WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 5, 1525-1544. Review Article ISSN 2277–7105

A COMPREHENSIVE REVIEW ON TREATMENT OF TYPES OF COLORECTAL CANCER

Prashanth K.[1] and Hanumantharayappa B.[*2]

[1]Research Scholar, Department of Pharmacology, Mallige College of Pharmacy, Bangalore, Karnataka, India.

[2]Associate Professor, Department of Pharmacology, Mallige College of Pharmacy, Bangalore, Karnataka, India.

Article Received on
18 Jan. 2025,

Revised on 07 Feb. 2025,
Accepted on 27 Feb. 2025

DOI: 10.20959/wjpr20255-35830

***Corresponding Author**
Hanumantharayappa B.
Associate Professor, Department of Pharmacology, Mallige College of Pharmacy, Bangalore, Karnataka, India.

ABSTRACT

Colorectal cancer (CRC) is a major worldwide health issue, ranking as the third most common cancer and the second most common cause of cancer mortality. This paper provides an extensive review of CRC, with emphasis on its epidemiology, risk factors, classification, treatment options, and new therapies. The rising incidence among younger populations highlights the need for effective prevention strategies, including lifestyle modifications. Surgical intervention remains the cornerstone for resectable cases, while chemotherapy, radiation, and immunotherapy are pivotal for non-resectable cases, despite their limitations. The classification of CRC into various types, predominantly adenocarcinomas, informs treatment strategies. Mucinous colorectal adenocarcinomas present unique challenges, including lower responses to standard chemotherapy regimens. Furthermore, novel therapies such as targeted molecular treatments, immunotherapies, and nanoparticle drugs are explored, emphasizing their potential in enhancing patient outcomes. The paper also addresses less common variants of CRC, including adenosquamous and spindle cell carcinomas, highlighting their distinct clinical features and treatment approaches. Overall, this study underscores the complexity of CRC and the necessity for ongoing research to improve diagnostic and therapeutic strategies, ultimately aiming to reduce the burden of this multifaceted disease.

KEYWORDS: Colorectal cancer, Chemotherapy, CRC, Therapies.

INTRODUCTION

Colorectal cancer (CRC) is a multifaceted disease involving both the colon and rectum of the large intestine.[1,2] CRC is the third largest cancer globally (6.1%), behind lung cancer (11.6%), breast cancer (11.6%), and prostate cancer (7.1%). CRC is the second highest cause of death from all cancers, with 9.2% of incidence (9% male and 8% female).[3] By 2040, CRC-related mortality is expected to reach over 3.2 million annually, resulting in over 1.6 million deaths. According to U.S. cancer data, CRC incidence has decreased by 1.2%, despite a worldwide rise in incidence and death rates.[4] This rapid disease progression has an enormous financial effect on countries, necessitating significant public health spending from GDP.[5] Epidemiological studies show that the incidence of CRC among young people is continuously increasing.[6] The risk factors causing CRC include age, gender, genetics, environment, socioeconomic level, nutrition, tobacco use, smoking, and lifestyle.[7,8] A balanced diet and moderate physical activity would stop nearly fifty percent of CRC cases.[9]

Surgical removal is the primary treatment for resectable CRC, whereas chemotherapy, radiation, and immunotherapy are commonly used for non-resectable cases. However, these medicines have limitations, including non-specificity and cytotoxicity in healthy cells, which can cause secondary problems.[10] These therapies can be combined based on the stage and severity of CRC. Despite combinational therapy, almost 50% of individuals relapse into acquired multidrug resistance CRC[11] New treatments for colorectal cancer include immune check point inhibitors (ICIs), CAR T cell therapy, TCR modifications, and cytokine therapy. Recent studies on the usage of probiotics.[12] RNA-based therapeutics, including siRNA, miRNA, and RNA aptamers[13], oncolytic virus therapies[14], and herbal remedies[15], have shown encouraging outcomes for curing CRC.

Symptoms of CRC include altered bowel habits, constipation (or diarrhoea), rectal bleeding, abdominal discomfort, and unexplained weight loss. Early discovery and removal of polyps during a colonoscopy is crucial for diagnosing, treating, and improving the prognosis of colorectal cancer (CRC).[16] CRC includes two sectors: the right side (RCRC), which affects the ascending and transverse colon, and the left side (LCRC), which affects the descending and sigmoid colons, as well as the rectum.[17] Although RCRC is less common than LCRC, it is on the rise, particularly among women's.[17,18] Patients with RCRC often have histological characteristics caused by recurring inflammation and repair.[19,20]

Classification of CRC

The World Health Organization (WHO) classifies colorectal carcinomas into 5 categories: adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma, spindle cell carcinoma, and undifferentiated carcinoma.

Adenocarcinomas account for approximately 90% of all colorectal cancer cases.[19-22]

Benign adenomatous polyps frequently give birth to invasive (malignant) neoplasms, which are the precursors of adenocarcinomas. Histological grading of adenocarcinomas can be used to predict prognosis in conventional adenocarcinomas and is independent of staging.

While moderately differentiated adenocarcinomas, which make up the majority of cases at diagnosis, show 50% to 90% discernible gland development, well-differentiated adenocarcinomas (low grade) have many recognizable epithelial glands, making up more than 95% of the tumor. High-grade poorly differentiated adenocarcinomas exhibit gland development of less than 50%.[20]

Mucinous Colorectal Adenocarcinoma (MCA) is one of the distinctive subtypes of adenocarcinoma, the most common histologic subtype of colorectal cancer. It is characterized by numerous mucinous elements, which make up at least 50% of the tumor bulk.[23]

Clinical pathology reveals that MCA is more common in the proximal colon compared to the rectal or distal colon.[24-26]

MCA is distinguished from non-MCA by the presence of plentiful extracellular mucin. Light microscopy and MRI are frequently employed for the diagnosis of different subtypes of carcinoma.[27-28]

Patients with MCA need to receive regular colorectal adenocarcinoma treatment, since no specific clinical guidelines are available for such patients. MCA patients showed a poorer response to neoadjuvant and adjuvant treatment than non-MCA patients, most likely because of the histology.[29-31]

Chemotherapy regimens like FOLFOX-4, XELOX (capecitabine and oxaliplatin), and FOLFIRI (folinic acid, fluorouracil, and irinotecan) are usually employed for the treatment of MCA.[32]

Targeted molecular therapy

Bevacizumab and cetuximab are utilized routinely in the molecular targeted treatment of advanced colon cancer. Anti-EGFR antibody cetuximab is used commonly concomitantly with chemotherapy. Little has been reported on the prognosis of the cetuximab treatment of patients with wild-type KRAS mucinous and non-mucinous colon cancers. Chemotherapy and anti-EGFR antibody treatment improved outcomes for CRC patients with left-sided tumors, but did not significantly help those with right-sided tumors.[33]

Patients with right-sided MCA presented a median overall survival of 24.5 months with bevacizumab-chemotherapy versus 16.4 months with cetuximab chemotherapy. Adding bevacizumab to chemotherapy was shown in a statewide population-based study to result in a greater overall survival duration compared to palliative care alone among CRC patients presenting with peritoneal metastases.[34]

A woman patient with locally advanced MCA of the transverse colon had four months of palliative metronomic bevacizumab and capecitabine. She had extensive surgery, and the therapeutic objective shifted from palliation to cure. This research is justified in the administration of targeted molecular therapy for patients with MCA.

According to the limited evidence in the literature, targeted molecular therapy is reserved for stage IV metastatic CRC patients and not for postoperative stage I/II/III patients. Bevacizumab is recommended in patients with RAS mutations on the right side of the tumor. The left-sided tumours of MCA, bevacizumab should be prescribed as first-line treatment followed by cetuximab as second-line treatment. As third-line treatment, regorafenib should be utilized when the first two fail.

Bevacizumab could be a first-line treatment for CRC patients with peritoneal metastases. For the treatment of MCA tumors in the right colon in KRAS mutation patients, we suggest bevacizumab as the first line of treatment for MCA.[35]

Hot chemotherapy (HC)

HC is commonly used to eliminate microscopic illness, particularly malignancy spread via the peritoneum.Patients with MCA are more likely to have peritoneal metastases than those without, making HC an important therapy choice. In 2014, a proposal was made to standardize HC delivery for CRC patients.[36]

Early postoperative intraperitoneal chemotherapy (EPIC) with floxuridine, MMC, or 5-FU is also suggested. HC is suggested as a first-line treatment for MCA patients with peritoneal metastasis. But more studies on overall response rate and OS are necessary.[37]

Nanochain medicines

New treatments for mucinous adenocarcinoma are under exploration.[38-39] Mucus, a hydrogel matrix covering epithelial surfaces, serves as a protective barrier against external environment for underlying tissues. This may impede drug absorption and efficacy.[40]

The mucous layer contains pores between 100 nm and 200 nm. Nanoparticles alone are able to pass through the layers and access the target areas.[41]

Absorption of drugs is dependent on lipophilicity as well as solubility. Good solubility enables drugs to dissolve in body fluids, while good lipophilicity enables drugs to permeate biological membranes. Blending weakly water-soluble lipophilic drugs with cyclodextrins produces water-soluble, highly permeable complexes through lipophilic membranes.[42]

To improve drug oral bioavailability, consider coating nanoparticles with polymer molecules and using a carrier that can cleave mucosal glycoprotein substructures[38,43]

Nanodrug therapy for breast, pancreatic, and lung cancer typically involves albumin-bound paclitaxel. Although nanodrugs have shown promise in treating mucinous adenocarcinoma.[44]

Immunotherapy

PD-1 and its ligand, PD-L1, restrain T cell activation, inhibiting the immune response to tumor cells. Blocking the PD-1 or PD-L1 pathway has significantly enhanced therapeutic outcomes in cancers like melanoma, non-small-cell lung cancer, and renal cell carcinoma.[45] dMMR tumors exhibit high expression of checkpoint molecules like PD-1, PD-L1, CTLA-4, LAG-3, and IDO. They target and adjust the immune microenvironment through the inhibition of clearance of tumors.[46] MCA is associated with an increased frequency of MSI-H. Anti-PD-1 therapy has been reported to be effective in cancer patients with MMR/MSI-H tumors, with 31.3% having an objective response and 69% having disease control for 12 weeks or more.[46-48]

MCA is associated with a greater proportion of MSI-H, making a promising target for PD-1 inhibitor therapy, while accounting for only around 15% of all CRC cases.[49]

Combination therapy have improved clinical outcomes for CRC patients, however less data exists for mucinous colorectal cancer patients. 77% of dMMR/MSI-H CRC patients had decreased tumor burden at baseline, and 76% and 87% had 9-month PFS with NIVO monotherapy and NIVO combined with ipilimumab (IPI).[50]

MMR/MSI-H CRC patients were treated with NIVO and low-dose IPI as first-line treatment, which had a 60% objective response rate (ORR) and an 84% rate of disease control. This implies that the immunotherapy combination may be an effective first-line therapy for CRC patients.[51]

The initial trial of a PD-1 inhibitor plus VEGF blockade in MSI-H CRC had a 90% disease control rate and 30% ORR with ongoing follow-up. This suggests that anti-VEGF may enhance anticancer effectiveness in immune checkpoint inhibition.[52]

Adenosquamous carcinoma

Primary adenosquamous carcinoma (ASC) of the colon is an extremely rare condition, and only 0.06% of all colorectal cancers have this condition. It was previously established as a tumor with adenocarcinoma (AC) and squamous cell carcinoma (SCC) components. Symptoms are similar to colorectal ACs, and the diagnosis is made primarily based on histologic examination. Surgical resection remains the first line of treatment for colorectal ASC, and adenosquamous colon cancer prognosis is poorer compared to AC alone.[53-57]

ASC patients present with clinical symptoms and signs that are comparable to those of colon AC patients, including alteration in bowel habits, abdominal pain, hematochezia, weight loss, etc. Patients with ASC have been shown to be susceptible to paraneoplastic disorders such hypercalcemia.[58]

To diagnose primary colorectal Ad-SCC, other etiologies of epidermoid carcinoma of the large intestine should be excluded. The colorectal cancer should not be attached to the normal squamous epithelium, and no squamous cell carcinoma in other organs should be present that could influence the colon or rectum by local extension or metastasis.[59]

Surgical resection is the primary treatment for colorectal Ad-SCC, but the significance of adjuvant chemotherapy is unknown due to its rarity.[59-62]

Despite its usefulness in radiation therapy postoperative treatment for squamous cell carcinoma and Ad-SCC, its capability still awaits further maximization. The most common drugs used in adjuvant chemotherapy are semustine, 5-fluorouracil, carmustine, and methotrexate.

Adjuvant treatment for anorectal Ad-SCC according to the Nigro regimen involves the use of 5-fluorouracil and mitomycin combined with radiotherapy.

We do not know whether the treatment of rectal Ad-SCC is identical to epidermoid tumors of the anal canal. We utilized FOLFOX (5-FU, leucovorin, and oxaliplatin) as adjuvant chemotherapy medications to a complex-type Ad-SCC patient with adenocarcinoma component and advanced stage. The patient is still disease-free one year post-surgery.[59- 63] Akahoshi documented PD-L1 over expression in adenosquamous tissue and dMMR upregulation in adenosquamous carcinoma versus other cancers. This implies that adenosquamous cancer possesses a distinct pathogenesis and tumor microenvironment.[64] Hirsch documented that colorectal cancer patients with dMMR status respond to **immunotherapy**.[65] Existing studies reveal that immunotherapy and Pembrolizumab target colorectal cancer with dMMR status.[66-68] Immunotherapy trials are mostly composed of adenocarcinoma, but its extension to Ad-SCC is limited owing to the latter's rarity. Evert's documentation of pembrolizumab's efficacy in metastatic Ad-SCC offers promising therapy alternatives.[69]

Squamous cell carcinoma (SCC)

SCC of the rectum occurs in individuals from 39 to 93 years of age with a median of 57 years. It occurs more in women than in men, in 66% women and 34% men. Patients present with advanced disease (Duke's C or Stage III).[70]

SCC of the rectum patients has similar symptoms to adenocarcinoma. The most common symptoms include rectal bleeding, stomach pain, bowel habit alteration, and weight loss. Symptoms persist for weeks or months.[70-73]

Surgery is the primary treatment of rectal squamous cell carcinoma. Surgery is usually the most appropriate method for treating this disease since it is an aggressive malignancy and

diagnosed late. Even though there are no randomized trials of the optimal treatment of adenocarcinoma of the rectum, surgery has been used extensively.

Surgery

Tumor features, including size, site, depth of invasion, and metastasis, may influence surgical choices. Surgical technique is based on the patient's frame and co-occurring conditions.

Local excision can be used in certain stage T1 (mucosa or sub mucosa) malignancies or stage T2 (musculoskeletal system) cancers. T2 lesions should be observed closely due to their potential to recur in as high a proportion as 20% following local excision.[74]

Low-risk adenocarcinoma tumors are those with good histological differentiation and without endovascular or lymphatic invasion.[75,76] This is a demonstration of absence of metastatic or local disease on CT, MRI, or R-EUS[74] In 1985, Lafreniere et al treated and successfully managed a man who was 60 years of age with resection locally, radiation, and chemotherapy. Two years postdiagnosis, the patient was well and alive.[70]

Treatment for end-stage cancer may involve anterior low resection (LAR) or abdominoperineal resection (APR) depending upon the location of the tumour. LAR is able to remove tumors from the proximal two-thirds of rectum. Sparing the anus permits anastomosis of the descending colon to the distal rectum or anus with rectal continuity preserved. APR is reserved for advanced lesions of the rectum that are distant and localized where free disease margins cannot be obtained. APR enables removal of rectum and anus, with exploration of the abdomen for metastatic disease, before ostomy is created. APR is linked to increased post-operative complications and less long-term patient satisfaction.[77]

Chemoradiation therapy (CRT)

Various studies have assessed the effectiveness of CRT for the treatment of rectum squamous cell carcinoma, either in isolation or combined with surgery. Due to the rarity of the disease, no standard treatment is available at present.

CRT has also been employed as a main therapy in surgical high-risk patients on the basis of multiple case reports. Early reports yielded mean outcomes, with no notable increase in mortality or continuity of the bowel.[72,78-79]

Rasheed et al.[80] and Clark et al.[81] compared the effectiveness of CRT in treating rectum squamous cell carcinoma among two different populations.

As opposed to previous occurrences[72,78], these therapy regimens largely included 5-fluorouracil in combination with mitomycin-C or cisplatin. These drug combinations transformed therapy for anus squamous cell carcinoma.[82-85] At about the same period, the advantage of the combination of radiotherapy and chemotherapy was established, and thus CRT became the treatment of choice for anal squamous carcinoma.[86-90] Surgery was reserved for salvage therapy.[91]

According to this paradigm, CRT was used in the treatment of rectum squamous cell carcinoma. Rasheed and Clark treated 13 patients with CRT and performed only three surgical resections. Histopathological examination revealed that only one of the three resected tissues had residual tumor. In rectum squamous cell carcinoma patients, the optimal chemotherapy regimen combined with radiation is yet to be determined. Trials in cancer patients with anal canal cancer can provide useful extrapolations. An important prospective randomized trial compared cisplatin with mitomycin C in patients with anal cancer.[92]

Endoscopy

Endoscopy has not yet been discussed as a treatment method for rectal squamous cell carcinoma, perhaps due to its rarity. In 2000, Lee et al.[93] demonstrated that argon plasma coagulation (APC) was effective in the treatment of rectum squamous cell metaplasia. Squamous cell cancer of the rectum does not have any well-defined sequence of metaplasia-dysplasia-carcinoma. If analogous to colon adenocarcinoma, APC could be an effective and safe treatment for these tumours. Endoscopic mucosal resection (EMR) excises lesions by resecting the sub mucosa and mucosa.

It has been applied to excise superficial cancer lesions, particularly among inappropriate surgical candidates[94] EMR adenocarcinoma therapy was found to lessen the rate of recurrence and surgical need in appropriate groups.[91] This therapy could possibly eliminate rectal squamous cell carcinoma.

Spindle cell carcinoma

Spindle cell carcinoma (SpCC), also referred to as sarcomatoid carcinoma, is a relatively rare due to the fact that it possesses histologic, cytologic and molecular characteristics of both

epithelial and mesenchymal neoplasms.[95,96] It is heterogeneous in pathologic features, clinical course, and prognosis.[97-99] In the past, the lack of familiarity with the condition resulted in routine misdiagnoses. Progress in pathologic molecular techniques has enhanced the precision of SpCC diagnosis.[100] Previous reports have failed to define a uniform treatment for SpCC. SpCC treatment has been mixed in previous literature.[101,102] SpCC may be treated by surgery, with a spectrum varying from local removal to radical resection.[99,101,103]

Application of radiation or chemotherapy in treatment has been variable. Chemotherapy examples regimens used include doxorubicin, dacarbazine, ifosfamide and mensa. Radiotherapy was most commonly applied after surgery to treat typical cancer risk factors are unconfirmed surgical margins, poor pathologic differentiation, and advanced stage of tumor.[102,104,106]

Undifferentiated carcinoma

The undifferentiated carcinoma type is very rare. So far, only a few cases have been reported in studies. We present a case of undifferentiated colon cancer with invasion of the duodenum and metastasis to distant lymph nodes.[107-109]

Adenocarcinomas represent approximately 95% of all colorectal carcinomas, and signet ring cell carcinoma and undifferentiated carcinoma are rare. Undifferentiated carcinoma presents with distinctions from signet ring cell carcinoma and poorly differentiated adenocarcinoma in not developing gland formation and signet ring cells.[110]

Surgery

Primary Treatment: Surgery is the mainstay of treatment for localized undifferentiated cancer. This involves resection of the tumor with a margin of healthy tissue and related lymph nodes.

Advanced cases: In cases where the cancer has invaded adjacent structures or has metastasized, surgery can still be performed to relieve symptoms or to resect as much as is feasible, although complete resection may not be possible.

Chemotherapy

Adjuvant chemotherapy: After surgery, chemotherapy is often employed to eliminate any residual cancer cells. For patients at high risk, standard regimens used are FOLFOX (5-FU,

leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin).

Neoadjuvant chemotherapy: In the case of large or spread-out tumours, chemotherapy can be given prior to surgery to shrink it and ease removal.

Radiation Therapy

Although not generally employed as the initial treatment of colon cancer, radiation therapy is sometimes employed combined with chemotherapy if the disease has become locally advanced or if persistent tumours remain after surgery.

Targeted Therapy and Immunotherapy

Targeted treatment for advanced undifferentiated carcinoma can be considered based on specific genetic markers present in the tumor. Immunotherapy is also applied to treat tumors with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).[111]

CONCLUSION

Colorectal cancer (CRC) is a significant global health issue, ranking as the third most prevalent cancer worldwide. By 2040, CRC-related mortality is anticipated to surpass 3.2 million annually, necessitating substantial public health spending to address this growing burden. The incidence of CRC among young individuals is on the rise, with risk factors including age, gender, genetics, environment, and lifestyle. These trends highlight the importance of early detection and intervention strategies to mitigate the impact of this disease. Surgical removal remains the primary treatment for resectable CRC, while chemotherapy, radiation, and immunotherapy are common for non-resectable cases. The emergence of new treatments, such as immune checkpoint inhibitors, nanoparticle drugs, and targeted molecular therapies, holds promise for improving outcomes and expanding treatment options for patients with CRC.

The classification of CRC by the World Health Organization into various categories, including adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma, spindle cell carcinoma, and undifferentiated carcinoma, helps predict prognosis and guide personalized treatment decisions. Furthermore, the prevalence of mucinous colorectal adenocarcinoma presents unique challenges in treatment and prognosis, with targeted molecular therapies, hyperthermic intraperitoneal chemotherapy (HIPEC), and immunotherapy showing potential in managing this subtype. Additionally, adenosquamous carcinoma, squamous cell carcinoma, spindle cell carcinoma, and undifferentiated carcinoma

present distinct clinical characteristics and treatment considerations, emphasizing the need for personalized approaches. Overall, advancements in targeted molecular therapies, immunotherapy, and emerging nanoparticle drug strategies offer hope for improving outcomes in these challenging colorectal cancer subtypes.

REFERENCES

1. Vogelstein B, et al. Genetic alterations during colorectal-tumor development. N Engl J Med, 1988; 319(9): 525-32.
2. Morgan E, et al. Global burden of colorectal cancer in 2020 and 2040. Incidence and mortality estimates from globocan, 2023; 72: 338–344.
3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin, 2021; 71: 7-33.
4. Kusnik A, et al. Trends in Colorectal Cancer Mortality in the United States. Gastroenterol, 2023; 16: 217–225.
5. Schuell B, et al. Side effects during chemotherapy predicts tumour response in advanced colorectal cancer. Br J Cancer, 2005; 93: 744-748.
6. Sehgal M, et al. Colorectal cancer incidence after colonoscopy at ages 45-49 or 50-54 years. Gastroenterology, 2021; 160 (6): 2018—28.
7. Thanikachalam K, Khan G. Colorectal cancer and nutrition. Nutrients, 2019; 11(1): 164.
8. Botteri E, et.al; Smoking and colorectal cancer: a meta-analysis. JAMA, 2008; 300(23): 2765—2778.
9. Available: https://www.iarc.who.int/featured-news/colorectal-cancer-awareness-month-2022/. Accessed 23 Feb 2023.
10. Schuell B, et al. Side effects during chemotherapy predict tumour response in advanced colorectal cancer. Br J Cancer, 2005; 93: 744-748.
11. Zhou J, Ji Q, and Li Q. Resistance to anti-EGFR therapies in metastatic colorectal cancer: underlying mechanisms and reversal strategies. J Exp Clin Cancer Res, 2021; 40: 328.
12. Ding S, Hu C, Fang J, Liu G. The Protective Role of Probiotics against Colorectal Cancer. Oxid Med Cell Longev, 2020; 2020(1): 8884583.
13. Liu J, Guo B. RNA-based therapeutics for colorectal cancer: Updates and future directions. Pharmacol Res, 2020; 152: 104550.
14. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. Cancer Sci, 2016; 107: 1373-1379.
15. Rajamanickam S, Agarwal R. Natural products and colon cancer: current status and

future prospects. Drug Dev Res, 2008; 69: 460-471.

16. Pawlina W, Ross MH. Histology: A Text and Atlas with Correlated Cell and Molecular Biology. 8th ed. LWW; 2020; chap 17.
17. Lee GH, et al. Is right-sided colon cancer different to left-sided colorectal cancer? - A systematic review. Eur J Surg Oncol, 2015; 41(3): 300–308.
18. Fu X, Qiu Y, Zhang Y. Screening, management and surveillance for the sessile serrated adenomas/polyps. Int J Clin Exp Pathol, 2014; 7(4): 1275–1285.
19. Turner JR, Lingen MW. Oral cavities and gastrointestinal tract. In: Kumar V, Abbas AK, Aster JC, eds. Robbins Basic Pathology. 10th ed. Elsevier Saunders; 2018; chap 15.
20. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: pathologic aspects. J Gastrointest Oncol, 2012; 3 (3): 153–173.
21. Nagtegaal ID, et al. WHO Classification of Tumors Editorial Board. The 2019 WHO classification of tumors of the digestive system. Histopathology, 2020; 76(2): 182–188.
22. Cunningham J, Kantekure K, Saif MW. Medullary carcinoma of the colon: a case series and review of the literature. In Vivo, 2014; 28(3): 311–314.
23. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification tumours of the digestive system. 4th ed. Geneva: World Health Organization Classification of Tumours; 2010.
24. Leopoldo S, et al. Two subtypes of mucinous adenocarcinoma of the colorectum: clinicopathological and genetic features. Ann Surg Oncol, 2008; 15(5): 1429–39.
25. Hugen N, et al. Prognosis and value of adjuvant chemotherapy in stage III mucinous colorectal carcinoma. Ann Oncol, 2013; 24(11): 2819–24.
26. Lupinacci RM, et al. Prognostic implication of mucinous histology in resected colorectal cancer liver metastases. Surgery, 2014; 155(6): 1062–8.
27. Chand M, Yu S, Swift RI, Brown G. Mucinous carcinoma of the rectum: a distinct clinicopathological entity. Tech Coloproctol, 2014; 18(4): 335–44.
28. Kim MJ, et al. Accuracy in differentiation of mucinous and nonmucinous rectal carcinoma on MR imaging. J Comput Assist Tomogr, 2003; 27(1): 48–55
29. Maisano R, et al. Mucinous histology of colon cancer predicts poor outcomes with FOLFOX regimen in metastatic colon cancer. J Chemother, 2012; 24(4): 212–6.
30. Mc Cawley N, et al. Mucinous rectal adenocarcinoma is associated with a poor response to neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. Dis Colon Rectum, 2016; 59(12): 1200–8.
31. Oberholzer K, et al. Rectal cancer: assessment of response to neoadjuvant chemoradiation

by dynamic contrast-enhanced MRI. J Magn Reson Imaging, 2013; 38(1): 119–26.

32. Liu Z, et al. Comparison of FOLFOX and FOLFIRI adjuvant chemotherapy regimens in the treatment of colorectal mucinous adenocarcinoma. Chin J Colorec Dis., 2016; 5(02): 159–62.
33. Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol, 2017; 28(8): 1713–29.
34. Razenberg LG, van Gestel YR, Lemmens VE, de Hingh IH, Creemers GJ. Bevacizumab in addition to palliative chemotherapy for patients with peritoneal carcinomatosis of colorectal origin: a nationwide population- based study. Clin Colorect Cancer, 2016; 15(2): 41–6.
35. Vernmark K, et al. From palliative to curative treatment—stage IV mucinous adenocarcinoma, successfully treated with metronomic capecitabine in combination with Bevacizumab and surgery—a case report. BMC cancer, 2015; 15: 884.
36. Turaga K, et al. Consensus guidelines from The American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. Ann Surg Oncol, 2014; 21(5): 1501–5.
37. Kelly KJ. Management of appendix cancer. Clin Colon Rectal Surg, 2015; 28(4): 247–55.
38. Pereira de Sousa I, et al. Nanoparticles decorated with proteolytic enzymes, a promising strategy to overcome the mucus barrier. Eur J Pharm Biopharm, 2015; 97: 257–64.
39. Marxen E, Mosgaard MD, Pedersen AML, Jacobsen J. Mucin dispersions as a model for the oromucosal mucus layer in vitro and ex vivo buccal permeability studies of small molecules. Eur J Pharm Biopharm, 2017; 121: 121–8.
40. Sigurdsson HH, Kirch J, Lehr CM. Mucus as a barrier to lipophilic drugs. Int J Pharm, 2013; 453(1): 56–64.
41. Pearson JP, Chater PI, Wilcox MD. The properties of the mucus barrier, a unique gel–how can nanoparticles cross it? Ther Deliv, 2016; 7(4): 229–44.
42. Loftsson T. Drug permeation through biomembranes: cyclodextrins and the unstirred water layer. Pharmazie, 2012; 67(5): 363–70.
43. Cu Y, Saltzman WM. Drug delivery stealth particles give mucus the slip. Nat Mater, 2009; 8(1): 11–3.

44. Hugen N, Brown G, Glynne-Jones R, de Wilt JH, Nagtegaal ID. Advances in the care of patients with mucinous colorectal cancer. Nat Rev Clin Oncol, 2016; 13(6): 361–9.
45. Topalian SL, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med, 2012; 366(26): 2443–54.
46. Le DT, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med, 2015; 372(26): 2509–20.
47. Xiao Y, Freeman GJ. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov, 2015; 5(1): 16–8.
48. Overman MJ, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol, 2017; 18(9): 1182–91.
49. Kim JH, Park HE, Cho NY, Lee HS, Kang GH. Characterization of PD-L1-positive subsets of microsatellite-unstable colorectal cancers. Br J Cancer, 2016; 115(4): 490–6.
50. Overman MJ, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol, 2018; 36(8): 773–9.
51. Lenz HJ, et al. Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). Ann Oncol, 2018; 29: 8714.
52. Hochster HS, et al. Efficacy and safety of atezolizumab (atezo) and bevacizumab (bev) in a phase I study of microsatellite instability (MSI)-high metastatic colorectal cancer (mCRC). J Clin Oncol, 2017; 35: 673.
53. Frizelle FA, Hobday KS, Batts KP, et al. Adenosquamous and squamous carcinoma of the colon and upper rectum: a clinical and histopathologic study. Dis Colon Rectum, 2001; 44: 341-6.
54. Cagir B, Nagy MW, Topham A, et al. Adenosquamous carcinoma of the colon, rectum, and anus: epidemiology, distribution, and survival characteristics. Dis Colon Rectum, 1999; 42: 258-63.
55. G H. Ober heterologue cancroide. Beitr Pathol Anat, 1907; 41: 348-412.
56. Choi JW, Park HU. Adenosquamous carcinoma of the ascending colon: a case report and review of the literature. Ann Coloproctol, 2013; 29: 83-6.
57. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet, 2014; 383: 1490-502.

58. Chevinsky AH, Berelowitz M, Hoover HC Jr. Adenosquamous carcinoma of the colon presenting with hypercalcemia. Cancer, 1987; 60: 1111-6.
59. Schneider TA 2nd, Birkett DH, Vernava AM 3rd. Primary adenosquamous and squamous cell carcinoma of the colon and rectum. Int J Colorectal Dis, 1992; 7: 144-7.
60. Frizelle FA, Hobday KS, Batts KP, Nelson H. Adenosquamous and squamous carcinoma of the colon and upper rectum: a clinical and histopathologic study. Dis Colon Rectum, 2001; 44: 341-6.
61. Nozoe T, Anai H. Adenosquamous carcinoma of the sigmoid colon: report of a case. Surg Today, 2001; 31: 830-2.
62. Dong Y, Wang J, Ma H, Zhou H, Lu G, Zhou X. Primary adenosquamous carcinoma of the colon: report of five cases. Surg Today, 2009; 39: 619-23.
63. Petrelli NJ, Valle AA, Weber TK, Rodriguez-Bigas M. Adenosquamous carcinoma of the colon and rectum. Dis Colon Rectum, 1996; 39: 1265-8.
64. Akahoshi S, Yamamura K, Komohara Y, et al. A Case Report of Metachronous multiple adenosquamous carcinoma of the Colon over-expressing PD-L1 and a literature review. Anticancer Res, 2021; 41(11): 5847–54.
65. Hirsch D, et al. Clinical responses to PD-1 inhibition and their molecular characterization in six patients with mismatch repair-deficient metastatic cancer of the digestive system. Journal of Cancer Research and Clinical Oncology, 2021; 147: 263-73.
66. Le DT, Kim TW, Van Cutsem E, et al. Phase II open-label study of Pembrolizumab in Treatment-Refractory, microsatellite Instability–High/Mismatch repair–deficient metastatic colorectal Cancer: KEYNOTE-164. J Clin Oncol, 2020; 38(1): 11–9.
67. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with Nivolumab plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite instability–high metastatic colorectal Cancer. J Clin Oncol, 2018; 36(8): 773–9.
68. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med, 2020; 26(4): 566–76.
69. Evert K, Stiegler C, Schäfer C, et al. Successful pembrolizumab therapy in metastasized adenosquamous carcinoma of the colon. Pathol, 2019; 40(5): 540–5.
70. Lafreniere R, Ketcham AS. Primary squamous carcinoma of the rectum. Report of a case and review of the literature. Dis Colon Rectum, 1985; 28: 967-972.
71. Cabrera A, Pickren JW. Squamous metaplasia and squamous-cell carcinoma of the rectosigmoid. Dis Colon Rectum, 1967; 10: 288-297.

72. Vezeridis MP, Herrera LO, Lopez GE, Ledesma EJ, Mittleman A. Squamous-cell carcinoma of the colon and rectum. Dis Colon Rectum, 1983; 26: 188-191.
73. Audeau A, Han HW, Johnston MJ, Whitehead MW, Frizelle FA. Does human papilloma virus have a role in squamous cell carcinoma of the colon and upper rectum? Eur J Surg Oncol, 2002; 28: 657-660.
74. Townsend CM, Sabiston DC. Sabiston textbook of surgery: the biological basis of modern surgical practice. 17th ed. Philadelphia: Saunders, 2004.
75. Lee SD, Haggitt RC, Kimmey MB. Squamous metaplasia of the rectum after argon plasma coagulation. Gastrointest Endosc, 2000; 52: 683-685.
76. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M. AJCC Cancer Staging Manual. 6th edition. New York: Springer-Verlag, 2002: 421.
77. Bossema E, Stiggelbout A, Baas-Thijssen M, van de Velde C, Marijnen C. Patients' preferences for low rectal cancer surgery. Eur J Surg Oncol, 2008; 34: 42-48.
78. Martinez-Gonzalez MD, et al. Case report of primary squamous carcinoma of the rectum. Rev Invest Clin, 1996; 48: 453-456.
79. Juturi JV, Francis B, Koontz PW, Wilkes JD. Squamouscell carcinoma of the colon responsive to combination chemotherapy: report of two cases and review of the literature. Dis Colon Rectum, 1999; 42: 102-109.
80. Rasheed S, Yap T, Zia A, McDonald PJ, Glynne-Jones R. Chemo-radiotherapy: an alternative to surgery for squamous cell carcinoma of the rectum--report of six patients and literature review. Colorectal Dis, 2009; 11: 191-197.
81. Clark J, Cleator S, Goldin R, Lowdell C, Darzi A, Ziprin P. Treatment of primary rectal squamous cell carcinoma by primary chemoradiotherapy: should surgery still be considered a standard of care? Eur J Cancer, 2008; 44: 2340-2343.
82. Bartelink H, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol, 1997; 15: 2040-2049.
83. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-coordinating Committee on Cancer Research. Lancet, 1996; 348: 1049-1054.
84. Flam M, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and

of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol, 1996; 14: 2527-2539

85. Cummings BJ, Keane TJ, O'Sullivan B, Wong CS, Catton CN. Epidermoid anal cancer: treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin C. Int J Radiat Oncol Biol Phys, 1991; 21: 1115-1125.
86. Flam MS, John MJ, Mowry PA, Lovalvo LJ, Ramalho LD, Wade J. Definitive combined modality therapy of carcinoma of the anus. A report of 30 cases including results of salvage therapy in patients with residual disease. Dis Colon Rectum, 1987; 30: 495-502.
87. Nigro ND. An evaluation of combined therapy for squamous cell cancer of the anal canal. Dis Colon Rectum, 1984; 27: 763-766.
88. Sischy B, et al. Definitive irradiation and chemotherapy for radio sensitization in management of anal carcinoma: interim report on Radiation Therapy Oncology Group study no. 8314. J Natl Cancer Inst, 1989; 81: 850-856.
89. Tveit KM, et al. Primary treatment of carcinoma of the anus by combined radiotherapy and chemotherapy. Scand J Gastroenterol, 1989; 24: 1243-1247.
90. Zucali R, Doci R, Bombelli L. Combined chemotherapy-- radiotherapy of anal cancer. Int J Radiat Oncol Biol Phys, 1990; 19: 1221-1223.
91. Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG. Abeloff's clinical oncology. 4th ed. Philadelphia: Churchill Livingstone Elsevier, 2008; chap 77.
92. Ajani JA, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA, 2008; 299: 1914-1921.
93. Lee SD, Haggitt RC, Kimmey MB. Squamous metaplasia of the rectum after argon plasma coagulation. Gastrointest Endosc, 2000; 52: 683-685
94. Ahmad NA, Kochman ML, Ginsberg GG. Endoscopic ultrasound and endoscopic mucosal resection for rectal cancers and villous adenomas. Hematol Oncol Clin North Am, 2002; 16: 897-906
95. Battifora H. Spindle cell carcinoma: ultrastructural evidence of squamous origin and collagen production by the tumor cells. Cancer, 1976; 37: 2275-2282.
96. Gupta R, et al. Spindle cell carcinoma of head and neck: an immunohistochemical and molecular approach to its pathogenesis. J Clin Pathol, 2007; 60: 472-475.
97. Ung M, et al. Characteristics and clinical outcomes of sarcomatoid carcinoma of the lung. Clin Lung Cancer, 2016; 17: 391-397.

98. Malla M, Wang JF, Trepeta R, Feng A, Wang J. Sarcomatoid carcinoma of the urinary bladder. Clin Genitourin Cancer, 2016; 14: 366-372.
99. Chang NJ, et al. Sarcomatoid carcinoma in head and neck: a review of 30 years of experience—clinical outcomes and reconstructive results. Ann Plast Surg, 2013; 71: S1-S7.
100. Lee AH. Recent developments in the histological diagnosis of spindle cell carcinoma, fibromatosis and phyllodes tumour of the breast. Histopathology, 2008; 52: 45-57.
101. Ellis GL, Corio RL. Spindle cell carcinoma of the oral cavity. A clinicopathologic assessment of fifty-nine cases. Oral Surg Oral Med Oral Pathol, 1980; 50: 523-33.
102. Olsen KD, Lewis JE, Suman VJ. Spindle cell carcinoma of the larynx and hypopharynx. Otolaryngol Head Neck Surg, 1997; 116: 47-52.
103. Viswanathan S, et al. Sarcomatoid (spindle cell) carcinoma of the head and neck mucosal region: a clinicopathologic review of 103 cases from a tertiary referral cancer centre. Head Neck Pathol, 2010; 4: 265-275.
104. Kim JH, Leeper RD. Treatment of anaplastic giant and spindle cell carcinoma of the thyroid gland with combination Adriamycin and radiation therapy. A new approach. Cancer, 1983; 52: 954-957.
105. Sneige N, et al. Low-grade (fibromatosis-like) spindle cell carcinoma of the breast. Am J Surg Pathol, 2001; 25: 1009-1016.
106. Mainwaring MG, Poor C, Zander DS, Harman E. Complete remission of pulmonary spindle cell carcinoma after treatment with oral germanium sesquioxide. Chest, 2000; 117: 591-593.
107. Yasui O, Tsukamoto F, Kudo K. Small cell undifferentiated carcinoma of the ascending colon with rapid enlargement after resection: report of a case and review of the literature. Tohoku J Exp Med, 2006; 209: 361-367.
108. Matsuda A, Sasajima K, Matsutani T, et al. Aggressive undifferentiated colon carcinoma producing granulocytecolony stimulating factor: report of a case. Surg Today, 2009; 39: 990-993.
109. Ashitomi Y, Yano M, Kono M, et al. undifferentiated carcinoma of the transverse colon with rhabdoid features that developed during treatment of non-small cell lung carcinoma with pembrolizumab: a case report. Surg Case Rep, 2020; 6: 196.
110. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. International Agency for Research on Cancer, 2010; 417.
111. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights: colon

cancer, version 2.2018. J Natl Compr Canc Netw, 2018; 16: 359-369.