aggressive pathological features of obstructed tumors allows better preoperative planning and may improve long-term outcomes **(Van Cutsem et al., 2016).**

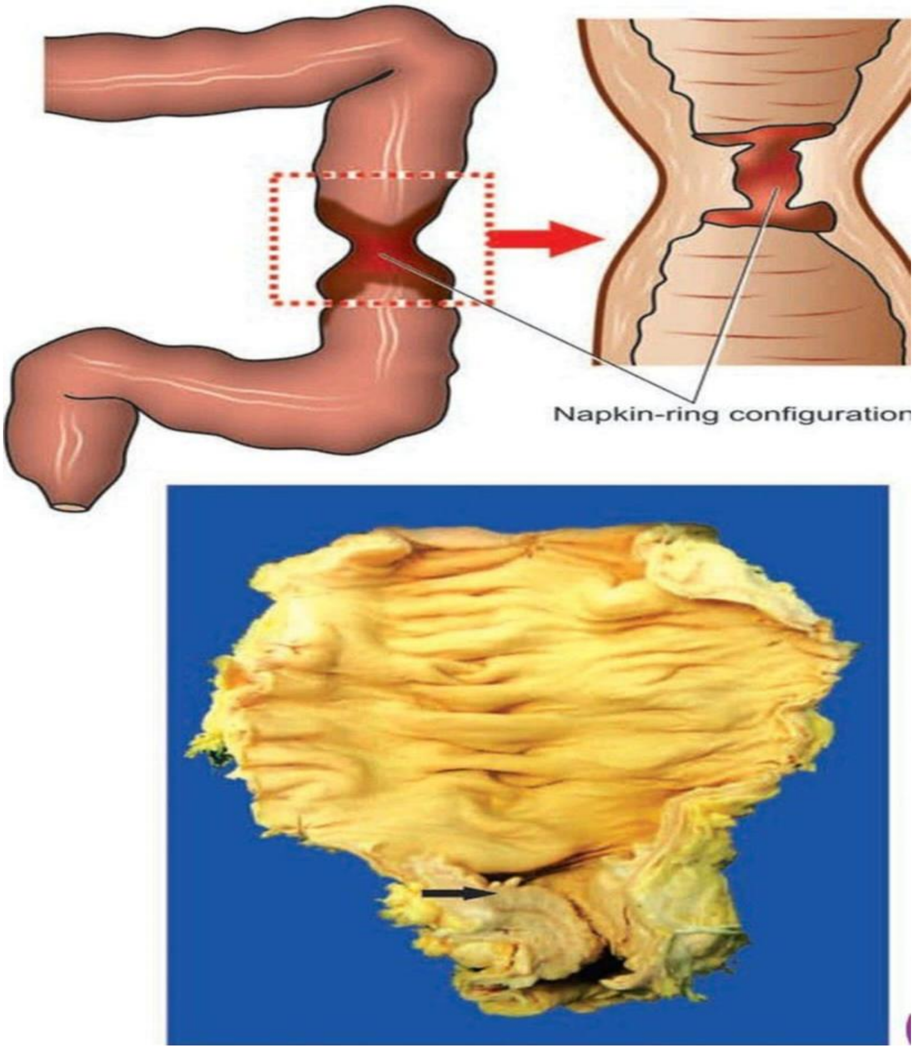

Figure 6: Gross appearance of a colorectal adenocarcinoma forming a napkin-ring, circumferential constricting lesion associated with luminal narrowing and may correlate with obstructive symptoms in colon cancer. **(Kumar, K et al,.2017)**

References:

1. Amin, M. B., Greene, F. L., Edge, S. B., Compton, C. C., Gershenwald, J. E., Brookland, R. K., ... & Winchester, D. P. (2017). The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA: a cancer journal for clinicians, 67(2), 93-99.
2. Kumar, V., Abbas, A. K., Fausto, N., & Aster, J. C. (2014). *Robbins and Cotran pathologic basis of disease, professional edition e-book*. Elsevier health sciences.
3. An, X., Zhao, J., Li, P., Wu, Z., & Meng, X. (2021). Clinicopathological features and prognosis of signet-ring cell carcinoma of the colon and rectum. Journal of Gastrointestinal Oncology, 12(2), 728–737. https://doi.org/10.21037/jgo-21-85
4. Arnold, M., Abnet, C. C., Neale, R. E., Vignat, J., Giovannucci, E. L., McGlynn, K. A., & Bray, F. (2020). Global burden of 5 major types of gastrointestinal cancer. Gastroenterology, 159(1), 335–349. https://doi.org/10.1053/j.gastro.2020.02.068
5. Benson, A. B., Venook, A. P., Al-Hawary, M. M., Arain, M. A., Chen, Y. J., Ciombor, K. K., Cohen, S., Cooper, H. S., Deming, D., Farkas, L., Garrido-Laguna, I., Grem, J. L., Gunn, A., Hecht, J. R., Hoffe, S., Hubbard, J., Hunt, S., Jeck, W., Johung, K. L., ... Darlow, S. D. (2021). Colon cancer, version

2.2021: NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network, 19(3), 329–359. https://doi.org/10.6004/jnccn.2021.0012

6. Betge, J., Pollheimer, M. J., Lindtner, R. A., Kornprat, P., Schlemmer, A., Rehak, P., Vieth, M., Hoefler, G., & Langner, C. (2012). Intramural and extramural vascular invasion in colorectal cancer: Prognostic significance and quality of pathology reporting. Cancer, 118(3), 628–638. https://doi.org/10.1002/cncr.26310
7. Boland, C. R., & Goel, A. (2010). Microsatellite instability in colorectal cancer. Gastroenterology, 138(6), 2073–2087. https://doi.org/10.1053/j.gastro.2009.12.064
8. Dekker, E., Tanis, P. J., Vleugels, J. L. A., Kasi, P. M., & Wallace, M. B. (2019). Colorectal cancer. The Lancet, 394(10207), 1467–1480. https://doi.org/10.1016/S0140-6736(19)32319-0
9. Gulinac, M., Yovchev, Y., Zashev, M., Kostov, G., & Hadzhiev, I. (2024). Histological grading in colorectal cancer. Pathology Research and Practice, 257, 155302. https://doi.org/10.1016/j.prp.2024.155302
10. Huang, A., Yang, Y., Shi, J. Y., Li, Y. K., Xu, J. X., Cheng, Y., & Gu, J. (2021). Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer. World Journal of Gastrointestinal Surgery, 13(12), 1567–1583. https://doi.org/10.4240/wjgs.v13.i12.1567
11. Keum, N., & Giovannucci, E. (2019). Global burden of colorectal cancer: Emerging trends, risk factors and prevention strategies. Nature Reviews Gastroenterology & Hepatology, 16(12), 713–732. https://doi.org/10.1038/s41575-019-0189-8
12. Knijn, N., Mogk, S. C., Teerenstra, S., Simmer, F., & Nagtegaal, I. D. (2016). Perineural invasion is a strong prognostic factor in colorectal cancer: A systematic review. American Journal of Surgical Pathology, 40(1), 103–112. https://doi.org/10.1097/PAS.0000000000000518
13. Liebig, C., Ayala, G., Wilks, J. A., Berger, D. H., & Albo, D. (2009). Perineural invasion in cancer: A systematic review of the literature and meta-analysis. Cancer, 115(15), 3379–3391. https://doi.org/10.1002/cncr.24396
14. Lin, J. S., Perdue, L. A., Henrikson, N. B., Bean, S. I., & Blasi, P. R. (2021). Screening for colorectal cancer: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA, 325(19), 1978–1998. https://doi.org/10.1001/jama.2021.4417
15. Lugli, A., Kirsch, R., Ajioka, Y., Bosman, F., Cathomas, G., Dawson, H., El Zimaity, H., Flejou, J. F., Hansen, T. P., Hartmann, A., Kakar, S., Langner, C., Nagtegaal, I., Puppa, G., Riddell, R., Shepherd, N., Swanson, P., Terris, B., Ueno, H., ... Quirke, P. (2017). Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Modern Pathology, 30(9), 1299–1311. https://doi.org/10.1038/modpathol.2017.46
16. Lynch, H. T., Snyder, C. L., Shaw, T. G., Heinen, C. D., & Hitchins, M. P. (2015). Milestones of Lynch syndrome: 1895–2015. Nature Reviews Cancer, 15(3), 181–194. https://doi.org/10.1038/nrc3878
17. Matsuda, A., Yamada, T., Takahashi, G., Matsumoto, S., Yokoyama, Y., Sonoda, H., ... & Yoshida, H. (2024). Significance of adjuvant chemotherapy for obstructive colorectal cancer after stent placement: a multicenter retrospective study. Anticancer Research, 44(6), 2737-2745.
18. **Valle, L., de Voer, R. M., Goldberg, Y., Sjursen, W., Försti, A., Ruiz-Ponte, C., ... & Hemminki, K. (2019).** Update on genetic predisposition to colorectal cancer and polyposis. *Molecular aspects of medicine*, *69*, 10-26.
19. **Ewing, J., Jr., et al. (2021).** *Ewing's Surgical Pathology* (16th ed.). Elsevier
20. Kumar, V., Abbas, A. K., & Aster, J. C. (2021). *Robbins & Cotran Pathologic Basis of Disease* (10th ed.). Elsevier.
21. **Kumar, V., Abbas, A. K., & Aster, J. C. (2021).** *Robbins & Cotran Pathologic Basis of Disease* (10th ed.). Elsevier.
22. **Kumar, V., Abbas, A. K., & Aster, J. C. (2021). *Robbins & Cotran Pathologic Basis of Disease* (10th ed.). Elsevier.**

23. **Jones, W., Tait, D., Livasy, C., Ganapathi, M., & Ganapathi, R. (2022).** PLK3 amplification and tumor immune microenvironment of metastatic tumors are linked to adjuvant treatment outcomes in uterine serous cancer. *NAR cancer*, *4*(3), zcac026.
24. **Sarela, A. I., Baker, C. R., & Halligan, S. (2023).** Colorectal cancer: Pathology and clinical features. In P. J. Gupta (Ed.), *Textbook of Surgical Oncology* (pp. 412–425).
25. **Zhang, L., Wang, Y., Liu, J., & Cheng, X. (2024).** Histopathological characteristics and molecular profiling of obstructive colorectal cancer: A multicenter comparative study. *World Journal of Gastrointestinal Oncology*, *16*(2), 145–158.
26. Morgan, E., Arnold, M., Gini, A., Lorenzoni, V., Cabasag, C. J., Laversanne, M., Vignat, J., Ferlay, J., Murphy, N., & Bray, F. (2023). Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN. Gut, 72(2), 338–344. https://doi.org/10.1136/gutjnl-2022-327736
27. Nagtegaal, I. D., Odze, R. D., Klimstra, D., Paradis, V., Rugge, M., Schirmacher, P., Washington, K. M., Carneiro, F., & Cree, I. A. (2020). The 2019 WHO classification of tumours of the digestive system. Histopathology, 76(2), 182–188. https://doi.org/10.1111/his.13975
28. Olén, O., Erichsen, R., Sachs, M. C., Pedersen, L., Halfvarson, J., Askling, J., Ekbom, A., Sorensen, H. T., & Ludvigsson, J. F. (2020). Colorectal cancer in Crohn's disease: A Scandinavian population-based cohort study. The Lancet Gastroenterology & Hepatology, 5(5), 475–484. https://doi.org/10.1016/S2468-1253(19)30423-1
29. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 71(3), 209–249. https://doi.org/10.3322/caac.21660
30. Sveen, A., Kopetz, S., & Lothe, R. A. (2020). Biomarker-guided therapy for colorectal cancer: Strength in complexity. Nature Reviews Clinical Oncology, 17(1), 11–32. https://doi.org/10.1038/s41571-019-0241-1
31. Ullman, T. A., & Itzkowitz, S. H. (2011). Intestinal inflammation and cancer. Gastroenterology, 140(6), 1807–1816. https://doi.org/10.1053/j.gastro.2011.01.057
32. Van Cutsem, E., Cervantes, A., Adam, R., Sobrero, A., Van Krieken, J. H., Aderka, D., Aguilar, E. A., Bardelli, A., Benson, A., Bodoky, G., Ciardiello, F., D'Hoore, A., Diaz-Rubio, E., Douillard, J. Y., Ducreux, M., Falcone, A., Grothey, A., Gruenberger, T., Haustermans, K., ... Arnold, D. (2016). ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of Oncology, 27(8), 1386–1422. https://doi.org/10.1093/annonc/mdw235
33. Wang, X., Wang, H., He, H., Lv, K., Yuan, W., Chen, J., & Yang, H. (2024). Clinicopathological and prognostic features of colorectal mucinous adenocarcinomas: A systematic review and meta-analysis. BMC Cancer, 24(1), 1161. https://doi.org/10.1186/s12885-024-12905-3
34. Yaeger, R., & Corcoran, R. B. (2019). Targeting alterations in the RAF-MEK pathway. Cancer Discovery, 9(3), 329–341. https://doi.org/10.1158/2159-8290.CD-18-1321