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Review Article

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Progressive and Focused Chemotherapy Approaches for Metastatic Colorectal Cancer

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ABSTRACT
Colorectal cancer is a widespread malignant tumour, ranking as the third most frequently diagnosed cancer and the second primary cause of death worldwide. Surgery or surgery along with radiotherapy and or chemotherapy for individuals with metastatic CRC (mCRC) were considered the main treatment methods until the early 2000s, when targeted therapies like cetuximab and bevacizumab came into play. The use of targeted treatments in healthcare environments has significantly improved patient survival rates. Up to now, the advancement of different kinds of targeted treatments has opened up new prospects and revealed new options for managing mCRC. Therapeutic strategies are continually updated to determine the most suitable targeted drugs informed by the results of current clinical studies. Despite advancements in these therapies, resistance remains a significant challenge, often leading to treatment failure, reduced progression-free survival, and cancer recurrence. Resistance mechanisms in CRC are intricate, involving genetic alterations, epigenetic changes, tumour heterogeneity, and the tumour microenvironment. Moreover, a considerable number of patients face relapses following these therapies. Consequently, it is crucial to explore more efficient treatment alternatives for CRC patients. Immunotherapy, an emerging field in oncology, represents a novel treatment approach that harnesses the body's immune system to combat cancer cells. The primary advantage of immunotherapy is its capacity to target cancer cells directly while limiting damage to healthy cells. Its recent application as a neoadjuvant therapy shows significant potential to transform the treatment landscape for both primary and metastatic CRC. Immune-modulation strategies have emerged as a promising new therapy to reduce this recurrence rate while minimizing undesirable systemic side effects. This review examines the microenvironment and the immunosuppressive conditions of tumour progression. It highlights the latest research advances in immunotherapy for colorectal metastasis and acknowledges immunotherapy as a promising treatment option with a hopeful future in clinical practice.

Keywords: Targeted Therapies, Immunotherapy, Metastatic CRC, Immune-Modulation, Neo-Adjuvant Therapy.

Introduction

Colorectal cancer (CRC) develops in the colon, a five-foot part of the large intestine, or in the rectum. Colon cancer and rectal cancer begin similarly and have numerous shared risk factors and symptoms. The two are commonly mentioned together as colorectal cancer. However, there are notable distinctions between them [1].

Colorectal cancer is a prevalent malignant tumour that is third in occurrence and second in death rates globally, with surgery alongside chemotherapy and radiotherapy being the primary treatment method. Due to the severe side effects of radiotherapy and low survival rates, it is expected that additional alternatives may arise [2]. Immunotherapy, an innovative treatment, has advanced significantly in colorectal cancer in recent years, surpassing targeted therapies, which offer greater specificity and improved survival rates compared to chemoradiotherapy. Among these, immune checkpoint inhibitor therapy has become the leading immunotherapy for colorectal cancer today [3].

Colorectal cancer development involves genetic and epigenetic changes that convert normal cells into cancerous ones. A feature of CRC is significant inter- and intra-tumour diversity on both clinical and molecular levels. Intra-tumour variability pertains to alterations in specific areas of a tumour, whereas temporal heterogeneity involves variations seen over time between the primary tumour and its corresponding metastases [4]. Chromosomal instability, microsatellite instability, abnormal DNA methylation, and defective DNA repair are mechanisms that cause genetic variability in tumours during the transformation of colorectal epithelial cells, which in turn affect patient prognosis and response to targeted therapies. In the age of personalized biological treatment, accurate molecular profiling of the tumour is essential for determining the treatment strategy [5]. As a result, the recognition and standardization of molecular biomarkers

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for cancer prognosis and prediction is becoming ever more significant. This document presents an overview of the validated and potential molecular biomarkers presently accessible for CRC. We aim to illuminate the molecular foundations of CRC development and advancement, its epidemiology, and key approved treatment protocols in an effort to comprehend the significance of molecular biomarkers in CRC management [6].

Colon cancer that hasn't metastasized to distant areas of the body is typically addressed through surgery, when possible. If surgery is conducted, physicians assess if the patient requires further therapies such as chemotherapy. In this examination, we compile bibliographic references to analyse, interpret, and assess the existing data critically. Prior to improvements in treatment and cancer detection, individuals with locally advanced CRC (high risk stage II and stage III tumours) and metastatic CRC (mCRC) received surgical intervention followed by postoperative (adjuvant) chemotherapy [7].

Cytotoxic chemotherapy continues to be the primary treatment approach for mCRC. Fluoro pyrimidines serve a crucial function as the foundation of combination therapies. Chemotherapy regimens like FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), or FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan), along with or without targeted therapies (anti-epidermal growth factor receptor [EGFR] antibody or anti-vascular endothelial growth factor [VEGF] antibody), are regarded as the primary treatment for mCRC [8]. When chemotherapy is administered, the physician must provide the patient with comprehensive information regarding side effects, as their intensity varies based on several factors, including the type of cytotoxic medications utilized and the length of the treatment. The medications focus on the molecules that play a role in tumour development and their associated signalling pathways in cancer cells, distinguishing them from regular cells [9]. Moreover, the tumour microenvironment, which encompasses blood vessels in the area surrounding the tumour and immune cells, is also influenced by these targeted medications to hinder tumour growth and enhance antitumor immune monitoring and response. The primary categories of targeted medications include monoclonal antibodies and small molecule inhibitors. These medications are beneficial because, in contrast to chemotherapy, they can be selected according to the molecular traits of tumour types [10].

Colorectal Cancer: A Summary

Approximately 75% of CRC cases are sporadic, while roughly 10% are inherited; the other 10-20% are familial cases, characterized by a family group of CRC patients where the genetic cause of occurrence is still uncertain. Typically, this cohort of patients, where the condition is likely linked to low-penetrance DNA variants, exhibits non-Mendelian inheritance and significant phenotypic diversity [11]. CRC initiation and advancement are distinguished by the recognized adenoma-carcinoma sequence. Colorectal carcinogenesis is a highly heterogeneous process characterized by the accumulation of somatic molecular mutations, influenced by several factors such as exposure to intestinal pathogens and the immune response of the host.

It is believed that solely cancer stem cells can initiate neoplastic transformation and facilitate tumour progression [12]. Colorectal mucosa epithelial cells are arranged along the crypt-villus axis. At the bottom of the crypt reside the colon stem cells, which are the less specialized cells capable of self-renewal and pluripotency. A cancer stem cell is produced in these cells by an oncogenic trigger, leading to the development of cancer [13]. A cancer does not arise from an oncogenic hit in a trans-amplifying differentiated cell. Nonetheless, various factors, such as microenvironmental influences, may trigger cell de-differentiation, leading to the formation of stem-like cells from trans-amplifying cells. A cancer-causing alteration in these stem-like cells might also lead to neoplastic change [14].

The epithelial-to-mesenchymal transition (EMT) is a biological process characteristic of epithelial cells, during which they shed their epithelial traits and gain mesenchymal properties, including mobility, resistance to apoptosis, self-renewal ability, and all the attributes of stem cells. Mesenchymal cancer cells can modify the components of the basement membrane and the extracellular matrix, thus initiating a metastatic process [15]. These results indicated that EMT is a process that produces a reservoir of stem-like cells facilitating cancer advancement, and signifies a universal biological mechanism that may serve as a target for treatment strategies. In the end, it is the joint impact of EMT and mesenchymal–epithelial transition (MET) that facilitates the metastatic advancement of CRC: EMT allows the primary tumour to escape and disseminate through mesenchymal intermediates, while MET reinstates the highly-proliferative epithelial stem cell phenotype of CRC (Figure 1). Evaluating whether genes associated with EMT and cell plasticity could act as molecular markers for CRC monitoring and early identification of metastatic disease would be intriguing [16].

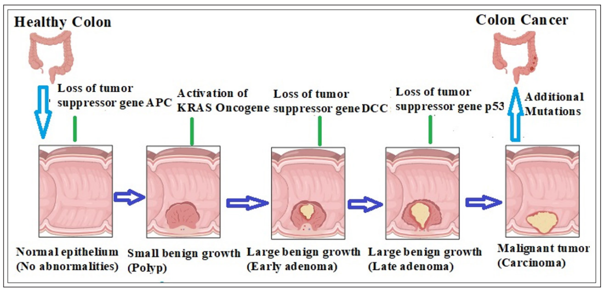

Figure 1: Multi -Hit Model of Colorectal Cancer

Macrophages and Colorectal Cancer Crosstalk Via CCL18

The tumour microenvironment (TME) consists of various cell types, including cancer cells, immune cells, and numerous molecules like cytokines, chemokines, and metabolites. Interactions between cancer cells and stromal cells play a crucial role in the malignant transformation and progression of cancer [17]. Peripheral monocytes migrate into tumours, receive signals from the TME, and differentiate into classically activated type 1 (M1) macrophages or alternatively activated type 2 (M2) macrophages. Tumour-associated macrophages (TAMs) consist of M1 and M2 types; M2 TAMs consistently promote angiogenesis, matrix degradation, and cancer cell migration, all of which are essential components for cancer metastasis [18]. Consequently, macrophages serve as an important therapeutic target for cancer. Cancer cells and TAMs possess unique and/

or shared secretions and metabolites, which collectively reprogram both sides. Cancer cells release VEGF or CCL2 to attract monocytes to tumours. In another regard, cancer cells and TAMs vie for vital nutrients necessary for survival, while lactic acid generated by cancer cells promotes the polarization of M2 TAMs [19].

Chemokine (C-C motif) ligand 18 (CCL18), part of the CC chemokine family, is mainly generated by M2 tumour-associated macrophages. Overexpression of CCL18 is seen in breast cancer, ovarian cancer, and glioma, among others, indicating a poor prognosis. Experiments conducted in vitro and in vivo suggest that CCL18 derived from M2 TAMs enhances metastasis in breast carcinoma and pancreatic ductal adenocarcinoma. CCL18 is a chemokine unique to primates, generated by both macrophages and dendritic cells [20]. This chemokine exhibits both constitutive and inducible expression levels. It is primarily linked to a tolerogenic reaction and plays a role in preserving immune system homeostasis during physiological states. Recently, CCL18 has been recognized as a crucial element of the intricate chemokine system associated with tumour biology (Figure 2). This chemokine promotes the differentiation and recruitment of T regulatory cells to the tumour environment, leading to the activation of a pro-tumour (M2-like) macrophage phenotype [21]. CCL18 is directly implicated in cancer cell invasion, migration, stimulation of epithelial-to-mesenchymal transition, and angiogenesis, highlighting its significant role in advancing cancer progression. Notably, this chemokine shows significant expression in tumour tissues, especially at the invasive front in later stages of colorectal cancer, with elevated levels found in patient serum, which correlates with a worse prognosis [22].

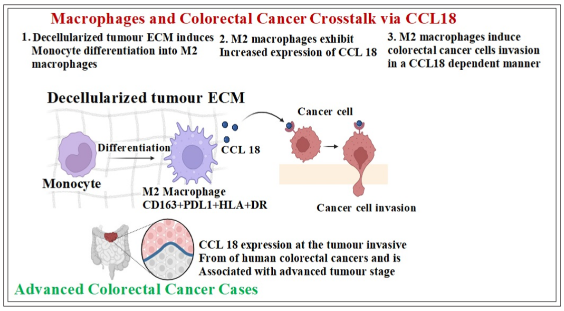

Figure 2: Colorectal Cancer Proliferation in Advance Phases

Pattern Typing of CRC Mutations

The immune system removes highly immunogenic cancer cells from the body. Tumour cells consistently experience somatic mutations and passively choose low-immunogenic variants to thrive in reaction to assessments of antitumor effects. The classification of the MMR/MSI system has played a crucial role in colorectal cancer treatment. Sixteen percent of CRCs exhibit hypermutation, with 75% linked to MSI-H and 25% possessing mutations in somatic mismatch repair genes and polymerase E (pole) [23]. MMR functions as a sophisticated enzyme proofreading mechanism during DNA replication, fixing mismatches in nucleotide pairing and moving between the two DNA strands. However, an insertion or deletion mutation during DNA replication cannot be fixed if the MMR system is defective. A truncated non-functional protein fragment, MSI, is ultimately produced due to a germ-line mutation in one of the MMR system genes (MLH1, MSH2, MSH6, PMS2, or TACSTD1/EpCAM), or hypermethylation of the MLH1 promoter [24]. The genome contains numerous microsatellite sequences that vary among individuals but are particular to the tissues of each person. To preserve genomic stability, mismatch repair (MMR) accurately detects and fixes base mismatches, small base deletions, and insertions that occur during DNA replication or recombination. MMR is categorized into distinct types: deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR) pMMR denotes typical MMR expression [25]. dMMR indicates mutations in genes that play a role in MMR repair, resulting in dysfunction in gene activity and diminished or absent MMR repair capability. MSI is a mutation characterized by code-shifting due to the insertion or deletion of repetitive elements in the microsatellites of tumour cells. pMMR presents as low-frequency microsatellite instability (MSI-L) or microsatellite stability (MS-S), while dMMR appears as high-frequency microsatellite instability (MSI-H). MSI plays a vital role in the advancement of CRC (Figure 3). The primary way CRC can integrate with MSI is by methylating and inactivating the hMLH1 promoter, leading to errors in mismatch repair among certified identity management professionals [26].

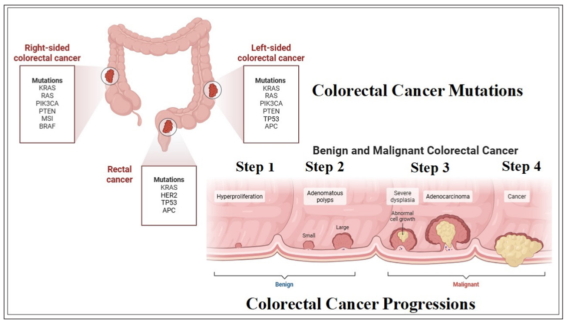

Figure 3: Colorectal Cancer Progression and Mutation

Prevention of Colorectal Cancer

Cancer prevention involves measures taken to reduce the risk of developing cancer. By inhibiting cancer, the quantity of new cancer cases in a group or population decreases. Hopefully, this will reduce the death toll resulting from cancer.

To stop new cancers from developing, researchers examine risk factors and protective factors. Anything that raises your likelihood of getting cancer is referred to as a cancer risk factor; anything that lowers your likelihood of developing cancer is termed a cancer protective factor [27].

Certain cancer risk factors can be prevented, yet many remain unavoidable. For instance, smoking and inheriting specific genes both pose risks for certain cancers, yet only smoking is preventable. Routine physical activity and a nutritious diet might serve as protective elements against certain cancer types. Minimizing risk factors and enhancing protective factors may reduce your likelihood, but it does not guarantee you won't develop cancer [28].

Various Methods for Cancer Prevention are Being Researched, Including

- modifying lifestyle or dietary patterns
- steering clear of substances recognized to induce cancer
- using medications to address a precancerous state or to prevent the onset of cancer

Examinations of the rectum and colon are conducted to identify colon cancer.
Along with inquiring about your personal and family medical history and conducting a physical examination, your doctor might carry out these tests and procedures:

A digital rectal examination (DRE) is an assessment of the rectum. The nurse or doctor places a gloved, lubricated finger into the lower section of the rectum to examine for any lumps or abnormalities [29].

The faecal occult blood test (FOBT) evaluates stool (solid waste) for blood that is detectable only under a microscope. A small amount of stool is put on a specific card or into a special container and sent back to the doctor or lab for analysis. Blood in the stool could indicate polyps (small protruding tissue), cancer, or other issues [30].

There are Two Categories of FOBTs
Guaiac FOBT: A stool sample placed on the designated card is analysed with a chemical. If blood is present in the stool, the special card alters its colour.

Immunochemical FOBT: A liquid is mixed with the stool sample. This combination is introduced into a device that has antibodies capable of identifying blood in the stool. If stool contains blood, a line shows up in a window on the device. This examination is also known as faecal immunochemical test or FIT [31].

Sigmoidoscopy is a procedure that examines the rectum and lower colon for polyps (small protruding tissue), irregular regions, or cancer. A sigmoidoscope is placed through the rectum into the sigmoid section of the colon. A sigmoidoscope is a slender, tube-shaped device equipped with a light and a lens for observation. It might also include a device to eliminate polyps or tissue samples, which are examined microscopically for indications of cancer [32].
Colonoscopy is a procedure that employs a colonoscope to examine the rectum and colon for polyps (small protruding tissue), unusual regions, or cancer. A colonoscope is a slender, tube-shaped device equipped with a light and a lens for inspection (Figure 4). It might also include a device to eliminate polyps or biopsy samples, which are examined microscopically for cancer indications [33].

Virtual colonoscopy is a procedure that employs a series of x-rays known as computed tomography to create a set of images of the colon. A computer assembles the images to form detailed visuals that could display polyps and any other unusual findings on the colon's inner surface. This examination is also referred to as colonography or CT colonography [34].

A biopsy involves extracting cells or tissues for microscopic examination to look for indications of cancer. Tumour tissue taken during the biopsy can be analysed to determine if the patient possibly carries the gene mutation associated with Lynch syndrome (also referred to as hereditary nonpolyposis colorectal cancer). This might assist in organizing treatment. Discover the kind of details available in a pathologist's report regarding the cells or tissue obtained during a biopsy at Pathology Reports [35].

DNA stool test analyses DNA in stool cells for genetic alterations that might indicate colorectal cancer. Once colon cancer is diagnosed, imaging tests are conducted to determine whether cancer cells have spread within the colon or to other areas of the body.

The method employed to determine if cancer has advanced within the colon or to other regions of the body is referred to as staging. The data collected during the staging procedure identifies the disease's stage [36].

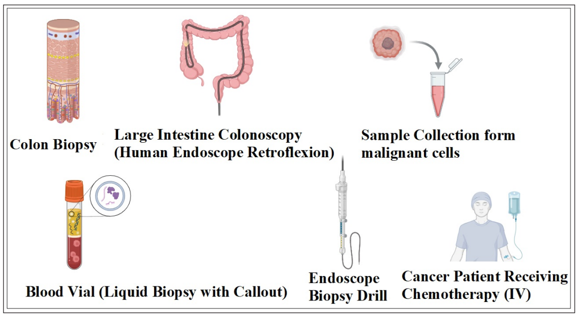

Figure 4: Colorectal Malignancy Diagnosis Through Biopsy

A CT scan (CAT scan) uses a computer connected to an x-ray device to create a sequence of detailed images of internal body areas, including the abdomen, pelvis, or chest. The images are captured from various perspectives and utilized to generate three-dimensional representations of tissues and organs. A dye can be injected into a vein or ingested to enhance the visibility of organs or tissues. This method is also referred to as computed tomography, computerized tomography, or axial computerized tomography [37].

MRI (magnetic resonance imaging) employs a magnet, radio waves, and a computer to produce a series of detailed images of regions within the colon. A material known as gadolinium is administered to the patient via a vein. The gadolinium accumulates near the cancer cells, making them appear more vibrant in the image. This technique is also known as nuclear magnetic resonance imaging (NMRI) [38].

A PET scan (positron emission tomography scan) involves injecting a small quantity of sugar (known as radioactive glucose) into a vein. The PET scanner revolves around the body and creates an image showing where sugar is utilized in the body. Cancer cells appear more vibrant in images due to their heightened activity and greater sugar absorption compared to normal cells [39].

- A chest x-ray is a form of radiation that penetrates the body to create images of the organs and bones within the chest.
- Surgery is a method to eliminate the tumour and determine how extensively it has spread throughout the colon.
- A lymph node biopsy involves taking out either a portion or the entirety of a lymph node. A pathologist examines lymph node tissue using a microscope to look for cancer cells. This can be performed during surgery or via endoscopic ultrasound-guided fine needle aspiration biopsy.
- The CEA assay is a test used to determine the concentration

of carcinoembryonic antigen in the bloodstream. CEA is secreted into the blood from both cancerous and normal cells. When detected in levels above normal, it may indicate colon cancer or other illnesses [40].

Therapy
Various methods exist for treating individuals with colon cancer. The types of treatments utilized include:

- Operation
- Cancer treatment with drugs
- Radiotherapy
- Focused treatment
- Immune therapy

Innovative treatment methods are undergoing testing in clinical studies.

- Colon cancer treatment can lead to side effects.
- Ongoing care might be necessary.

The subsequent categories of treatment are utilized:

Operation
Surgery is the primary treatment for every stage of colon cancer. The cancer is excised through one of these surgical methods:

Polypectomy
When cancer is detected in a polyp (a small protruding tissue fragment), the polyp is typically excised during a colonoscopy.

Local Excision
When cancer is detected in its initial stage, the physician might extract it without incising the abdominal wall. The doctor might insert a tube with a cutting instrument through the rectum into the colon to remove the cancer. This procedure is referred to as a local excision [41].

Colon Resection with Anastomosis
If the tumour is more extensive, the physician will carry out a partial colectomy (excising the tumour along with a slight portion of adjacent healthy tissue). The physician might subsequently carry out an anastomosis (stitching the healthy sections of the colon together). The physician typically removes lymph nodes adjacent to the colon and analyses them microscopically to check for cancer presence [42].

Colon Resection with Colostomy
When the physician cannot reconnect the two ends of the colon, a stoma (opening) is created on the body's exterior for waste elimination. This process is referred to as a colostomy. A pouch is positioned over the stoma to gather the waste. At times, a colostomy is required only until the lower intestine has recuperated, after which it can be undone. If the physician must excise the complete lower colon, the colostomy could be long-lasting [43].

Radiofrequency Ablation
Utilizing a specialized probe with small electrodes to destroy cancer cells. At times, the probe is placed directly through the skin, requiring only local anaesthesia. In other situations, the probe is placed through a cut in the abdomen. This is performed in the hospital under general anaesthesia [44].

Cryosurgery
A procedure that employs a device to freeze and eliminate abnormal tissue. This kind of therapy is also referred to as cryotherapy. Discover additional information regarding Cryosurgery for Cancer Treatment [45].

Radiation therapy and/or chemotherapy might be administered prior to surgery to reduce the tumour size, facilitate cancer removal, and assist with bowel management post-surgery. Therapy administered prior to surgery is referred to as neoadjuvant treatment. Once all the visible cancer is excised during surgery, certain patients may receive radiation therapy and/or chemotherapy post-surgery to eliminate any remaining cancer cells. Therapy administered following surgery to reduce the chances of cancer recurrence is known as adjuvant therapy [46].

If the cancer has metastasized to the liver and is inoperable, a complete hepatectomy followed by a liver transplant after chemotherapy may be performed. Total hepatectomy involves surgically removing the complete liver, succeeded by a transplant of a healthy liver from a donor.

Chemotherapy
Chemotherapy, often referred to as chemo, employs medications to hinder the proliferation of cancer cells, either by annihilating the cells or by preventing them from replicating. Systemic chemotherapy involves the administration of chemotherapy drugs either orally or through injection into a vein or muscle [47]. Administered this way, the medications enter the blood and can target cancer cells across the body. Chemotherapy administered systemically for colon cancer comprises capecitabine, 5-fluorouracil (5-FU), camptothecin derivative, leucovorin (a vitamin that enhances the efficacy of 5-FU), oxaliplatin, tipiracil and trifluridine may be used in combination. Additional chemotherapy medications not mentioned here might also be utilized [48].

Chemotherapy can be used alongside different types of medications. For instance, it could be used alongside the targeted therapy medications bevacizumab, cetuximab, or panitumumab aflibercept, ramucirumab, regorafenib, fruquintinib [49].

Regional chemotherapy for colon cancer involves administering drugs directly into the hepatic artery (the primary artery supplying blood to the liver) through a procedure known as chemoembolization. Chemoembolization of the liver artery can be utilized to address cancer that has metastasized to the liver. This is achieved by occluding the hepatic artery and administering anticancer medications between the occlusion and the liver [50]. The liver's blood vessels subsequently transport the medications into the liver. A limited quantity of the medication gets to different areas of the body. The obstruction might be transient or lasting, depending on the method employed to obstruct the artery. The liver keeps receiving blood from the hepatic portal vein, which transports blood from the stomach and intestines [51].

The method of administering chemotherapy varies based on the type and stage of the cancer being addressed.

Discover additional information regarding the functioning of chemotherapy, its administration, typical side effects, and further details at Chemotherapy to Treat Cancer and Chemotherapy and You: Support for People with Cancer [52].

Radiation Treatment

Radiation therapy employs high-energy x-rays or various forms of radiation to eliminate cancer cells or inhibit their growth. Colon cancer is occasionally addressed using two forms of radiation therapy aimed at treating colon cancer:

- External radiation therapy utilizes a device outside the body to direct radiation towards the part of the body affected by cancer.
- Internal radiation treatment employs a radioactive material enclosed in needles, seeds, wires, or catheters that are inserted directly into or close to the tumour. Internal radiation therapy can be utilized for colon cancer that has metastasized to the liver [53].

Focused Treatment

Targeted treatment employs medications or other agents to pinpoint and assault particular cancer cells. Your physician might recommend biomarker testing to aid in anticipating your reaction to specific targeted therapy medications. Discover additional information regarding Biomarker Testing in Cancer Therapy [54].

Immunotherapies Targeting Immune Checkpoints

Immunotherapy is a new therapeutic approach for various kinds of tumours. Tumor immunotherapy triggers an immune response mediated by immune cells via the neoantigen found on various tumours. The effectiveness of tumour immunotherapy in producing enduring antitumor effects has shown that immune cells, primarily T cells, can be harnessed to destroy tumour cells. Microsatellite instability (MSI) indicates faulty DNA mismatch repair (dMMR), and an MSI/dMMR status is seen in around 5% of mCRC instances [55]. Since MMR pathways correct DNA replication mistakes, MSI-high tumours contain numerous somatic mutations, resulting in increased neoantigen exposure that promotes the onset of an antitumor immune response. Consequently, MSI-high tumours exhibit a strong response to immunotherapy [56].

Patients diagnosed with metastatic colorectal cancer (mCRC) are typically managed with chemotherapy alone, focusing on alleviating symptoms and enhancing quality of life. Multimodal therapy, comprising surgery, ablation, and RT, was linked to improved survival; individuals who underwent RT showed a statistically significant rise in median overall survival relative to those who did not, and had a higher likelihood of disease control while facing a lower chance of disease progression [57].

Radiation Therapy Guided by Imaging

Image-guided radiation therapy (IGRT) is a sophisticated medical method that utilizes high- definition imaging, including computed tomography (CT) scans, X-rays, cone beam computed tomography (CBCT), or magnetic resonance imaging (MRI), to accurately identify and target tumours in the body, with CBCT being the imaging technique of choice for rectal cancer [58]. In contrast to traditional radiotherapy that depends on external references for precision, IGRT facilitates real-time observation and modifications, guaranteeing that the therapy is administered with exact precision. This not only optimizes the elimination of malignant cells, but also reduces the exposure of adjacent healthy tissues to radiation [59]. IGRT is frequently utilized for tumours susceptible to movement, such as the rectum and mesorectum, necessitating precise target volume delineation. IGRT is beneficial for patients undergoing intensity-modulated RT (IMRT) and, in particular, stereotactic body RT (SBRT), to verify that the radiation beams precisely hit the tumour [60].

IMRT

IMRT is a sophisticated radiation therapy technique used in oncology. It employs advanced technology to accurately target radiation at tumours, enhancing the equilibrium between tumour destruction and safeguarding healthy tissues [61]. IMRT attains this accuracy by dynamically modifying the intensity and configuration of radiation beams, customizing the treatment to align with the tumour's distinct contours through various imaging methods like CT, MRI, and positron emission tomography scans. Unlike traditional RT, which delivers standard doses, IMRT generates a highly accurate, three-dimensional distribution of doses. This tailored method amplifies the therapeutic effect on cancer cells while limiting radiation exposure to nearby healthy tissues, potentially decreasing RT-related side effects on the bladder, large intestine, and small intestine [62].

BRT

SBRT is a cutting-edge and extremely precise form of radiation therapy utilized in radiation oncology, noted for its exceptional ability to target high doses of radiation at tumour locations while reducing exposure to adjacent healthy tissues. Such precision is attained via advanced technology and image-guidance systems that enable clinicians to accurately identify the tumour in three-dimensional space [63]. SBRT has transformed the method of RT, marking the beginning of a fresh era of non-invasive, effective cancer therapy. SBRT is generally not advised for rectal cancer treatment but may be an option for patients with early-stage rectal cancer who are ineligible for surgery or have recurrent rectal cancer [64].

Innovative RT Methods for Precise Tumour Elimination

Nanoparticle-assisted RT: This method employs nanoparticles to target radiation straight to the tumour. The nanoparticles are covered with antibodies that identify the tumour cells, enabling radiation to be directed specifically at the tumour while minimizing the dose to adjacent healthy tissues. Nanoparticle-assisted RT is still in the initial phases of development for CRC, yet it holds the promise of greatly enhancing the effectiveness of RT [65]. Agonists of toll-like receptors (TLRs) have been identified as possible agents to activate the innate immune system, thereby eliciting an antitumor T-cell response. Nevertheless, the opposing effects of TLR activation present difficulties, requiring the creation of nanoparticle delivery systems. When optimally engineered, these nanoparticles can home in on specific cells such as dendritic cells or macrophages, enhancing the therapeutic effect [66]. Utilizing nanoparticles to deliver TLR agonists aligns with the objective of specifically targeting the innate immune system for CRC treatment. Nanoparticles offer benefits including enhanced solubility, bioavailability, targeting, stability, and reduced toxicity, thereby enhancing the therapeutic efficacy of phototherapy [67]. A study highlights the function of nanoparticles as transporters in CRC, outlining the targeting of PSs at different levels, ranging from organs to molecules. In addition, the combined use of photodynamic therapy and photothermal therapy is explored as a more effective method, particularly for tumours located deep within the body. While numerous nanomaterials are still being researched and developed, their anticipated advantages in CRC treatment are likely to be considerable soon [68].

Recent Developments in Chemotherapy for CRC

Present chemotherapy protocols for CRC primarily involve a combination of fluoropyrimidine (5-FU or capecitabine) with oxaliplatin and/or irinotecan along with capecitabine. It is also advised to include leucovorin in this combination, based on the patient's needs and the selected treatment plan [69]. The medication plan utilized relies on various factors including the stage of the disease (adjuvant chemotherapy is not advised in stages 0 and 1), the accessibility of medications, and the patient's ability to tolerate chemotherapy [70]. Bevacizumab, a monoclonal antibody (mAb), is presently utilized as the primary therapy in conjunction with chemotherapy. The guidelines from the American Society of Clinical Oncologists discourage the regular use of adjuvant therapy in stage II colon cancer patients who have a low risk of recurrence [71]. Adjuvant therapy should be provided to patients diagnosed with stage IIB and stage IIC colon cancer. It might also be available to patients with stage IIA colon cancer exhibiting high-risk characteristics. The importance of adjuvant therapy for stage II colon cancer treatment is contentious, yet it remains a consideration for patients with high-risk disease [72].

Recent Developments in Chemotherapy Medications Repurposing Existing Drugs

This collection includes repurposed medications that have completed clinical trials, confirming their safety and effectiveness in treating CRC [73]. The addition of these medications highlights their demonstrated efficacy in the systematic and regulated setting of clinical trials and therefore have succeeded in the in vitro/in vivo stages. It is essential to emphasize, however, that the selection shown here constitutes merely a small portion of the possible candidates in the area of repurposed medications [74].

Recent Developments in Targeted Treatment for CRC

Targeted therapy is a cancer treatment focusing on particular biological molecules to halt tumour cell growth and multiplication. By comprehending the main pathways associated with the onset and dissemination of CRC, it becomes feasible to create medications that, in principle, would specifically target and eliminate these cancer cells [75]. Targeted therapy depends on small molecule drugs that can readily penetrate cells and monoclonal antibodies. Focusing on the EGFR pathway, the EGFR is a member of the ErbB family that serves as a transmembrane receptor tyrosine kinase (Table 1) [76]. When its ligand binds, EGFR either homodimerizes or heterodimerizes with other ErbB receptor tyrosine kinases, resulting in the activation of downstream pathways such as the RAS-RAF-MAPK and PI3K-Akt pathways [77]. Mutations impacting the EGFR and its downstream signalling pathway have been demonstrated to play a crucial role in various cancers, including CRC. These mutations result in irregular cell growth, resistance to programmed cell death, and invasion [78].

Table 1: FDA-Authorize Focused Medicaments for Colorectal Cancer

Active Pharmaceutical Ingredient	Target	Medicament Action
Aflibercept	VEGF-A, VEGF-B, PlGF	Fusion protein that comprises the binding regions of VEGF from VEGF-1 and 2 linked to the Fc segment of immunoglobulin G1 (IgG1)
Regorafenib	VEGFR, EGFR, KIT, PDGFR, BRAF	Compact molecule blocker of membrane-associated and cytoplasmic receptor tyrosine kinases
Ramucirumab	VEGFR-2	Fully human mAb (IgG1)
Larotrectinib	TRK	Small compound of tyrosine kinase blocker
Entrectinib	TRK, ALK, ROS1	Fully human mAb (IgG1) small molecule of tyrosine kinase blocker
Encorafenib	BRAF(V600E-mutant)	Small element kinase restraints
Nivolumab	PD-1	Fully human mAb (IgG4)
Ipilimumab	CTLA-4	Fully human mAb (IgG1)
Cetuximab	EGFR	Chimeric mouse/human mAb (IgG1)
Bevacizumab	VEGF-A	Humanized mAb (IgG1)
Panitumumab	EGFR	Fully human mAb (IgG1)
Pembrolizumab	PD-1	Humanized mAb (IgG4)

Focusing on BRAF

BRAF is a serine/threonine kinase essential for activating the RAF/MEK/ERK signaling pathway that promotes cell proliferation. Approximately 8%-12% of colorectal cancers contain the BRAF-V600E mutation [79]. Encorafenib and Binimetinib: Encorafenib acts as a BRAF inhibitor with extended efficacy relative to earlier BRAF inhibitors; in contrast, binimetinib functions as a MEK inhibitor [80]. The phase III study BEACON evaluated the impact of triple therapy (encorafenib/binimetinib/cetuximab), double therapy (encorafenib/cetuximab), and control treatments (chemotherapy/cetuximab) in mCRC patients with the BRAF-V600E mutation who experienced disease progression following one or two previous treatment lines [81]. The research indicated a better median overall survival for both triplet and doublet therapies in comparison to controls [mOS: 9.3 months vs 5.9 months; HR = 0.60, 95% confidence interval (CI): 0.47-0.75]. ASCO recommends the administration of cetuximab combined with encorafenib (approved by the FDA in 2020) for patients with BRAF-V600E mCRC that has advanced despite at least one previous treatment line [82].

Focusing on Human EGFR-2

Human EGFR-2 (HER2) is part of the ErbB tyrosine kinase receptor family. When HER2 is overproduced, it typically forms heterodimers with other members of the ErbB family. As a result, tyrosine residues in the cytoplasmic section of the heterodimer experience autophosphorylation [83]. This triggers a series of signalling pathways that promote cell growth and contribute to tumour formation. Approximately 5% of patients with mCRC are estimated to have a HER2 mutation [83]. Trastuzumab and tucatinib: Trastuzumab is a humanized recombinant monoclonal antibody aimed at the extracellular portion of HER2. In the same way, Tucatinib is an orally administered small molecule tyrosine kinase inhibitor that specifically targets HER2 [84]. The pairing of tucatinib with trastuzumab recently obtained accelerated FDA approval (January 2023) for treating HER2 + mCRC that has not responded to irinotecan, oxaliplatin, and fluoropyrimidine. The phase II MOUNTAINEER trial showed that HER2 + mCRC receiving tucatinib and trastuzumab had an objective response rate of 38.2% (95%CI: 27.7-49.3) and a median response duration of 12.4 months (95%CI: 8.3-25.5) [85].

Conclusion

Colorectal cancer is a diverse condition, marked by variability both between and within tumours. Molecular changes accumulate in the colorectal mucosa through different mechanisms, such as MMR gene changes, chromosomal instability, and alterations in CpG island methylation, which subsequently contribute to the development and advancement of cancer. All these processes give unique characteristics to each tumour regarding malignancy, aggressiveness, invasiveness, and treatment response. Despite the rise in CRC cases, its mortality has likely declined due to preventive measures, early identification, and advancements in treatment methods. Surgery, along with neoadjuvant chemotherapy, adjuvant chemotherapy, and radiation, is presently the cornerstone of CRC treatment. Recent progress in medical sciences has made human genomics, transcriptional, and epigenetic data more obtainable.

Colorectal cancer is a diverse disease marked by variability both between and within tumours. Molecular changes build up in the colorectal mucosa through different processes, such as MMR gene modifications, chromosomal instability, and changes in CpG island methylation, ultimately resulting in the onset and advancement of cancer. All these mechanisms provide distinct characteristics to every tumour regarding malignancy, aggressiveness, invasion, and treatment response. Despite the rise in CRC cases, its mortality rate has likely declined due to preventive measures, timely detection, and advancements in treatment strategies. Precision therapy, tailored to the molecular characteristics of the tumour, is frequently used alongside chemoradiotherapy.

As a result, personalized therapy for conditions like CRC is now achievable. Indeed, because of the significant tissue variability among individuals, personalized treatment is regarded as essential. Nevertheless, clinical trials remain necessary to furnish evidence for the ongoing enhancement of advanced CRC treatment. These clinical trials will aid in supplying evidence for optimal practice guidelines to be adhered to moving forward. In a swiftly changing area, various protocols of systemic and local chemotherapy, along with distinct antibodies based on mutational status, are employed to turn non-resectable hepatic metastatic disease into a resectable condition, offering a possibility of cure. Additional studies ought to concentrate on identifying the best treatment strategy, considering the various therapeutic alternatives and individual differences. In upcoming studies, it will be crucial to understand the specific mechanisms and toxicity metrics through which ICIs develop resistance. This will encourage the advancement of innovative diagnostic and therapeutic choices to overcome the constraints of current ICI treatments and help more CRC patients.

References

1. Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. JAMA. 2021. 325: 669-685.
2. Saha S, Ghosh S, Ghosh S, Nandi S, Nayak A. Unraveling the complexities of colorectal cancer and its promising therapies -an updated review. Int Immunopharmacol. 2024. 143: 113325.
3. Fadlallah H, El Masri J, Fakhereddine H, Youssef J, Chemaly C, et al. Colorectal cancer: recent advances in management and treatment. World J Clin Oncol. 2024.15: 1136-1156.
4. Birrer DL, Tschuor C, Reiner C, Fritsch R, Pfammatter T, et al. Multimodal treatment strategies for colorectal liver metastases. Swiss Med Wkly. 2021.151: 20390.
5. Nayak A. Unraveling the complexities of colorectal cancer and its promising therapies-An updated review. Int Immunopharmacol. 2024.143: 113325.
6. Abedizadeh R, Majidi F, Khorasani HR, Abedi H, Sabour D. Colorectal cancer: a comprehensive review of carcinogenesis, diagnosis, and novel strategies for classified treatments. Cancer Metastasis Rev. 2024. 43: 729-753.
7. Laska E, Richter P. Incidence versus treatment outcomes and survival in patients before age 40 with colorectal cancer. Pol Przegl Chir. 2024. 96: 9-17.
8. Effendi-Ys R. Colonoscopy, biomarkers, and targeted therapy in colorectal cancer. Acta Med Indones. 2022. 54: 476-486.
9. Binefa G, Rodríguez-Moranta F, Teule A, Medina-Hayas M. Colorectal cancer: from prevention to personalized medicine. World J Gastroenterol. 2014. 20: 6786-808.
10. Yu X, Zhu L, Liu J, Xie M, Chen J, Li J. Emerging role of immunotherapy for colorectal cancer with liver metastasis. Onco Targets Ther. 2020.13: 11645-11658.
11. Yang W, Zheng H, Lv W, Zhu Y. Current status and prospect of immunotherapy for colorectal cancer. Int J Colorectal Dis. 2023. 38: 266.
12. Haynes J, Manogaran P. Mechanisms and strategies to overcome drug resistance in colorectal cancer. Int J Mol Sci. 2025. 26:1988.

13. Marginean EC, Melosky B. Is There a role for programmed death ligand-1 testing and immunotherapy in colorectal cancer with microsatellite instability? part I-colorectal cancer: microsatellite instability, testing, and clinical implications. Arch Pathol Lab Med. 2018. 142: 17-25.
14. Zhang C, Stampfl-Mattersberger M, Ruckser R, Sebesta C. Kolorektales Karzinom, Colorectal cancer. Wien Med Wochenschr. 2023.173: 216-220.
15. Laska E, Richter P. Delayed diagnosis, disease and secondary prevention, especially in young patients with colorectal cancer. Pol Przegl Chir. 2024. 96: 38-46.
16. Ding Y, Wang Z, Zhou F, Chen C, Qin Y. Associating resistance to immune checkpoint inhibitors with immunological escape in colorectal cancer. Front Oncol. 2022. 12: 987302.
17. Turano M, Delrio P, Rega D, Cammarota F, Polverino A, Duraturo F, Izzo P, De Rosa M. Promising colorectal cancer biomarkers for precision prevention and therapy. Cancers (Basel). 2019. 11:1932.
18. Ohishi T, Kaneko MK, Yoshida Y, Takashima A, Kato Y, Kawada M. Current targeted therapy for metastatic colorectal cancer. Int J Mol Sci. 2023. 24:1702.
19. Stigliano V, Sanchez-Mete L, Martayan A, Anti M. Early-onset colorectal cancer: a sporadic or inherited disease? World J Gastroenterol. 2014. 20: 12420-30.
20. Bess SN, Greening GJ, Muldoon TJ. Efficacy and clinical monitoring strategies for immune checkpoint inhibitors and targeted cytokine immunotherapy for locally advanced and metastatic colorectal cancer. Cytokine Growth Factor Rev. 2019. 49: 1-9.
21. Li Y, Cheng Z, Li S, Zhang J. Immunotherapy in colorectal cancer: Statuses and strategies. Heliyon. 2024.11: e41354.
22. Satapathy BS, Mukherjee B, Baishya R, Chatterjee Debnath M, Dey NS. Lipid nanocarrier-based transport of docetaxel across the blood brain barrier. RSC Adv. 2016. 6: 85261-85274.
23. Dey NS. Mechanistic approach of nano carriers for targeted in cancer chemotherapy: a newer strategy for novel drug delivery system. Polymers. 2022. 2321: 1-17.
24. Dey NS, Mukherjee B, Maji R, Satapathy BS. Development of linker-conjugated nanosize lipid vesicles: a strategy for cell selective treatment in breast cancer. Current Cancer Drug Targets. 2016. 16: 357-372.
25. Mukherjee B, Dutta L, Mondal L, Dey NS, Maji R. Nanoscale formulations and diagnostics with their recent trends: a major focus of future nanotechnology. Current Pharmaceutical Design. 2015. 21: 5172-5186.
26. Maji R, Dey NS, Satapathy BS, Mukherjee B. Preparation and characterization of tamoxifen citrate loaded nanoparticles for breast cancer therapy. International Journal of Nanomedicine. 2014. 9: 3107-3118.
27. Dey NS, Sarkar S, Mohanta T, Pramanik S. Nano formulation devices technology for targeting breast cancer chemotherapy. J Chem Can Res. 2025. 3: 1-9.
28. Mukherjee B, Satapathy BS, Dey NS, Ruma Maji R. Potentials and challenges of active targeting at the tumor cells by engineered polymeric nanoparticles. Current Pharmaceutical Biotechnology. 2013. 14: 1250-1263.
29. Mukherjee B, Dey NS, Maji R, Bhowmik P, Das PJ, Paramita Paul P. Current status and future scope for nanomaterials in drug delivery. Hard copy of the book “Application of Nanotechnology in Drug Delivery” in INTECH OPEN book chapter. 2014. 16: 525-544.
30. Dey NS, Dasgupta RK, Deb Roy S. Nanomedicine for targeted drug delivery in cancer chemotherapy, in recent advances in smart drug delivery, INTECH OPEN book chapter edited volume, “Smart drug delivery systems”-futuristic window in cancer therapy. 2023.02: 1-21.
31. Dey NS, Pal S, Saha P, Samanta A, Ram PK, Shahjaha MD. Development of metronidazole loaded multiple emulsion for sustained release medication. International Journal of Pharmaceutical Sciences, 2025. 3: 2661-2670.
32. Dey NS, Kundu R. Recent progress and upcoming paths: current developments in chemotherapy for metastatic prostate cancer treatment. Journal of Chemotherapy and Cancer Research. 2026. 4: 1-10.
33. Pal S, Dey NS, Ram PK, Shahjaha MD. Multiple emulsions for sustainable drug delivery, International Journal of Pharma Growth Research Review. 2025. 05: 42-48.
34. Witt JS, Rosenberg SA, Bassetti MF. MRI-guided adaptive radiotherapy for liver tumours: visualising the future. Lancet Oncol. 2020. 21: e74-82.
35. Petrowsky H, Fritsch R, Guckenberger M, De Oliveira ML, Dutkowski P, Clavien PA. Modern therapeutic approaches for the treatment of malignant liver tumours. Nat Rev Gastroenterol Hepatol. 2020.17: 755-72.
36. Lee J, Shin IS, Yoon WS, Koom WS, Rim CH. Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver ma lignancies: Meta-analyses and a systematic review. Radiother Oncol. 2020.145: 63-70.
37. Javadrashid D, Mohammadzadeh R, Baghbanzadeh A, Safaee S, Amini M, et al. Simultaneous microRNA-612 restoration and 5-FU treatment inhibit the growth and migration of human PANC-1 pancreatic cancer cells. Excli J. 2021. 20: 160.
38. Derakhshani A, Hashemzadeh S, Asadzadeh Z, Shadbad MA, Rasibonab F, Safarpour H, et al. Cytotoxic T-lymphocyte antigen-4 in colorectal cancer: Another therapeutic side of capecitabine. Cancers. 2021. 13: 2414.
39. Martin-Romano P, Ammari S, El-Dakdoukti Y, Baldini C, Varga A, et al, Chemotherapy beyond immune checkpoint inhibitors in patients with metastatic colorectal cancer. Eur J Cancer. 2020. 137: 117-26.
40. André T, Cohen R, Salem ME. Immune checkpoint blockade therapy in patients with colorectal cancer harboring microsatellite Instability/Mismatch repair deficiency in 2022. Am Soc Clin Oncol Educ Book. 2022. 42: 1-9.
41. Almquist DR, Ahn DH, Bekaii-Saab TS. The role of immune checkpoint inhibitors in colorectal adenocarcinoma. Bio Drugs. 2020. 34: 349-62.
42. Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. Cancer Cell 2020. 37: 443-55.
43. Pelka K, Hofree M, Chen JH, Sarkizova S, Pirl JD, Jorgji V, et al. Spatially organized multicellular immune hubs in human colorectal cancer. Cell. 2021. 184: 4734-4752. e20.
44. Dong C, Ding Y, Weng S, Li G, Huang Y, Hu H, Update inversion 2021 of CSCO guidelines for colorectal cancer from version 2020. Chin J Cancer Res. 2021. 33: 302.
45. Shiga T, Hiraide M. Cardiotoxicities of 5-fluorouracil and other f luoropyrimidines. Curr Treat Options Oncol, 2020. 21: 1-21.

46. Marmorino F, Boccaccino A, Germani MM, Falcone A, Cremolini C. Immune checkpoint inhibitors in pMMR metastatic colorectal cancer: A tough challenge. Cancers. 2020. 12: 2317.
47. Hubbard JM, Tőke ER, Moretto R, Graham RP, Youssoufian H, et al. Safety and activity of Poly PEPI1018 combined with maintenance therapy in metastatic colorectal cancer: An open-label, multicentre, phase 1b study. Clin Cancer Res: An Off J Am Assoc Cancer Res. 2022. 28: 2818-2829.
48. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020. 6: 1-21.
49. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin. 2021. 71: 209-249.
50. Dong C, Ding Y, Weng S, Li G, Huang Y, Hu H, Update inversion 2021 of CSCO guidelines for colorectal cancer from version 2020. Chin J Cancer Res. 2021. 33: 302.
51. Shiga T, Hiraide M. Cardiotoxicities of 5-fluorouracil and other fluoropyrimidines. Curr Treat Options Oncol. 2020. 21: 1-21.
52. Hubbard JM, Tőke ER, Moretto R, Graham RP, Youssoufian H, Lőrincz O, et al. Safety and activity of PolyPEPI1018 combined with maintenance therapy in metastatic colorectal cancer: An open-label, multicenter, phase 1b study. Clin Cancer Res: An Off J Am Assoc Cancer Res. 2022. 28: 2818-29.
53. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020. 6: 1-21.
54. Bejarano L, Jordão MJ, Joyce JA. Therapeutic targeting of the tumor microenvironment. Cancer Discov. 2021. 11: 933-59.
55. Yang Y, Li Y, Chen K, Zhang L, Qiao S, Tan G. Dual receptor-targeted and redox-sensitive polymeric micelles self-assembled from a folic acid-hyaluronic acid-SS-vitamin e succinate polymer for precise cancer therapy. Int J Nanomed. 2020. 15: 2885.
56. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal Al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin. 2021. 71: 209-249.
57. Dong C, Ding Y, Weng S, Li G, Huang Y, Hu H. Update inversion 2021 of CSCO guidelines for colorectal cancer from version 2020. Chin J Cancer Res. 2021. 33: 302.
58. Shiga T, Hiraide M. Cardiotoxicities of 5-fluorouracil and other fluoropyrimidines. Curr Treat Options Oncol. 2020. 21: 1-21.
59. Pelka K, Hofree M, Chen JH, Sarkizova S, Pirl JD, Jorgji V. Spatially organized multicellular immune hubs in human colorectal cancer. Cell. 2021. 184: 4734-4752.
60. Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. Cancer Cell. 2020. 37: 443-55.
61. Bejarano L, Jordão MJ, Joyce JA. Therapeutic targeting of the tumor microenvironment. Cancer Discov. 2021. 11: 933-959.
62. Yang Y, Li Y, Chen K, Zhang L, Qiao S, et al. Dual receptor-targeted and redox-sensitive polymeric micelles self-assembled from a folic acid-hyaluronic acid-SS-vitamin e succinate polymer for precise cancer therapy. Int J Nanomed. 2020. 15: 2885.
63. Almquist DR, Ahn DH, Bekaii-Saab TS. The role of immune checkpoint inhibitors in colorectal adenocarcinoma. Bio Drugs. 2020. 34: 349-362.
64. André T, Cohen R, Salem ME. Immune checkpoint blockade therapy in patients with colorectal cancer harboring microsatellite Instability/Mismatch repair deficiency in 2022. Am Soc Clin Oncol Educ Book. 2022. 42: 1-9.
65. Martin-Romano P, Ammari S, El-Dakdoukti Y, Baldini C, Varga A, et al. Chemotherapy beyond immune checkpoint inhibitors in patients with metastatic colorectal cancer. Eur J Cancer. 2020. 137: 117-26.
66. Gohil SH, Iorgulescu JB, Braun DA, Keskin DB, Livak KJ. Applying high dimensional single-cell technologies to the analysis of cancer immunotherapy. Nat Rev Clin Oncol. 2021. 18: 244-56.
67. Javadrashid D, Mohammadzadeh R, Baghbanzadeh A, Safaee S, Amini M, Lotfi Z, et al. Simultaneous microRNA-612 restoration and 5-FU treatment inhibit the growth and migration of human PANC-1 pancreatic cancer cells. Excli J. 2021. 20: 160.
68. Derakhshani A, Hashemzadeh S, Asadzadeh Z, Shadbad MA, et al. Cytotoxic T-lymphocyte antigen-4 in colorectal cancer: Another therapeutic side of capecitabine. Cancers. 2021. 13: 2414.
69. Wu CWK, Reid M, Leedham S, Lui RN. The emerging era of personalized medicine in advanced colorectal cancer. J. Gastroenterol. Hepatol. 2022. 37: 1411-1425.
70. Sartore-Bianchi A, Pietrantonio F, Lonardi S, Mussolin B, Rua F, et al. Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: The phase 2 CHRONOS trial. Nat. Med. 2022. 28: 1612-1618.
71. Hu LF, Lan HR, Huang D, Li XM, Jin KT. Personalized immunotherapy in colorectal cancers: where do we stand? Front. Oncol. 2021. 11: 769305.
72. Ge P, Wan N, Han X, Wang X, Zhang J, Long X, Wang X, Bian Y. Efficacy, safety, and cost-effectiveness analysis of aflibercept in metastatic colorectal cancer: A rapid health technology assessment. Front Pharmacol. 2022. 13: 914683.
73. Ros J, Rodríguez-Castells M, Saoudi N, Baraibar I, Salva F, Tabernero J, Élez E. Treatment of BRAF-V600E mutant metastatic colorectal cancer: new insights and biomarkers. Expert Rev Anticancer Ther. 2023. 23: 797-806.
74. Oh DY, Bang YJ. HER2-targeted therapies - a role beyond breast cancer. Nat Rev Clin Oncol. 2020. 17: 33-48.
75. Casak SJ, Horiba MN, Yuan M, Cheng J, Lemery SJ, et al. FDA Approval Summary: Tucatinib with Trastuzumab for Advanced Unresectable or Metastatic, Chemotherapy Refractory, HER2-Positive RAS Wild-Type Colorectal Cancer. Clin Cancer Res. 2023. 29. 4326-4330.
76. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020. 17: 807-821.
77. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, Ladwa R, O'Byrne K,

Kulasinghe A. Immune Checkpoint Inhibitors in Cancer Therapy. Curr Oncol. 2022. 29: 3044-3060.

78. Wu M, Huang Q, Xie Y, Wu X, Ma H, et al. Improvement of the anticancer efficacy of PD-1/PD-L1 blockade via combination therapy and PD-L1 regulation. J Hematol Oncol. 2022. 15: 24.
79. Mitra A, Barua A, Huang L, Ganguly S, Feng Q, et al. From bench to bedside: the history and progress of CAR T cell therapy. Front Immunol. 2023. 14: 1188049.
80. Juat DJ, Hachey SJ, Billimek J, Del Rosario MP, Nelson EL, et al. Adoptive T-Cell therapy in advanced colorectal cancer: a systematic review. Oncologist. 2022. 27: 210-219.
81. Tang YL, Li DD, Duan JY, Sheng LM, et al. Resistance to targeted therapy in metastatic colorectal cancer: Current status and new developments. World J Gastroenterol. 2023. 29: 926-948.
82. Dey NS, Rao MEB. Quantum dot: novel carrier for drug delivery. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2011. 2: 448-458.
83. Dey NS, Majumder S, Rao MEB. Multiple drug delivery systems for controlled release. Tropical Journal of Pharmaceutical Research. 2008.7: 1067-1075.
84. Trimaglio G, Tilkin-Mariamé AF, Feliu V, Lauzéral-Vizcaino F, et al. Colon-specific immune microenvironment regulates cancer progression versus rejection. Oncoimmunology. 2020. 9: 1790125.
85. Dey A, Mitra A, Pathak S, Prasad S, Zhang AS, Zhang H, et al. Recent advancements, limitations, and future perspectives of the use of personalized medicine in treatment of colon cancer. Technol Cancer Res Treat. 2023. 22: 15330338231178403.